STATE UNIVERSITY OF MEDICINE
AND PHARMACY "NICOLAE TESTEMITANU"

BASICS OF ONCOLOGY

SOFRONI DUMITRU • CUCIERU CRISTINA
BACALÎM LILIA • VÎRLAN MARIANA • ȘVEȚ VERONICA

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PREFACE

Discoveries in the field of oncology have fundamentally changed the horizon of diagnostic and treatment possibilities, forcing a perpetual need for information. Oncology is not a medical specialty exercised by an isolated individual, this is a multidisciplinary "concept"- the only effective way to approach the complex problems targeted by this disease.

Thus, the oncology book appeared with the participation of the entire staff of the Oncology Department. Importantly, each contributing professor, lecturer or assistant of the department presented chapters for the textbook with knowledge of the matter and focused on the topic in which they are most competent, providing key opinions.

The academic work elaborated, details the evolution and the best current practices applicable in oncology, representing a reflection of the achievements and a synthesis of the progress that this branch of medicine has registered in recent years.

Studying this field we are attracted by the permanent metamorphoses and inspired by a dose of optimism related to the possibility of curing more and more patients and turning cancer into a treatable chronic condition.

The textbook attempts to respond to the challenges by providing accessible information that reflects recent changes in oncology in its complexity and dynamism.

The need for the appearance of an autochthonous work resides in contributing to the development, facilitation and modernization of studies at the contemporary level, predilection for english-speaking students of the State University of Medicine and Pharmacy "N. Testemițanu".

All the material presented in this publication is based on the contributors' own experience with the presentation of sources published in the last 5-10 years.

This work aims to provide useful and immediate information to those with a special interest in oncology while serving as an incentive to consult other more complex materials.

With regards and success
in the deeper knowledge of
contemporary oncology ***Authors***

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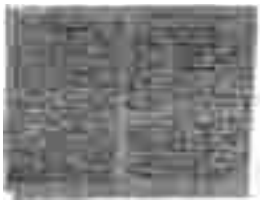
INTRODUCTION. HISTORIC. DEONTOLOGY. ORGANIZATION AND STRUCTURE OF ONCOLOGICAL ASSISTANCE IN REPUBLIC OF MOLDOVA

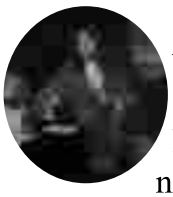


Introduction. Oncological pathologies exist from the appearance of the human species, but the first communications about tumors appear only a few thousand years (3-5) BC, so in the *Egyptian Papyrus* written about 3000-1500 BC discovered by *Edwin Smith* in 1862 - is the oldest description of human cancers and refers to 8 cases of breast tumors.

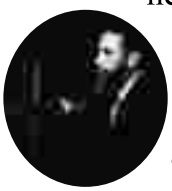
The term **Oncology** comes from the Greek words *ονκος onkos = mass, tumor* and the suffix *«logy» = science* is the branch of medicine that deals with the study and treatment of malignant tumors.

The word *cancer* is derived from the *Greek karkinos* (crab, crab) mentioned in the writings of Hippocrates from Kos (460-375 BC), as well as from the *Latin cancrum* taken by Galen us from the works of Hippocrates.

Galenus from Pergamum (129-199 AD) make the first attempts to classify the cancer, so the *ulcerate* forms he called *karkinos,* and the solid *one - carcinomas.*



With the invention of the microscope by Antoni van Leeuwenhoek (1632-1723) began the era of histological investigations, the basis of which was laid by Marcello Malpighi (1628-1694), opened a new era in cancer research.



An enormous progress in the study and formulation of the developmental concepts of malignant tumors takes place in the 19th century, which is the result of the discovery of X- rays by Röntgen in 1895 and radium by the Curie

couple (Piere and Maria Sclodovscaia) in 1898, radiological investigations in cancer and its treatment by radiotherapy.

Modern conceptions of cancer histogenesis have been formulated by Rudolf Virchow. Which is the basis of morphopathological investigations, without which no treatment method is currently done. Since 150-200 years ago, the main method of treatment in oncology was dominated by surgery. Radiation therapy has been developed since 1920, and chemotherapy was introduced after 1945.

Recent years have also confirmed the success of molecular therapies which target tumor alterations that underlie carcinogenesis. A new generation of medications, monoclonal antibodies, and small molecules that target specific receptors and biological signaling pathways essential for malignant cell survival and progression have revolutionized the treatment of some cancers and restored hope to many patients. Perhaps none of the cancer therapies have generated more enthusiasm in recent years than immunotherapy. A simple initial concept, it required decades of study to witness the spectacular introduction of effective immunotherapeutic agents in neoplasms such as malignant melanoma, bronchopulmonary cancers or malignant haematological diseases two or three years ago.

There are currently a wide range of therapeutic methods for malignancies that can be listed in the following order:

- surgical (radical and palliative);
- radiotherapy (neoadjuvant and adjuvant);
- chemotherapy with cytostatics (neoadjuvant and adjuvant);
- hormone therapy (neoadjuvant and adjuvant) and substitution;
- immunotherapy;
- targeted therapy with monoclonal antibodies;
- laser therapy etc.

The history of oncology. Organization and structure of oncology care in the Republic of Moldova

The first oncological institution in the Romanian area begins with the founding of the Oncological Institute in Cluj-Napoca in 1929 by Ion Moldovan.

The development of the oncology service in Moldova begins in 1950,

when the Oncology Dispensary was opened by Ipatie Sorocean in Chișinău.

In 1960, the Oncological Institute of Scientific Research was founded on it, having at that time only 2 departments (surgery and radiotherapy).

The found ers of the Institute are considered: P. Hohlov, V. Crivoseev and Ghivi Honelidze - the first director of the Institute.

Department of Oncology is founded by Professor V. Pavliuc in 1976, the hematology one was founded in 1991 by professor Ion Corcimaru.

Organization and structure of oncology care in Republic of Moldova

The institution of methodological coordination, scientific studies and the performance of specialized and highly qualified oncological assistance is the Oncological Institute and the Oncology Department of USMF "Nicolae Testemitanu".

Student training year V, of oncology residents and related cycles, recycling of oncologists and other categories in the general network- the study process is carried out within the Department of Oncology.

There is an oncology departments in each district, where the district oncologist works, coordinating the entire oncology activity.

Basic objectives of cancer care:

1. Organizing the service for the active detection of patients in the preclinical and early stages by performing prophylactic examinations of large population groups, especially those with high risk of disease. These groups are suposed on modern methods of investigation (Rological, endoscopic, USG, computed tomography, histological, cytological and others).
2. Organizing the qualified and professional treatment process of patients with confirmed tumor diagnosis. It must be acknowledged that even today a large percentage of cancer patients are treated in general conditions (about 25-30%), where patients do not have the opportunity to receive a complete cure with the application of many methods that do not have those institutions.
3. Improving the system for recording the incidence of cancer and oncological mortality by switching to centralized information processing of results through computer technology.

The main task of the oncology service is to dispense patients with either malignant tumors or benign tumors.

To perform the dispensary process, all patients are divided into the following *clinical groups:*

- ***Group 1a*** - patients with suspected cancer (patients in this group should be examined, investigated and the diagnosis of cancer should be confirmed or denied within 10 days).
- ***Group 1b*** - patients with precancerous conditions (benign tumors, various chronic inflammatory diseases, genetic and immunobiological precancerous syndromes). Patients require etiopathogenetic treatment excluding malignancy of precancerous diseases.
- ***Group II*** - patients with malignant tumors, which require special treatment (radio-chemo-hormone-immunotherapy, etc.).
- ***Group IIa*** - patients with malignant tumors, which may be exposed to radical treatment (surgical, radiotherapy, associated, complex).
- ***Group III*** - patients who underwent radical treatment practically considered healthy at the time of examination).
- ***Group IV*** - patients with advanced malignancies, who are indicated for symptomatic therapy.

For patients in group IV, it is required to complete some protocols indicating the causes of the outdated processes - these are:

1. Diagnostic errors (clinical, radiological, endoscopic, histological).
2. Incomplete investigations.
3. Unexcused procrastination.
4. Occult, asymptomatic evolution of the disease.
5. Late addressing of the patient.

It should be noted that the percentage of outdated causes of cancer belongs to the first three causes listed above and constitutes 60-70% of patients, which requires a high and careful vigilance from doctors, especially those in the general network.

Oncological ethics

The name comes from the Greek words: *deon* - duty and *logos* - science, which provides the attitude and relationships between doctor - patient, nurse - patient, doctor - doctor, doctor - nurse. It is considered that a special change of optics of both doctors and the public is needed through a well-directed oncology education.

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THE EPIDEMIOLOGY OF HUMAN CANCER

Epidemiology is the field that studies the frequency, distribution (by sex, age, profession, space, time, etc.) and determinants of cancer (causes, individual and collective risk factors, conditions of spread) in the human population, this definition being applicable in other human pathologies.

It focuses on the study of events that occur in various populations, not at the individual level. Moreover, the interest of epidemiology in identifying the precursors of various oncological diseases (intra-epithelial cervical neoplasia as a precursor of cervical cancer, atrophic gastritis as a precursor of gastric cancer, etc.) confirms the importance of this discipline in disease prevention and control, development of screening programs. Another important role is to study the distribution of diseases in a population, to provide information on their etiology and to determine the risk.

Epidemiology developed initially as a field related to infectious diseases, and only later to chronic diseases. Although the epidemiology of cancer is not a new science, it did not reach maturity until the second half of the twentieth century, when infectious diseases (*eg* tuberculosis) declined in incidence and mortality, and the development of new media and statistics, such as and the centralization of global records has made it possible to study the incidence and mortality of cancer.

The first epidemiological findings belonged to clinicians. For example, B. Ramazzini (1713) observes the increased frequency of breast cancer in nuns, linking it to celibacy. The English physician P. Pott (1775) points out the more common occurrence of scrotal cancer in young hornari, and R. Stern (1844) publishes a report on uterine and breast cancer in Verona, showing the relationship between marital status and disease. With the development of the industry and the widening of the professional spectrum, more and more associations have been observed between various environmental factors and cancer.

Epidemiological research includes issues such as:

- Demonstration of variations in geographical and temporal incidence.
- Correlating the incidence in different communities with the prevalence of environmental agents and social factors.

- Comparison of groups of people with and without cancer.
- Removal of suspicious agents (primary prevention) and observation of results.
- Quantitative observations that test the applicability to humans of the models and mechanisms by which the disease is produced.

Epidemiology can take two main forms, depending on the intervention of the investigator:

1. Observational - involves the investigator's observation of events that are to occur, in particular the exposure of subjects to a particular agent or the outcome of that exposure. This is in turn divided into:

- **Descriptive** (study of the distribution of cancers in the population, generates hypotheses).
- **Analytics** (study of the causal relationships of some environmental factors with cancers through case-control, cohort or cross-sectional studies; test hypotheses).

2. Experimental - verification of the hypotheses identified by the first two study modalities by assigning to the subjects a type of treatment by randomization. This type of research includes:

- animal model experiments
- therapeutic studies
- clinical observation
- public health actions.

Elements of descriptive epidemiology

Descriptive epidemiology focuses on identifying epidemiological processes, measuring and describing them. Its main role is to generate hypotheses, which will be tested later, using analytical studies.

To this end, descriptive studies record new cases of cancer, reconstruct the evolution of the epidemiological phenomenon and establish the criteria for the distribution of the disease in the community involved. This statistical information is obtained from national, regional or institutional cancer registries, allowing to find out the number of people affected, the time period studied and the characteristics of the population studied.

The cancer registry involves the accumulation and centralization of data (patient history, diagnosis, treatment, etc.) on various types of cancer.

The goals of the cancer *registry are:*

- knowing the incidence of cancer and the anatomical locations by sex, age groups and socio-economic environment;

- highlighting changes in the incidence and evolutionary trends of cancer in various locations;
- monitoring and evaluating the effectiveness of cancer control / prevention measures;
- setting public health priorities for primary, secondary and tertiary prevention programs;
- can provide source material for etiological studies.

The cancer registry uses the ICD-O (*International Classification of Disease for Oncology*) to encode elements of topography and morphology for each cancer. Moreover, this code can also provide information on the behavior of the tumor (bening, maling, in situ, borderline).

The health indicators used in descriptive epidemiology (*incidence* , *prevalence* and *mortality*) allow the assessment of the health status of the population.

Morbidity indicators: Incidence

The incidence measures the probability of developing the disease (cancer risk) and compares its rates between populations, being the best indicator of cancer frequency, very sensitive in the practice of diagnosis and/or detection.

Incidence is the number of new cases occurring in a population at risk of disease over a period of time (usually 1 year), and is usually expressed as the number of cases per 100,000 people. In children (cancers are very rare), the incidence is expressed as the number of cases per 1,000,000 people.

$$\text{Incidence} = \frac{\textbf{Number of new cancer cases} \text{ within a specified period of time}}{\text{Total population at the beginning of the time period}}$$

Morbidity indicators: Prevalence

This reflects the spread of a disease in a population. The prevalence increases with the incidence and duration of the disease in the community, and decreases with mortality and cure rates. Cancers with low mortality, and those in which current therapeutic methods allow a significant prolongation of survival, have a high prevalence, but which are associated with increased care costs.

*Prevalence is the estimate of the total number of people with cancer (new and pre-existing cases) who are alive at a given time (*point prevalence *) or after a defined period of time (*periodic prevalence*), and is expressed as the number of cases per 100,000 people.*

$$\text{Prevalence} = \frac{\textbf{Total number of cancer cases} \text{ in a specified time period}}{\text{The total population during that time period}}$$

Mortality rates

The population record service can provide data on mortality, based on death certificates completed by the doctor.

Mortality rates are expressed as the number of cancer deaths per 100,000 people per year.

$$\text{mortality} = \frac{\textbf{Total number of cancer} \text{ deaths in a population in a specified period of time}}{\text{The total population at that time}}$$

The increase in cancer mortality is dependent on demographic factors (increase in the elderly population), diagnosis (adequate facilities) and therapeutic (available oncological treatment).

Mortality can provide information on the prognosis of oncological sites or the effectiveness of various early detection and prevention strategies. In rapidly fatal locations, incidence and mortality have similar values.

Elements of molecular epidemiology in oncology

The notion of molecular epidemiology refers to the combination of molecular biology techniques with epidemiological research. Although this approach is not new in medicine, it has been applied in cardiology and the pathology of infectious diseases since the 1980s, and its use in oncology is relatively recent. Molecular epidemiology complements the classical one by introducing biomarkers (biochemical and molecular) to understand the mechanisms of carcinogenesis and the sequence of events that occur between exposure to a risk factor and the appearance of a tumor.

Unlike conventional epidemiology, where there is a direct correlation between exposure to a risk factor and the risk of developing / dying from cancer, molecular epidemiology seeks to identify various biomarkers that may influence this causality. These include *exposure markers* (eg the

presence of HPV in cervical cancer), *dose markers* (the amount of this risk factor present), *internal markers* (the presence of DNA alterations secondary to the activation of a carcinogen), *biological markers* (the presence of the p53 mutation as due to exposure to a carcinogen), *markers suggesting altered function/structure* (presence of chromosomal instability), *susceptibility markers* (presence of a genetic polymorphism that may influence carcinogen metabolism or elimination), *markers related to cancer subtype* (estrogen or progesterone receptors in cancer breast) and *prognostic markers* (polymorphism of genes involved in chemotherapeutic metabolism).

The aims of molecular epidemiology are:

- Understanding the mechanisms of carcinogenesis in various types of cancer.
- Defining tumor heterogeneity.
- Identifying populations at high risk for cancer.
- Prediction of treatment response and prognosis.
- Identification of biomarkers for early diagnosis and progression.
- Development of new therapeutic targets.

It is now established that oncological diseases are both genetic and epigenetic diseases. Another notion, that of **epigenetic epidemiology**, includes the study of the variability of epigenetic traits and the risk of disease in a studied population. By influencing genomic stability and gene expression, epigenetic changes can influence carcinogenesis both individually and in future generations. The identification of epigenetic markers in association with cancer, as well as their possible use as biomarkers is of increasing interest. Some epigenetic traits can serve as diagnostic and prognostic indicators.

Current trends in cancer in the world

The evolution of cancers in Europe

In Europe, there are differences in both incidence and general and organ-specific mortality. About 60% of cancers are in low- and middle-income countries, mainly because the reporting of cases in these regions is not strict enough. In 2012, there were an estimated 3,715 new cancers per 100,000 inhabitants in Europe (excluding non-melanic skin cancers) and 1,933 cancer deaths per 100,000 inhabitants.

The most common forms are: breast, colorectal, bronchopulmonary and prostate cancer. Bronchopulmonary cancer was the leading cause of cancer death, especially in males, followed by colorectal, breast and gastric cancer.

Cancer epidemiology in Moldova

Oncological structure of malignant tumors in the Republic of Moldova.

Table 2. Dynamics of the incidence of the most common malignant tumors in the Republic of Moldova

	a.2017			a.2018		
	Total cases 9882			Total cases 10021		
	location	Nr.	% _	location	Nr.	% _
I	Colorectal cancer	1234	34.7	Colorectal cancer	1338 ↑	37.7
II	Breast cancer	1118	60.6	Breast cancer	1125 ^	61.0
III	Skin cancer	1038	29.3	Skin cancer	980 ↓	27.6
IV	Lungs cancer	853	24.0	Lungs cancer	925 ^	26.0
V	Hemoblastosis	802	22.6	Hemoblastosis	615	17.3
VI	Prostate cancer	513	30.0	Prostate cancer	594 ^	34.8
VII	Thyroid cancer	406	11.4	Stomach cancer	445 ^	12.5
VIII	Stomach cancer	403	11.3	Oral cavity cancer	412 ^	11.6
IX	Oral cavity cancer	384	10.8	Uterine body cancer	373 ^	20.2
X	Uterine body cancer	346	18.8	Cervix uteri cancer	372 ^	20.2
XI	Bladder cancer	336	9.5	Bladder cancer	299	8.4
XII	Cervix uteri cancer	321	17.4	Kidney cancer	290 ^	8.2
XIII	Pancreas cancer	258	7.3	Liver cancer	280 ↑	7.9
XIV	Liver cancer	253	7.1	Pancreas cancer	275 ↑	7.7
XV	Kidney cancer	243	6.9	Thyroid cancer	252	7.1
XVI	Ovarian cancer	187	10.1	Ovarian cancer	214 ^	11.6

According to the table, the number of cases increased in 2018 (10021) compared to 2017 (9882), so by 139 more cases.

After localization, the first 5 places of the tumors return:

1. Colorectal cancer - 1338 cases;

2. Breast cancer - 1125 cases;
3. Skin cancer - 980 cases;
4. Bronchopulmonary cancer - 925 cases;
5. Hemoblastosis - 615 cases.

The incidence of major tumors in the world

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ETIOPATHOGENY OF CANCER. EXOGENOUS AND ENDOGENOUS FACTORS

What is cancer in the modern scientific conception? How does a healthy cell turn into a cancerous cell?

Tumors are a set of malignant diseases that occur as a result of cell proliferation. The processes of carcinogenesis are very varied, but have common features for most human cancers. The main common features refer to the multiplicity of factors involved and the existence of a long time between the first influence and the appearance of cancer. There are internal and external factors (the latter being decisive). The internal factors are represented by the genetic constitution of each individual who is more or less vulnerable and exposed to the disease. The discovery of oncogenes and anti-oncogenes (or tumor suppressor genes) explains personal sensitivity, for example for such a tumor as retinoblastoma. In this context, it becomes clear that out of a hundred heavy smokers, many will develop lung cancer: some at a young age, most at an advanced age, while some of them will live a long life and will not be affected by cancer.

First of all, as a result of the actions of internal and external factors, a transformation or „mutation" of a cell is determined, which acquires the possibility of becoming cancerous. This initial phenomenon is also called „initiation".

In order to change and multiply, in order to form a „clone" with cancer potential, the cell needs additional interventions. This multiplication, also called promotion, requires other factors. These two stages lead to the recognition of the factors that favor the first, being called initiators, and those that favor the second being called promoters. This can explain the phenomenon of malignant tumors, in most cases, not earlier than 40-50 years. Carcinogenesis has a long evolution, starting with the influence of carcinogens and the appearance of the first cancer cell. This cell and its offspring multiply excessively, but at first an asymptomatic occult phase, called preclinical, persists. When the tumor reaches the size of 1 cm or

the weight of one gram, which corresponds to the number of cells of 10x9 (1 billion), it becomes detectable. If the right treatment is performed, the patient will be healed, and if not, the result will be fatal - death (Fig. 1).

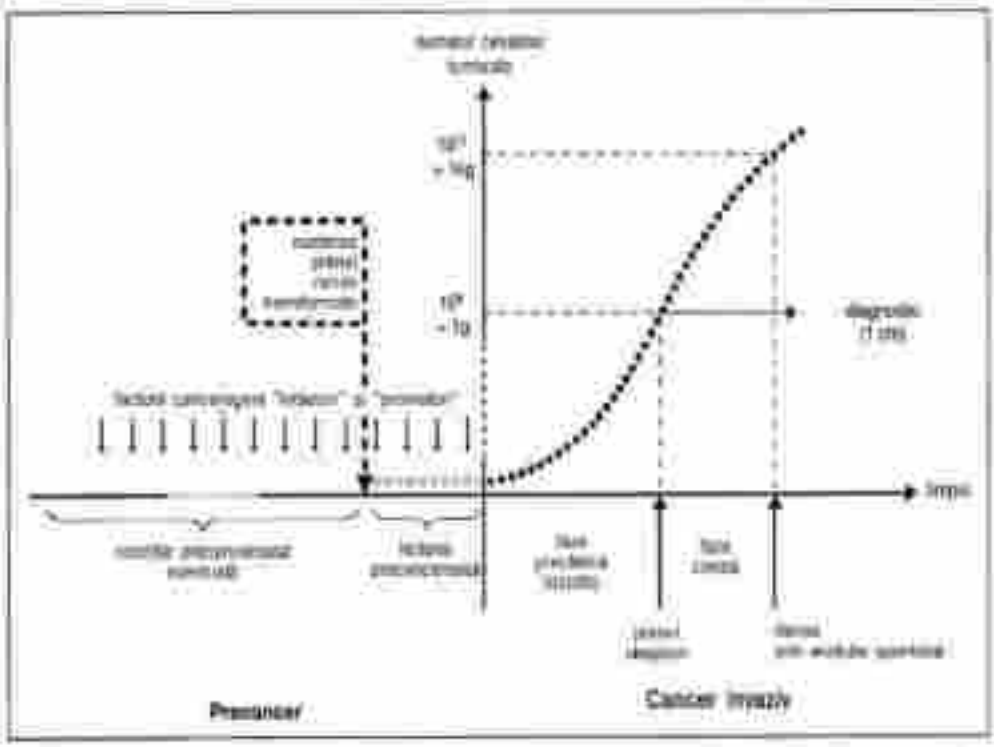

Fig.1. *Oncogenesis*

Carcinogenic factors (carcinogenic):

Internal factors :

1. hormonal:

a) hyperestrogenemia in breast cancer;
b) hyperandrogenemia in prostate cancer.

2. Immunological:

a) multiple myeloma (plasmacytoma);
b) macroglobulinemia, Waldenström's disease;
c) agamaglobulinemia X (Bruton's disease - exclusively in boys);
d) immunodeficiency with thymus, etc.;
e) acquired immunodeficiencies (the appearance of cancers after a transplant or in AIDS).

External factors :

1. chemicals (the number of carcinogens is greater than 20):
   a) of cultural origin: tobacco, betel, qat;
   b) of professional origin: benzene, arsenic, slate, vinyl chloride, wood dust, sawdust, tar, soot, chromium, nickel, aromatic amines, rubber industry;
   c) of food origin: nitrosamines, aflatoxins, smoked foods, animal fats;
   d) iatrogenic: anticancer drugs, estrogens (Bojan O., 1984).

2. physical - first of all, radiation is the cause of many cancers. Whatever the sources of radiation, they have enough energy to lead to DNA damage.

Slightly penetrating solar ultraviolet radiation is the cause of skin cancers: spino-cell carcinoma, basal cell carcinoma or melanoma. People with „fragile" skin (blondes and redness), who have only a small amount of protective melanic pigment, if exposed to sunlight, will get cancer more often than the rest of the population. Thus, the Australian population of British origin, which arrived on the continent in the sec. XVIII-XIX, was exposed to strong sunlight and was affected by a number of cancers.

Natural or artificial ionizing radiation, used in contemporary industry or for therapeutic purposes (radiodiagnostics, radiotherapy), has a high carcinogenic power. The first radiophysicists (W. Roentghen, 1895, Mari Sklodowska-Curie, 1898) and the first radiologists (Jean Bérgonié) paid an expensive tribute to the development of science.

More recently, the Chernobyl accident (1986) resulted in a significant number of cancers, especially thyroid cancer. The most radiosensitive are the rapidly renewing cells (hematopoietic line, epithelium). Iodine tropism for the thyroid gland remains very vulnerable in the presence of radioactive iodine. The child and the fetus are at high risk. Therefore, radiological investigation of pregnant women should be limited. The most radio-induced cancers are skin, breast, lung, thyroid, and leukemia (the result of a 1945 nuclear explosion in Japan).

The responsibility for electromagnetic waves in carcinogenesis is controversial. Recent studies suggest an increased risk of brain tumors due to the widespread use of mobile (cellular) phones, but in the end, this risk has not been confirmed.

3. infectious - animal studies began many years ago with Rous sarcoma in chickens, which has been shown to be linked to a virus. Confirmed human oncogenic viruses with molecular mechanisms in oncogenesis

were later identified. However, few cancers are virus-induced in humans.

DNA virus:

- HHV8 (human herpes virus) - in Kaposi's disease and AIDS (due to immunodeficiency);
- EBV (Epstein-Barr virus) - in Burkitt's lymphoma (in Africa), immunoblastic lymphoma (in all countries), nasopharyngeal cancer (in Southeast Asia, in North Africa);
- HBV (hepatitis B virus) - in hepatocellular carcinoma;
- HPV (human Papilloma virus of various types) - in anogenital cancer, cervical cancer, skin cancers).

Retroviruses:

- HTLV-1 (Human T-cell Leukemia virus) - in adult T-cell leukemias (in Africa, the Caribbean, South America). Recently, there have been growing claims that one of the causes of gastric cancer is Helicobacter pylori infection, which leads to gastroduodenal ulcer. The gastric one eventually maligns.

In North Africa (Egypt, Algeria) the highest incidence of bladder cancer is recorded, the main cause being closely related to the presence of a parasite - schistosome or bilhartziosis, after the name of the scientist Thomas Bilhartz, who discovered it.

Prophylactic measures to combat the above-mentioned infections have contributed to the obvious reduction of cervical cancer in civilized countries (sexual hygiene, condom use). Vaccination against the hepatitis B virus has sharply reduced the number of cases of hepatocellular cancer, and the eradication of Epstein-Barr virus has reduced the number of Burkitt's lymphomas in Africa and nasopharyngeal cancer in North Africa and South Asia. The fight against human immunodeficiency virus AIDS has also facilitated the reduction of Epstein-Barr virus and Kaposi's tumor (Grros L., 1970; Benycsh – Melnic M., 1974; Zeuthen I., Klein G., 1974; Crişan M., 1984).

4. Hereditary- some cancers rarely manifest as hereditary diseases (5–10%): this is the case with retinoblastoma, of which 40% are hereditary. Molecular biology has identified oncogenic and antioncogenic genes, transmitted by heredity, that play a favorable or unfavorable role in the origin of cancer. Retinoblastoma, mentioned above, is an eye tumor in young children, which is the result of the absence of the Rb anioncogen in one of the parents. The study of these genes is in its infancy.

These advances stay at the origin of oncogenetics, the aim of which is

to identify people at risk, justifying special surveillance or detection and in significant cases to give genetic advice to affected families. This is the case with the aggregation of breast, colon, uterine, ovarian, prostate and thyroid cancers.

Usually, hereditary cancers that do not exceed 5% of all cancers located in the breast, colorectal, ovarian, multiple endocrine neoplasms, etc. they are dependent on those genes. See tab. 1.

Table 1. Hereditary cancers

Diseases	Gene	The location of the tumor
Li-Fraumeni syndrome	p53	Breast, multiple locations
Hereditary breast cancer	BRCA-1	Breast, ovaries
Lynch syndrome	HNPCC	Colon, stomach
Neurofibromatosis type 1 (Recklinghauzen)	NF1	Nervous system, multiple locati-ons
Neurofibromatosis type 2	NF2	Nervous system
Adenomatous polyposis (Gardner syndrome)	Aft	Colon, rect
Hereditary melanoma	MTS1	Skin
Bouneville tuberous sclerosis	TSC 2	Nervous system, kidneys
Hereditary retinoblastoma	Rb1	Retina
Multiple endocrine neoplasms type 1	MEN 1	Pituitary, parathyroid, pancreas
Multiple endocrine neoplasms type 2	MEN 2	Thyroid (medullary), parathyroid, adrenal
Maladia Von Hipel-Lindau	HL	Kidneys, adrenal glands, nervous system
Wilms tumor	WT1	Kidney
Peutz-Iegers disease	STK-11	Colon, testicle
Basal cell neuromatosis (Gorlin syndrome)	PTC	Skin carcinoma

Conditions, precancerous diseases.

The term belongs to the great scientist A. Babeş with additions by the Frenchman Menetrié. Chronic inflammatory diseases of various organs, genetic and immunobiological precancerous syndromes refer to precancerous conditions. If left untreated, these diseases can progress to cancer. Example - cervical dysplasia, chronic atrophic gastritis etc.

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PRINCIPLES OF TUMOR BIOLOGY

The development of cancer is a multistage process characterized by the accumulation of a number of genetic mutations, called *oncogenesis*. Genetic alterations can take the form of mutations (changes in the DNA code sequence), deletions (loss of a DNA sequence), amplifications (multiple copies of the same DNA sequence), or epigenetic changes (differences in gene expression that are not attributed to intrinsic changes in the DNA sequence but of alterations that alter the ability of a gene to be transcribed).

1. The genetic basis of malignant transformation

The causes that lead to cancer are numerous and varied, including environmental factors (exogenous factors) and gene predisposition, hormones and age (endogenous factors). These factors determine or contribute to the transformation of normal cells into cancer cells by disrupting a wide range of physiological pathways. Regardless of the etiology, however, all cancers occur as a result of genetic and epigenetic events. Most of these events occur during the life of the individual, at the level of somatic cells. In the absence of repair, somatic or acquired mutations will be transmitted to daughter cells leading to the formation of a *clone.* Because they occur in somatic cells, such mutations cannot be passed on to offspring and are therefore not hereditary. Sometimes, certain mutations that predispose to cancer occur in the germ cells. Such mutations are passed from one generation to the next and result in the family aggregation of specific cancers.

Whether it occurs spontaneously in a single individual or occurs in several people in a family as a hereditary trait, cancer is considered a disease with a genetic mechanism, because the initiation and development of a tumor involves the cascade of multiple mutations in different genes which controls proliferation, DNA repair, the mitotic cycle, and cell death.

DNA contains the genetic information encoded to achieve the specific characteristics of an organism. The fundamental unit of hereditary information is **the gene.** A gene is a segment of DNA that determines a character (a gene - a protein - a character). There are about 100 to 210,000 genes in the genome. Gene expression refers to the **transcription** of a gene.

The 5-terminal end of any gene that contains the nucleotides involved in express regulation is called the **promoter**.

Most exogenous carcinogens are mutagenic, thus these agents have the ability to induce DNA mutations either by forming covalent bonds („adducts") of DNA or by causing chromosomal damage (eg double-strand breaks - DSB). Mutations fall into several categories: transitions, transverse, insertions, deletions, and chromosomal translocations. **Gene amplification** is also a mutation that causes the number of genes to increase from the 2 copies present in the diploid genome to hundreds of copies in cancer cells.

A change in the structure of a normal gene, called a mutation, produces a gene variant (allele) that is normal or altered (abnormal).

Cancer develops as a result of mutations in genes that control cell proliferation and death. These genes can be separated into at least two major categories: ***oncogenes*** and ***tumor growth suppressor genes (antioncogenes).***

It takes an average of six mutations for a normal cell to turn into a cancer cell. The average mutation rate is about $^{10-6}$ per gene and per cell. The probability that any of the ^{14} cells in a human body will undergo six successive mutations is approximately $10^{14} \times 10^{-36}$ or 10^{-22}. The appearance of cancer is explained by two mechanisms.

Some mutations stimulate cell proliferation, causing a large population of target cells for subsequent mutations.

Other mutations affect the stability of the entire genome, increasing the overall rate of mutations. Multiple cell gene mutations are needed to create malignancy.

Most cancers are *monoclonal* (a tumor is formed by the clonal expansion of a single cell precursor that has undergone mutations in key genes causing uncontrolled growth).

There are two major classes of mutated involved genes that contribute to carcinogenesis: oncogenes and tumor suppressor genes (GSTs).

I. Protooncogenes - genes whose functions become amplified in carcinogenesis.

Transforming a normal cell into a malignant one requires a series of mutations in genes called *oncogenes* that contribute to neoplasia when

their function is altered . Oncogenes are genes that play a key role in controlling cell proliferation and encoding growth factors and transcription factors. They promote the autonomic growth of cancer cells, and their normal cellular counterpart is represented by proto- ***oncogenes***. Normal cell genes are called protooncogenes, and their activated variants are ***cellular oncogenes*** (c- *onc*). Activation of these genes is the result of gainful mutations. These genes continuously stimulate growth, leading to uncontrolled proliferation and malignant transformation. Oncogenes have a dominant effect at the cellular level and consequently a single mutant (activated) allele is sufficient to modify the cellular phenotype. There are currently hundreds of human oncogenes involved as proto-oncogenes that have the potential to be converted to oncogenes.

Onogens are the „engine" of cancer. Dominant oncogenes encode proteins that are activated in tumors by mechanisms such as translocation, amplification, and point mutations.

In the normal cell, protooncogenes are the regulators of cell proliferation and differentiation; the activated (oncogenic) variant is characterized by the ability to promote cell growth in the absence of mitogenic signals. The product of the synthesis of oncogenes is called *oncoprotein* and resembles the normal product called protooncoprotein which is a normal regulatory element. The synthesis of oncoproteins in malignantly transformed cells is not dependent on growth factors or other external stimulatory signals.

A large number of protooncogenes have been identified in the last two decades. Protooncogenes play multiple roles, participating in cellular functions associated with cell growth and proliferation. Oncogene-encoded proteins can function as receptors for growth factors, growth factors, transduction signal molecules, transcription factors, and cell cycle components.

Proto-onogens normally function in a wide variety of biological processes. Depending on the cellular level at which the proteins encoded by them act, oncogenes can be classified into several categories:

- oncogenes encoding cell growth factors (eg PDGFRB);
- oncogenes encoding growth factor receptors (eg EGFR, RET);
- oncogenes encoding components of intracellular signaling pathways (eg RAS, ABL);

- oncogenes encoding nuclear proteins in particular transcription factors (eg MYC);
- oncogenes encoding proteins involved in cell cycle control (eg MDM2).

Being *dominant genes*, most mutations responsible for the activity of oncogenes occur in somatic cells, germline mutations being probably incompatible with embryonic development.

Activation of oncogenes in somatic cells can be achieved through several mechanisms:

- by point mutations (eg ras family genes *; ras protooncogene* encodes a G membrane protein responsible for cell *signal transduction ; ras* gene mutations are involved in 30% of cancers including melanomas, lung and pancreas);
- chromosomal translocations (over 40 such translocations with activating potential of oncogenes have been described, especially in lymphomas and leukemias);
- gene amplification, a phenomenon that results in the production of several copies of structurally normal oncogenes (eg *myc* and *erb oncogenes* ;
- viral insertion (insertion mutation) as in the case of oncogenic retroviruses eg HTLV1;
- triggering of transduction signals that are stimulated when decreasing factors bind to surface receptors, and these pathways contain proto-oncogne involved in the biological signal chain.

Some human oncogenes are represented by the RAS family. RAS proteins transduce the mitogenic signal and their activity is regulated by binding to guanosine triphosphate (GTP) or guanoside diphosphate (GDP). Thus, RAS activity reflects the balance between guanoside nucleotide factors (GEF) that activate RAS and guanoside triphosphate activating proteins that hydrolyze RTP bound to GTP to GDP. Onogenic RAS mutations affect terminal amino acids important for interaction with GAP. For example, the NF-1 gene is a GAP that loses its function due to mutations in neurofibromatosis. Activated RAS triggers three parallel pathways: the MAP kinase pathway (which activates transcriptional factors), the RAL/CDC42 pathway (which regulates membrane and decytoskeletal changes), and the PI3K pathway (which affects several cellular functions, including protein synthesis and apoptosis).

II. Tumor suppressor genes (antioncogenes) - genes whose functions are lost during carcinogenesis

Tumor suppressor genes (GSTs) inhibit cell proliferation. Mutant versions of GST in cancer cells have lost their activity. Both copies of the allele must be inactivated before the function of the tumor suppressor gene is lost, resulting in the absence of a normal protein. This means that two events or mutations must occur in the first and then in the second allele. Mutations with loss of function of these genes lead to uncontrolled cell proliferation and growth and inefficient apoptosis. Tumor growth suppressor genes are manifested as *recessive genes* at the cellular level, for the conversion of the phenotype it is necessary to lose or mutate both alleles (allelic inactivation). Cytogenetic studies have identified several mechanisms for inactivating the second copy of a suppressor gene in hereditary cancers:

- somatic recombination deletions - the first proof of the existence of this phenomenon in somatic cells;
- loss of a chromosome associated with duplication of the remaining chromosome;
- The loss of a functional copy of a tumor growth suppressor gene has been termed loss *of heterozygosity (* LOH). Loss of heterozygosity is the most common mechanism of inactivation of the second allele produced by the inheritance of a mutant tumor growth suppressor gene.

Tumor growth suppressor genes encode proteins with extremely diverse functions: membrane receptors (eg PTCH), cytoplasmic proteins (eg APC, NF1) or nuclear proteins (p53, Rb1, VHL, WT1, TM, BRCA1, etc.).

Tumor growth suppressor genes were classified by Vogelstein and Kinzler (1996) into two major categories: *gate-keeper genes and caretaker* geness.

Gate-keeper genes are genes that encode proteins directly involved in the control of cell growth (for example, inhibiting mitosis or promoting apoptosis). The function of these genes is critical for tumor suppression. Examples of *gate-keeper genes* are: APC, VHL, TP53, NF1 or PTEN. Germline mutations in all of these genes cause genetic diseases with an increased risk of developing cancer and have a dominant genetic transmission (see Li-Fraumeni syndrome).

Caretaker genes are genes that encode proteins involved in maintaining

genome stability and are now considered to be part of the DNA repair gene family. Between *the gate-keeper genes* and *caretaker* genes there is no precise delimitation. Thus, the BRCA1 and BRCA2 genes are *gate-keeper genes* by their activity but also by transcription control and *caretaker genes* by their intervention in the repair of double-stranded DNA ruptures.

Alterations in these genes increase the frequency of mutations throughout the genome, including proto-oncogenes and tumor suppressor genes, and cause genomic instability. Enzymes that promote protein degradation by proteosomes function as suppressor genes.

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ONCOLOGICAL DIAGNOSIS

Cancer is the result of a complex biological process by which a cell clone acquires the properties of continuous growth, gets out of control of homeostatic regulation mechanisms, becomes locally invasive and metastasizes.

Starting from a single cell, the malignant transformation goes through several stages, most of which do not show a clinical expression (latency period). Although most tumor growth is clinically inapparent, at some point it causes clinical signs and symptoms that suggest a diagnosis.

In the oncology clinic, the importance of the diagnosis has a particular dimension because any error or delay in the diagnosis has unfavorable repercussions for patients. Their lives depend on the precocity of the diagnosis and its correctness.

The diagnosis of cancer is conditioned both by the patient's behavior and by the doctor's degree of instruction. On the one hand, the patient should be aware that the presence of „alarm" symptoms (eg functional disorders, bleeding, lymphadenopathy) should not be ignored, and investigations useful for early diagnosis should be postponed, and the physician should have sufficient knowledge to suspect the existence of a malignant process and trigger diagnostic procedures.

For this reason, the prompt diagnosis of cancer is directly related to the level of education of patients and the level of professional training of doctors.

The doctor who consults a potential cancer patient is responsible for facilitating a prompt diagnosis so that the patient has the best chance of a cure.

Diagnosis of malignancy

Diagnosis is *the process by which the certainty of the presence of the disease is established* , basic element that allows the treatment and prognostic evaluation of patients.

The history of the disease, the physical examination, the formulation of hypotheses, the laboratory examinations, the imaging studies on locations, the anatomo-pathological diagnosis, the staging and the evaluation of the

prognostic factors represent the (theoretically consecutive) stages of the diagnostic process in oncology.

Principles of diagnosis in oncology

The diagnosis of cancer must meet the following essential conditions:

- precocity;
- certainty;
- complete form.

Early diagnosis of cancer

The concept of diagnostic „precocity" (although own and other diseases) is due to the apparently staged evolution of neoplasms, during which there is a localized phase, long enough to allow early diagnosis and treatment, potentially curative (radical surgical resection, associated or not other therapeutic methods - radio-, chemo-, hormone therapy, etc.).

The doctor can influence the patient's prognosis by establishing the diagnosis of neoplasia as soon as possible (if possible, in the preclinical period, or at least in an early stage of the disease, when the first symptoms appear), which offers the best chance of cure in the vast majority of solid tumors.

Ex: The chances of a stage I cervical cancer being cured are 80-90%, while in stage IVA (bladder and rectal extension) survival is only 10-15%.

Certainty of cancer diagnosis

Cancer-specific treatments (surgery, chemotherapy, radiation therapy) are aggressive and accompanied by many functional, aesthetic and psychological side effects. The administration of such therapeutic sequences to patients for whom there is no histological confirmation of the malignancy, and who in reality have another pathological entity, involves severe medical and legal risks and consequences. In contrast, in patients diagnosed with benign lesions, who are in fact cancers and have not undergone specific treatment, the disease will continue to develop into late stages.

Consequently, the diagnosis of cancer must be ***suggested*** by history (history, data on the onset and course of the disease)**,** by means of imaging exploration (radiographs, ultrasounds, computed tomography, magnetic resonance imaging, scintigraphy, etc.) and ***confirmed*** by histopathological examination. The definitive diagnosis of a malignant (respectively benign) tumor will therefore depend on the macro- and microscopic examination (and possibly immunohistochemistry, etc.) of a tissue specimen (tumor, adenopathy, metastasis).

Exceptions to this rule are some solid tumors with locations that are difficult to approach bioptically / surgically and / or in advanced stages, requiring rapid initiation of therapy. In these situations it is necessary to practice at least a *fine needle aspiration biopsy* (FNAB). If the cytological examination reveals cells with certain malignancies, corroborated with the suggestive elements provided by the clinical and paraclinical examination, antineoplastic treatment may be decided.

Complete formulation of the diagnosis

In oncology, it is not enough to establish with certainty the presence of the disease to make a correct therapeutic decision. Assessing the extent of the disease (staging) is a mandatory stage of diagnosis, and it is also necessary to specify the histological type and other factors with prognostic value: the status of regional and juxtaregional lymph nodes, intravascular invasion, the degree of deep invasion (malignant melanoma, gastrointestinal cancers, bladder, uterus, etc.), degree of tumor differentiation (G), tumor markers, etc.

Also, the identification of the patient's complications, pathological history and comorbidities is of great importance in the therapeutic decision.

Stages of cancer diagnosis

In the face of clinical suspicion of cancer, the subsequent stages of diagnosis are:

- supporting and confirming the diagnosis of neoplasia (imaging and pathological examinations, respectively);
- appreciation of the real extension (staging) and aggressiveness of the disease;
- evaluation of the patient's status and reactivity (functionality of different devices and systems);
- placing the case in a prognostic group;
- formulating a therapeutic strategy;
- establishing the principles of monitoring, the frequency of regular checks, diagnosing possible recurrences and returning to treatment.

Clinical diagnosis

A *symptom* is largely a sensation or a pathological event reported by the patient. A *sign* is a clinical feature that can be observed, measured, or demonstrated by another person.

There are no pathognomonic signs or symptoms, or at least particular to a particular neoplasm. „Oncological" signs and symptoms can result from two categories of cancer effects:

- *local*, of the formation itself (tumor, lymphadenopathy, metastasis)
- *general*, neoplastic disease - affects the whole body (systemic).

Symptoms and (suspicious) signs that a malignancy may initially manifest can also be classified as *direct* or *indirect*.

Local signs of suspicion

1. **The direct signs** are the expression of an abnormal tumor growth which may be the primary tumor, a regional lymphadenopathy or a metastasis. They are often the first to appear, but also the most suggestive; may be detected accidentally or in the context of other conditions (minor trauma, nonspecific pain).

The main direct signs are: a *lump* (tumor, induration, swelling); an *ulcer / wound* with no tendency to heal; a *skin lesion* that grows rapidly in size, changes color, or ulcerates.

Palpation of the primary tumor is a relatively rare diagnostic circumstance, except for advanced tumors or organs accessible for clinical examination: the breast, testicle, soft parts of the trunk or extremities, bone system, skin, and mucous membranes.

Regional tumor lymphadenopathy is the most common direct sign, found in 60-70% of cancer patients, being the main reason for presenting to the doctor. For example, malignant lymphomas, ENT cancers, malignant melanoma, or breast cancer are commonly diagnosed with peripheral lymphadenopathy.

An important element - which must be well known by doctors and patients - is ***the character pain***, in the initial stages, of the malignant lesion (primary tumor and lymphadenopathy, regardless of location), this being one of the main causes of delayed diagnosis, along with the fear of patients being diagnosed with cancer and the hope of (self) healing.

2. **Indirect signs** of cancer are more common than direct and functional.

The most common indirect signs are:

- *Abnormal secretions* with serous, hemorrhagic, purulent appearance in the nipple, vagina, rectum, nostrils, mouth.
- *Bleeding* is sometimes pathognomonic (postmenopausal metrorrhagia in uterine cancer).
- *Signs of compression* are various: mediastinal (upper cavity compression syndrome: edema „in the cape", jugular turgor, venous cutaneous ecstasy), intracranial hypertension (HIC).

- *Obstructive*: transit disorders, mechanical jaundice, dysphagia, dyspnea, hemorrhoidal syndromes, pollakiuria, nocturia.
- *Perforation*: acute abdomen.
- *Infectious* and neurological signs: neuralgia, paresis, sphincter disorders, sciatic pain associated with edema of a lower limb and urinary disorders.

Signs and symptoms of systemic suspicion

The main general effects noted by the cancer patient are: general malaise, asthenia, fatigue, prolonged fever/ low fever, profuse sweating, anorexia and weight loss. In malignant lymphomas, the so-called „ *type B symptoms* „ (fever, night sweats, weight loss, pruritus) are the expression of an aggressive malignant disease. Also, a wide variety of systemic signs and symptoms may be due to a paraneoplastic syndrome, depending on the organ / system affected by it.

Significant and / or rapid weight loss (frequently associated with anorexia - premature satiety / lack of appetite - especially in broncho-lung, esophageal, pancreatic cancers) is present in about 2/3 of cancer patients at various stages of the disease, and, although it usually occurs late, in many cases it is the first symptom that causes the presentation to the doctor. An involuntary loss of more than 5% of initial weight within 6 months is also a prognostic indicator of cancer progression.

Of these, the *American Cancer Society* has identified 7 signs / symptoms called „alarm" that (although not characteristic of a particular neoplasm, nor do they necessarily appear in the early stages of its development) should raise the suspicion of the onset / progression of cancer (especially if they are progressive or repetitive) and trigger symptom-based diagnostic investigations (*eg* bone pain in breast cancer will indicate scintigraphy).

9.1. The 7 „Alarm" Signs and Symptoms of all Cancer

1. palpable nodules or indurations in the soft parts;
2. wounds that do not heal, swellings that do not go away;
3. changes in the appearance of a pre-existing skin lesion (nevus pigmentation, etc.);
4. changes in intestinal or urinary transit;
5. non-physiological blood loss (bleeding);
6. progressive / permanent swallowing / eating disorders (dysphagia);
7. persistence of dysphonia or cough, change in the character of the cough in a smoker

The physical examination must be performed completely, systematically and methodically. A thorough history is required; regardless of the patient's allegations, all devices and systems will be evaluated, including skin and mucous membranes, mental and neurological status, etc. Initially, the thermal curve, blood pressure, diuresis, intestinal transit, weight curve, height, weight, body surface (for the correct calculation of the cytostatic dose) are recorded, and the performance status (general condition of the patient) assessed on either scale will be specified. Karnofsky, or ECOG / WHO (Table 1).

Table 1. Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status Scale Conversion

ECOG/WHO		Karnofsky PS	
0	Fully active, able to carry on all pre- disease performance without restriction	**100**	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	**80**	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	**60**	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	**40**	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated. Death not imminent
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	**20**	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	**0**	Dead

General physical examination

It must be executed completely, systematically and methodically.

Initially, height, weight, body surface area are recorded (for calculating the dose of chemotherapy). At the beginning of the examination, the weighted *status* (general condition of the patient) assessed either on the Karnofsky scale or on the ECOG / WHO / Zubrod scale (10) is specified .

Local examination

For each oncological approach, the local examination will focus on the primary lesions and will follow certain particular rules of execution, respecting the classic stages: inspection, palpation, percussion and (rarely) auscultation. The local examination (of the tumor lesion) will follow the achievement of the condition of a therapeutic "target", measurable (appreciation of the two maximum diameters), which will be followed in order to evaluate the response to the treatment.

After the clinical examination, a clinical diagnosis (one or more) of *assumption is made* that will guide further explorations.

Usual paraclinical examinations are common to all locations; is required:

- thermal curve, diuresis curve, weight curve, blood pressure, intestinal transit.

The clinical examination is completed by formulating one (or more) clinical diagnoses *of assumption* (differential diagnosis) that have the role of guiding subsequent explorations.

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PRINCIPLES OF ONCOLOGICAL SURGERY

Historically, surgery is the oldest treatment and, until relatively recently, the only one with a chance of curing cancer patients.

The first excision of a tumor is mentioned in the Edwin Smith Papyrus (circa 1600 BC, but is believed to be based on a mention from 3000 BC). Prior to the introduction of asepsis and anesthesia, surgery was reserved for the treatment of abscesses and trauma. The few interventions performed on tumors were generally amputated. More modern ways of surgery have been described since the 19th century. For example, in 1809 a very large ovarian tumor was successfully excised, and in 1890 William Halsted developed radical mastectomy, which became the first commonly used surgical procedure in breast cancer.

In the last decades of the twentieth century, technical advances and the deepening of tumor biology have rapidly changed the surgical therapy of cancer. The role of surgery continues to evolve as cancer management is influenced by the explosive growth of knowledge in genetics, molecular biology and tumor immunology.

Surgical treatment continues to provide the only hope of cure for most patients with malignant solid tumors. Surgery can also provide optimal palliation in patients with advanced malignancy. It is estimated that more than 90% of cancer patients have undergone or will undergo surgery to diagnose, treat, or manage complications of the disease. In light of these data, surgery has four roles in the management of cancer patients:

- ✓ *prophylactic*: treatment of lesions with high potential for malignant transformation;
- ✓ *diagnosis*: establishing a definite diagnosis of the disease and histological type;
- ✓ *staging*: determining the actual extent of the disease;
- ✓ *therapeutic*:
  - with the intention of oncological (curative) radicalism, in localized disease or with loco-regional extension, tumor recurrences or oligometastases;
  - cytoreductive purposes, in advanced forms;
  - for palliative purposes, to combat serious symptoms that endanger the lives of patients, aimed at improving the quality of life;

- with intent to control (second look) or therapeutic screening;
- for the purpose of reconstruction of anatomical defects after curative therapy.

Surgical treatment has only one absolute contraindication: evolving neoplasms, in which therapeutic methods capable of reducing the acute phase of the malignant disease must be applied, and the surgery will be performed later.

The prophylactic role of surgery

Surgery has a well-defined role in preventing cancer in selected patients. Thus, in a number of acquired or inherited conditions, surgery can prevent cancer and the surgeon must be educated in the spirit of recognizing lesions with an increased risk of progression to malignancy. Although a relatively small number of solid tumors have a definite and relevant genetic component, the last decade has significantly changed the clinical approach and current indications for prophylactic surgery, which are based on genetic testing, family investigation and patient desire. Prophylactic surgery is discussed on a case-by-case basis, weighing the risks and benefits for each patient. In order to take into account the prophylactic excision of an organ, there are a number of conditions that must be met:

- the genetic mutation that can cause the neoplasm must have a high penetration;
- the method by which individuals at risk are identified must have high sensitivity and specificity;
- there must be a method to check the absence of the disease at pre- and post-operative time
- the mortality associated with the surgery should be relatively low;
- the function of the removed organ must be replaceable.

The diagnostic role of surgery

The diagnosis of cancer cannot be made without histological confirmation of malignancy by a biopsy and the biopsy should be repeated in case of uncertain diagnosis. In this sense, the diagnostic role of surgery is major and consists in obtaining tumor tissue for histopathological examination, the only one that provides the diagnostic certainty of malignancy.

Diagnostic surgical techniques

There are currently four commonly used techniques for obtaining suspicious tissue for histopathological examination:

Fine needle aspiration biopsy (FNAB)

Fine needle aspiration is the simplest diagnostic method that involves aspirating tissue fragments through a needle guided into the area of suspicion of the disease. This procedure does not always require the intervention of a surgeon or local anesthesia, involving the aspiration of cells and tissue fragments by means of a needle with a fine lumen (caliber from 22 to 25G), possibly guided imagistically in the suspicious area. This technique can be useful in puncturing a thyroid, breast, lung, soft tissue tumor, or lymph node.

The cytological examination has a diagnostic value if its result is positive, but does not exclude the presence of malignancy in case of a negative result.

Core-needle biopsy (CNB)

It is the technique by which a fragment of tumor tissue is extracted using a special needle with a larger lumen (14-16G), equipped with a core-cutting device, eg Bioptry®, Vim-Silverman®, TruCut®, High Speed Drill® which allows the evaluation of tumor histoarchitecture, being sufficient for the histopathological diagnosis of most solid tumors. The puncture can be performed percutaneously (by palpation of a tumor mass / lymphadenopathy, or by imaging guidance), or endoscopically (at the level of the cavities). This tissue sampling technique is also cost-effective and can usually only be performed under local anesthesia.

Core biopsy can be used to diagnose suspicious tumors of the breast, prostate, uterus, ENT, liver, bone and soft tissue, bladder, peritoneal cavity. It allows obtaining a complete histological diagnosis (histological type, degree of differentiation, immunohistochemical and molecular examinations, etc.), as well as differential diagnosis, but also therapeutic planning (neoadjuvant therapy, or surgical resection with / without adjuvant therapy). For large soft tissue tumors and bone lesions, CNB will be the first method considered for diagnosis. Bleeding is the most common complication, and the procedure is not recommended for patients with severe vascularized tumors, coagulopathies, and cavities and the CNS.

Incisional biopsy

It involves the surgical removal of a fragment of a large tumor for purely diagnostic purposes, generally using local anesthesia; it is usually performed when the aspiration puncture or core biopsy is non-diagnostic or technically unfeasible.

In practice, it is most commonly used in the extemporaneous examination, in order to determine the extent of surgical resection (depending on the benign / malignant nature, or even the histology of the tumor).

Excision biopsy

It involves the complete removal of all suspicious tissue so that the edges of the resection are located in healthy tissue (it is equivalent to radical surgical resection, with curative visa, as a therapeutic procedure for small tumors). It is preferable to the incisional one, when possible, being the optimal method for the definitive diagnosis, out of the 4 described.

The role of staging surgery (pre-therapeutic assessment)

The precise definition of the real extent of the disease is the second mandatory step, after the diagnosis of malignancy.

Staging is a classification of the anatomical extent of a cancer in an individual, while grouping patients into categories according to this. Staging is essential for treatment and requires a thorough knowledge of both anatomy and tumor imaging or biology.

Staging surgical techniques

The surgical act plays an important role in the staging of neoplastic disease:

Lymphadenectomy

Excision of loco-regional ganglia

It is routinely performed in cancers of the breast, colon, testis, bladder, with primarily prognostic intent. The presence and extent of lymph node invasion is the most important risk factor for the development of metastatic disease in many cancers. For example, the status of axillary lymph nodes in breast cancer is the most important prognostic factor (along with the stage of the primary tumor) in premenopausal women.

Sentinel node evaluation

Sentinel node biopsy (SLNB) is currently used in the staging of breast cancer and malignant melanoma due to lower morbidity, and is being studied in other cancers, including gastric and colon cancer.

The last decade has seen a trend towards the use of minimally invasive tumor staging techniques. First, the sentinel lymph node (or nodes) must be located. To do so, a surgeon injects a radioactive substance, a blue dye, or both near the tumor. The surgeon then uses a device to detect lymph nodes that contain the radioactive substance or looks for lymph nodes that

are stained with the blue dye. Once the sentinel lymph node is located, the surgeon removes the node. The sentinel node is then checked for the presence of cancer cells by a pathologist. If cancer is found, it may remove additional lymph nodes, either during the same biopsy procedure or during a follow-up surgical procedure. SLNB is usually done at the same time the primary tumor is removed. In some cases the procedure can also be done before or even after removal of the tumor.

Laparoscopy

Laparoscopic staging of cancer patients has become a current routine practice in intra-abdominal cancers (liver, pancreas, gastric). Biopsies of solid organs, lymph nodes and lesions suggestive of malignancy may be obtained.

Thoracoscopy - this method allows a direct inspection of the pleural cavity, respectively visceral and parietal pleura, lung surface, the degree of damage to the intrathoracic lymph nodes and tumor invasion in the organs of the mediastinum and other anatomical structures. Thoracoscopy is completed by taking the biopsy material from the most suspicious place or places.

Mediastinoscopy - is a minimally invasive surgical method of reference in the exploration of the middle and upper mediastinum. For diagnostic purposes, it is used for biopsy of the mediastinal lymph nodes and in the staging of bronchopulmonary cancer (very important for establishing the optimal therapeutic course).

In recent years, robotic surgery has been used to increase the use of laparoscopic procedures in a variety of cancers.

The therapeutic role of surgery

The main goal of cancer surgery is to completely remove the tumor or cancerous tissue from a specific area of the body. Surgery is more useful if the disease is in an early stage, if it is localized and has not spread to other parts of the body. The operation can sometimes be done to treat a cancer that has spread from the original site (called the primary tumor) to other regions. The new tumor is called a metastasis or secondary tumor.

The surgeon will also remove a small amount of normal tissue around the cancer (called the surgical margin) - to make sure there are no cancer cells left. If the cancer cells cannot be completely removed, they can cause the cancer to recur. The amount of tissue normally removed depends on the type and location of the tumor. A microscope or other instruments are often used to ensure the removal of all affected tissue. Depending on the

type of cancer, the surgeon may also remove the lymph nodes near the tumor. Lymph node removal surgery is called lymph node dissection. The lymph nodes are then sent to the laboratory for examination under a microscope to see if they have cancer cells.

In the case of breast cancer surgery, for example, the doctor may remove the cancer by removing the entire breast (mastectomy) or removing only the portion of the breast that contains the cancer and some of the surrounding tissue (lumpectomy). In the case of lung cancer surgery, the doctor may remove part of the lung (lobectomy) or the entire lung (pneumonectomy) in an attempt to make sure that all the cancer has been removed.

Cytoreductive surgery

Sometimes the entire cancer may not be removed, either because the tumor is too large, or because the cancer is located near organs that may be damaged, or because the cancer is too small to be seen. Also, sometimes the patient's health does not allow surgery - it can be too risky.

In some cases, when the entire tumor cannot be removed, the operation is done to remove as much of the cancerous tissue as possible (primary debulking surgery). Surgery to reduce the number of cancer cells in the body is called cytoreductive surgery. Cytoreductive surgery can make chemotherapy and radiation more effective.

Palliative cancer surgery

Palliative surgery is a surgical procedure used to relieve symptoms and improve quality of life. Such an operation can be performed if the tumor cannot be removed, but it can remove certain blockages to relieve symptoms. It can also help control pain by eliminating cancer that affects the organ or nerve. It can significantly improve the quality of life for people with advanced cancer or the spread of the disease. It can sometimes reduce bleeding - some cancers cause bleeding, such as in areas with many blood vessels, such as the uterus, or cancers of the delicate organs. Bleeding can also be a side effect of some drugs used to treat cancer.

Reconstructive oncological surgery

Reconstructive or plastic surgery can be used to repair tissue that has been damaged by cancer or cancer treatments, including surgery to remove a tumor. Various techniques can be used to repair or rebuild body structures - grafts, implants and prostheses. For example, after a breast removal (mastectomy), breast reconstruction may be possible.

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PRINCIPLES AND INDICATIONS OF RADIOTHERAPY

Radiotherapy (RT) is a discipline that specializes in the use of ionizing radiation for therapeutic purposes, primarily in cancer patients, which aims to ensure loco-regional tumor control.

Although RT may be used as a unique therapeutic method in certain circumstances, it is most commonly part of the multidisciplinary treatment of cancer patients in various sequences associated with surgery and / or chemotherapy.

Historic

The first mention of the use of radiation for therapeutic purposes dates back to 1896, almost immediately after the discovery of X-rays.

In 1895, Wilhelm Röntgen (1845-1923) announced the discovery of a new type of radiation, which would have allowed „photographing the invisible." These (later called X-rays or X-rays) were the first radiation applied in clinical practice (first in diagnosis and then in therapy). Thus, just a few months after describing X-rays (1896), Emil Grubbe proposed their use in the treatment of cancer and irradiated a patient with recurrent breast cancer. Radiation therapy was thus the second method of treating malignant tumors after surgery. In its first decades of development, the results were modest and marked by numerous severe side effects, especially skin. For more than a century, however, RT has continued to play a significant role in the treatment of cancers, benefiting from considerable technical advances.

The improvement of RT results and the reduction of its side effects occurred gradually, after the discovery of the Coolidge tube in 1920 and especially after the appearance of radiotherapy installations with high intensity radiation (cobalt therapy devices, linear accelerators) after 1950, and through the subsequent rapid advances of irradiation and accumulation of data on fractionation and dose calculation in target tumor volumes.

Types of radiotherapy

Numerous types of ionizing radiation are used in the treatment of

benign and malignant tumors. In clinical practice, external irradiation with photons or electrons is the most common form of radiation therapy.

A. External radiotherapy (TEN, teletherapy)

Represents the irradiation of a tissue with a beam of radiation emitted by a source at a distance from it (outside the patient), administered as:

- contact and surface radiotherapy - low energy X-rays (40-50, respectively 50-150 kilo-electron volts, keV), produced by Chaoul type devices;
- orthovoltaic radiotherapy (conventional) - medium energy X-rays (150-500keV), produced by classic X-ray machines;
- megavoltage radiotherapy:
  1. telegammatherapy (60Co, 137Cs) - high energy γ radiation (1.17-1.20 megaelectron-volts, MeV);
  2. linear accelerator (LINAC) - X radiation (4-40 MeV); electrons (6-30MeV);
  3. cyclotron - corpuscular radiation (protons, deuterons, helium nuclei, etc.).

B. Brachytherapy

Brachytherapy (gr. Brachys, short distance) is a form of radiation therapy in which irradiation sources are placed inside or in the immediate vicinity of the tumor. Depending on the placement of the sources, we distinguish three types of brachytherapy:

- *endocavitary / endoluminal*: the sources are located in different cavities or lumens of the body (eg vagina, uterus, trachea, esophagus), through specially designed devices called applicators;
- *interstitial*: the sources (most commonly Iridium-192, 192Ir) are rigid needles or flexible wires implanted directly in the tumor tissue (eg prostate, breast, sarcomas, tumors of the oral cavity) arranged according to various systems (eg Paris [more advantageous in terms of dose distribution], Manchester);
- *contact or surface*: the sources (mounted in a mold) are applied directly to the lesion (eg skin neoplasms).

C. Metabolic radiotherapy (systemic isotopic radiotherapy)

It uses radioactive isotopes, administered intravenously or by oral ingestion, to treat tumors that have a selective binding affinity. The subsequent disintegration of these isotopes (and the release of radiation) determine the expected clinical therapeutic effects.

Aims and results of radiotherapy

A. Therapeutic indication and intent

- Curative - to maximize the chance of tumor control, without causing unacceptable side effects (a certain degree of toxicity, although undesirable, can still be assumed).

RT is frequently used with curative intent for localized malignancies; the decision to use either surgery or RT, or both, involves factors that depend on the tumor (eg resectable without a serious compromise of organ function?) and the patient (eg good candidate for surgery?). RT can also help to cure patients when used as an adjunct, when the risk of recurrence after curative surgery (radical or conservative) is increased (large tumors with lymph node invasion).

- Palliative - in the absence of hope for long-term healing or survival, treatment will focus on combating symptoms or independent conditions that may affect the patient's quality of life or self-care (eg painful and / or fractured bone metastases). No major side effects are accepted in palliative care.

Sometimes, in the palliation of solid tumors, high doses of irradiation (75-80% of the curative ones) are needed to alleviate the symptoms (eg cervical hemorrhages, lymphomas, multiple myeloma) or to obtain the control of the tumor / cytoreduction and a longer survival, but the latter are not the main purpose of therapy.

B. The place of radiotherapy in the multimodal treatment of cancer

Radiotherapy alone

The most common indications for RT as a single treatment (in certain clinical situations and stages of the disease) are: incipient cancers of the ENT sphere, skin cancers (except for malignant melanoma).

Preoperative radiotherapy (neoadjuvant)

The theoretical advantages of preoperative RT are:

- sterilization of tumor cells from the periphery of the tumor, the most likely to be dislocated / seeded locally and / or disseminated remotely during surgery.
- reduction of the volume of some voluminous tumors, in order to allow an initially impossible radical resection, or a more conservative resection, with the preservation of the organ function.

The disadvantages of preoperative RT are:

- the modification of the real extension of the tumor from anatomo-pathological aspect and the more difficult assessment of the prognostic factors, because the patient is irradiated before a possible staging at the time of the surgical exploration.
- increased risk of postoperative complications: delayed wound healing, fibrosis, post-radicular lymphorgia (however, it has been shown that a preoperative dose of 40-45Gy does not significantly prevent surgery, although it may involve delayed healing); if the time interval between RT and surgery exceeds 2 months, the vascular changes (post-radical fibrosis) are permanent.

Postoperative radiotherapy (adjuvant)

The theoretical advantages of postoperative RT are:

- more precise indication, depending on the data obtained from surgical and morphopathological examination (excludes a group of patients who would not benefit due to the absence of radiosensitivity of the tumor, or even the indication of postoperative RT itself);
- irradiated tumor volume better defined by the surgical description and sometimes by some intraoperative landmarks (metal clips);
- can be administered after wound healing.

The disadvantages of postoperative RT are:

- the absence of the effect on the insemination of the malignant cells during the surgical gesture;
- altered tumor vascularization and increased risk of radioresistance;
- increased risk of complications after pelvic and abdominal radiotherapy (sclerotic scarring disorders with blockage of venous and lymphatic circulation; transit disorders / intestinal obstruction on the bridle).

Intraoperative radiotherapy

Intraoperative radiotherapy consists of irradiating the tumor bed immediately after resection of the tumor, during surgery. Requires special equipment - mobile linear accelerator in case of electron irradiation or mobile low energy X-ray source. It is an option for irradiating the tumor bed in conservatively operated breast cancer.

Radio-chemotherapy

The combination of chemo-radiotherapy in solid tumors can be:

- sequential (increases both local and systemic control): breast cancer, pediatric tumors, lymphomas, etc.;
- concomitant (increases tumor radiosensitivity): advanced loco-regional cancers of the ENT sphere, cervical cancer, rectal, anal, bladder, bronchopulmonary cancer, etc.

C. Side effects of radiation therapy

Table 1. Acute side effects of radiotherapy and their treatment

Normal tissue	Acute effects	Signs and symptoms	Tratament
Skin	Rash	Rash	talc
	Desquamation	prurit	topical steroids
	dry / wet	pain	topical antibiotics (superinfections)
	Epilation		
Oropharyngeal-mucosa	Mucositis	odynophagy, dysphagia	oral hygiene
	Dysgeusia	hypersecretion	xylocaine gel, analgesics
		halitosis (superinfections)	antibiotics
Esophagus	Oesophagitis	dysphagia	xylocaine, analgesics
		odynophagy	antibiotics
Lung	Pneumonia	cough	observation
		dyspnoea	oxygen therapy and corticosteroids
		pleural pain	in severe cases
Intestine	Gastroenteritis	nausea, vomiting	antiemetics, diet
		cramps, diarrhea	antidiarrheals, diet
Urine Bladder	Cistitis	dysuria, pollakiuria	local analgesic
Rect	Proctitis	tenesmus	anticonstipaciens
			analgesics
Bone marrow	(Pan) cytopenia	asthenia	transfusions
	Hemorrhage	reducing time	and volume
	febrile irradiation	neutropenia	

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CANCER IMMUNOLOGY AND IMMUNOTHERAPY

I. General principles of tumor immunology

The human body has many defense mechanisms capable of limiting the appearance and growth of tumor cells.

The immune system (SI) is a complex anatomical and functional network of cells and tissues that operates synchronously to prevent / neutralize biological (non-self) aggressions on the body (self).

T cells play a central role in adaptive immunity as effectors and as regulators. T cell activation includes T cell receptor dimerization (TCR), CD4 or CD8 accessory molecules, and signal modulation by CD3.

T cells recognize the antigen via the T cell receptor (TCR) as the main mechanism of T cell activation. T cells are co-regulated by multiple receptors with either co-stimulatory or co-inhibitory role. Co-inhibitory receptors are also called immune checkpoints.

Helper T cells - express CD4 molecules on the cell surface (LyTh CD4 +)

LyTh responds to antigenic stimulation by releasing various cytokines (eg IL-2) that are essential for CTL activation, macrophage induction (Th1), promotion of humoral responses (Th2), and alteration of B cell subset supporting CTL activation and antibody production. Natural and induced regulatory (Treg) T cells (nTreg and iTreg) represent a heterogeneous Lyt population, „educated" in the thymus, and highly specialized for suppressive function. Activated T cells (CTL) kill tumor cells by apoctosis through exocytosis granules and Fas ligand-mediated mechanisms.

Antibody-producing B (LyB) cells are involved in the adaptive tumor response and also serve as antigen presenting cells (APCs). They originate in the marrow; When stimulated by antigen (either directly or indirectly), LyBs are specifically activated - through interactions with LyTh - and differentiate into Ig (Ac) - forming plasma cells, which can recognize native Ags. Dendritic cells (DC, Langerhans cells) are the most effective antigen presenting cells (APC) of the immune system, involved in the delicate balance of T cells in tumor immunity. Several subpopulations of lymphoid and myeloid cells act as immune suppressors.

The ability of cancer to „escape" the immune response is aided by the fact that most tumor antigens are self proteins that prevent the generation

of an immune response via tolerance mechanisms such as the development of regulatory T cells. Cancer escapes the immune system not only through the presence of suppressor factors secreted or expressed by the tumor but also through the tumor's ability to modulate antigen expression and develop mechanisms of resistance to immune effectors.

II. Cancer immunology and immunotherapy

Immunotherapy involves the use of biological agents that act on the body's natural defense mechanisms against tumors, and / or substances involved in the differentiation, proliferation and activity of immune cells.

There are two general forms of immunotherapy: „active" by stimulating in vivo an intrinsic immune response against tumor either nonspecific with cytokines or specific with monoclonal antibodies or tumor vaccines and „passive" or „adoptive" immunotherapy involving antibodies outside the body (ex vivo) then administration to patients.

The two arms of the immune system are: the inherited immune system and the adaptive immune system. One of the functions of the innate immune system is to detect the presence of tumor pathogens and antigens and present them to the adaptive immune system.

Both the adaptive arm and the innate arm of the immune system offer extensive opportunities for therapeutic interventions. However, most studies focus on interventions involving the T-cell-mediated immune response, cell therapies, tumor vaccines, immune checkpoint modulators, bi-specific „connector" antibodies (also known as bi-specific T cell engagers), dual-specific antibodies, small molecules, oncolytic viruses and immune adjuvants. The first approved methods of using T cells to induce an antitumor response were cell therapies (sipuleucel T), immune checkpoint modulators (ipilimumab, pembrolizumab, and nivolumab), bi-specific „connector" antibodies (blinatumomab), and most recent modality represented by oncolytic viruses (laherparepvec talimogens).

The immune response can be activated to mediate tumor destruction by one or more mechanisms. This includes increasing immune effector and modifying tumor cells to increase susceptibility to immune effector. Recent advances in understanding the essential aspects of cellular immunology and tumor-host immune interactions have led to the development of immune therapies capable of mediating the elimination of metastatic cancer cells in humans. These include both non-specific approaches, such as those

involving direct immunization of patients with a variety of immunogens, and ways of adoptive transfer of activated effector cells.

Passive (adoptive) immunotherapy

„Passive" or „adoptive" immunotherapy involves the preparation of antibodies and cells outside the body (ex vivo) followed by administration to the patient. It mainly targets the tumor, but can also use the immune system.

Antitumor monoclonal antibodies

Monoclonal antibodies that bind to surface cell antigens can cause the destruction of tumor cells by:

- antibody-dependent cellular cytotoxicity (ADCC);
- complement-dependent cytotoxicity (CDC);
- alteration of transduction signals (transmission) in tumor cells;
- removal of critical antigens from the cell surface.

These antibodies can also be used as vectors for radioisotopes, toxins or cytostatics with minimal systemic toxicity. Three main classes of monoclonal antibodies are currently used in clinical practice: unconjugated, conjugated, and radioimmunoconjugated.

Unconjugated monoclonal antibodies

Unconjugated monoclonal antibodies (AcMo) (against receptors or their ligands) directly affect signaling pathways by inhibiting ligand-receptor interactions. They can indirectly stimulate host defense mechanisms, such as antibody-mediated cellular cytotoxicity (ADCC) or complement-mediated lysis, thus having antitumor activity. The major obstacles to AcMo action remain:

- heterogeneous tumor antigenicity induced by intratumoral genetic heterogeneity;
- the reduced fraction of injected AcMo that binds to the tumor;
- inability of AcMo to penetrate bulky solid tumor masses;
- binding of AcMo to precirculating antigens (cross-linking of AcMo).

Among the antigen-specific monoclonal antibodies we mention: Rituximab (MabThera®, Obinutuzumab (Arzerra), Alemtuzumab (MabCampath®), Trastuzumab, Pertuzumab (Omnitarg®), Panitumumab (Vectibix®) and Cetuximab (Erbitux®).

Conjugated and radioimmunoconjugated monoclonal antibodies

Conjugated agents result from the binding of an antibody or protein to a toxin or radioisotope. This class of agents confers specificity by locating cytotoxicity directly on the cellular target of interest. Genetic engineering has made it possible to obtain „fusion genes" that associate the cytotoxic portion of bacterial genes (eg diphtheria toxin or exotoxin of Pseudomonas species) or antitumor antibiotics with target ligands (eg cytokines IL-2, TGF-α), these chimeric proteins are located specifically at the level of cells that express high affinity receptors. Among the conjugal monoclonal antibodies may be listed: Gemtuzumab ozogamicin (Mylotarg®), Brentuximab vedotin, TDM-1 (Ado-trastuzumab emtasin, Kadcyl Inotuzumab ozogamicin), 90Y-Ibritumomab tiuxetan (Zevalin-T®),

Bi-specific T cell engagers (BiTEs)

A bispecific monoclonal antibody is an artificial protein composed of fragments of two different monoclonal antibodies and, consequently, can bind to two different types of antigens. Bi-specific antibodies are able to connect T lymphocytes and tumor cells, inducing T lymphocyte activation to exert antitumor cytotoxic activity by producing perforins and granzime in an antigen-independent manner (without the need to activate classical costimulation pathways). Blinatumomab (Blincyto) is a bispecific humanized antibody directed against CD19 receptors on B cells and CD3 receptors on T cells, stimulating the recognition of B cell precursors in acute lymphoblastic leukemia (ALL) by T cells.

Active immunotherapy

„Active" immunotherapy uses means to stimulate (in vivo) the intrinsic immune response either nonspecifically with cytokines or specifically by antibodies or vaccines. This type of therapy acts directly on the immune system. Cytokines Interleukin-2 (IL-2) and Aldesleukin (IL-2 recombinant) may cause tumor destruction by one or more general mechanisms or may act indirectly by stimulating cellular anti-tumor activity or humoral effector mechanisms.

Interferons

Interferons (IFNs) are glycoproteins originally described in 1957 by Isaacs and Lindenmann as a product of virally infected cells that protect

against other viral infections. The main antitumor effect of IFN may be antiproliferative. Types of interferons: IFN-α, IFN-β, IFN-γ.

Autologous cell therapy

Sipuleucel T is an autologous immune cell vaccine designed to stimulate the immune system in patients with advanced hormone-resistant prostate cancer.

Oncolytic viruses

Talimogene laherparepvec (T - vec) is a live herpes simplex virus (HSV) vaccine type 1 live genetically modified to produce GM-CSF. Thus, intralesional injection of genetically modified HSV type 1 leads to intratumoral viral replication and GM-CSF production. Intratumoral replication of the virus leads to lysis of tumor cells and the release of tumor antigens.

Immune control point modulators

Immunotherapy was relaunched as an effective therapeutic weapon against cancer in 2013, when checkpoint receptors were identified that resulted in unprecedented results. The study of the relationship between the dendritic cell (PCA) and the T lymphocyte led to the identification of new categories of receptor that when manipulated could lead to a useful therapeutic response. Immune blockade with anti-CTLA-4 and PD-1 T cell checkpoint antibodies are effective methods to reverse immunosuppression and promote an effective immune response against several cancers. Through immunotherapy, we relearn T cells to recognize tumor cells. Immunotherapy is performed with Ipilimumab (Yervoy, Nivolumab, Pembrolizumab, Atezolizumab.

Vaccine therapy

In cancer therapy, the goal of active immunotherapy (vaccination) is to generate or amplify the immune response against tumor cells. Most tumors express tumor-specific antigens that can become specific targets for the immune system. These are proteins expressed only at a certain stage of cell differentiation (eg AFP, CEA), or expressed in small amounts in normal cells but at a higher level in tumor cells, such as growth factors, their receptors and oncogene-encoded proteins.

The use of B.C.G. (tuberculosis vaccine) in the treatment of malignancies such as multiple myeloma, leukemia and especially bladder cancer is being evaluated.

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TARGETED MOLECULAR THERAPIES

Research in the field of molecular biology by: identifying oncogenes, tumor suppressor genes and mechanisms of tumor immunology, explains the survival and proliferation of the malignant cell and updates argues the advantage of „targeted molecular therapies" less harmful to the normal cell. Thus, the target therapy represents a new class of agents that specifically target the molecular mechanisms of the neoplastic cell: biological signaling pathways, gene expression, growth regulation, cell cycle control, proteins, apoptosis and angiogenesis. The use of these molecules may be alone, or in combination with systemic chemotherapy, to increase the effectiveness of the treatment.

„Molecular targets" are classified according to their genetic or functional properties into: activated gene products, translocations, growth factors and their receptors, aberrant transduction signaling pathways, apoptosis pathways, factors controlling angiogenesis, tumor microenvironment, disordered proteins, DNA repair mechanisms and aberrant epigenetic mechanisms.

Molecular therapy targets the following mechanisms: Cellular signaling: growth factors and growth factor receptor tyrosine kinases; oncogenes and farnesyl transferase; cell cycle proteins (cyclin d1); protein kinases (PKC, PKA, MAPK); COX-2; Apoptosis: Mdm2; Bcl-2, Bcl-xL; Gene transcription: histone deacetylation; DNA methyltransferase; Angiogenesis and metastasis: proangiogenetic factors and their receptors: e.g. Vascular Endothelial Growth Factor (VEGF), or its receptor (VEGFR); endothelial cell proliferation; metalloproteinases.

The molecular characteristic of the tumor identifies potential therapeutic targets, as well as predictive markers of response to target therapies, so that patients can be selected, for which personalized (targeted) therapy is recommended. The success of target therapies is also the identification of „driver" genes (genes that play a key role in tumor progression and survival) and „passenger" (genes whose presence is not essential for tumor survival and development) and the possibility of identifying „driver" mutations involved. in the development of a tumor.

Similar to systemic chemotherapy, the malignant cell may develop

resistance to target therapies and progress. Thus, sometimes under the influence of administered treatments, new mutations occur, with the activation of other signaling pathways or changes in the status of surface receptors and eventually the aggressiveness of the tumor changes. In these cases, metastatic tumor rebiopsy is recommended.

Biological cancer therapy is represented by:

- monoclonal antibodies, designated by the suffix „-mab" act extracellularly, by blocking the ligand-receptor interaction (both by ligand binding and by blocking the receptor), having a high specificity; requires intravenous administration.
- the so-called "small molecules" designated by the suffix "-ib" are tyrosine kinase and multikinase inhibitors, which interact directly with the intracellular kinase domain of the receptor, as competitive inhibitors of ATP binding; are available in oral forms.

Biological therapy works by:

- blocking cell-induced signaling via the receptor:
  - Family of EGFR (epidermal growth factor receptors): Erlotinib, Gefitinib, Lapatinib, for non-microcellular bronchopulmonary cancer (NSCLC); Trastuzumab, Pertuzumab Lapatinib for Breast Cancer; Cetuximab, Panitumumab for Colorectal Cancer; Vandetanib for Spinal Cord Cancer; Pan-HER inhibitors (Lapatinib, Neratinib, Afatinib);
  - PI3K / AKT / mTOR pathway: The pathway of phosphatase and tensin homologue (PTEN) / phosphoinositol-3-kinase (P13K) / serine / threoninkinase Akt / mammalian target of rapamycin (mTOR) plays a central role in various cellular functions (survival, proliferation, cell cycle progression and neovascularization). Akt functions as a cardinal node to which signals involving well-known tyrosine kinase receptors (HER-2, VEGF, c-Kit, PDGF, and IGF-1) converge downstream, which in turn recruit P13K and subsequently Akt to the membrane. Akt activation promotes survival by inhibiting transcription and proapoptotic proteins (eg p53, Bax and caspase-9) and stimulates protein synthesis and cell growth via activation of the rapamycin pathway (mTOR) (7). MTOR inhibitors fall into two categories: rapalogs (sirolimus, temsirolimus, everolimus and ridaforolimus) and kinase inhibitors (inhibits both TORC1 and TORC2, with greater potential to

inhibit cell growth, metastasis, invasion, angiogenesis and tumor progression; there are several molecules in phase I clinical trials);

- The RAS-RAF-MEK-ERK pathway: The RAF serine / threonine kinase / extracellular mitogen kinase (MEK) / extracellular signal kinase (ERK) / mitogen-activated protein kinase (MAPK) pathway is overactivated in various cancers (thyroid, liver, pancreas, colorectal, ovarian, prostate, breast, renal, broncho-pulmonary, melanoma, acute myeloid leukemia). BRAF Inhibitors: Vemurafenib, Dabrafenib for Malignant Melanoma; MEK inhibitors: Trametinib, Binimetinib for Malignant Melanoma; KIT and Bcr-Abl inhibitors;
- KIT and Bcr-Abl inhibitors: Specific translocation between chromosomes 9 and 22 (resulting in the Philadelphia chromosome, Ph1, t(9:22) fuses the Bcr and Abl genes leading to a chimeric protein with active tyrosine kinase function that directs the uncontrolled proliferation of Chronic myeloid leukemia (CML) cells, as well as granulocyte growth factor (c-Kit encoded) CD117 receptor - which is involved in the oncogenesis of stromal gastrointestinal tumors (GIST) or protuberant dermatofibrosarcoma be effectively inhibited by a number of targeted molecules: Imatinib mesylate, Dasatinib, Nilotinib;
- ALK (anaplastic lymphoma kinase) inhibitors: ALK is a tyrosine kinase initially identified in patients with large cell anaplastic lymphoma (ALCL), being activated by a chromosomal translocation. It is part of the insulin receptor family, and its physiological role is less well known. Intracellularly, ALK can activate the Ras / MAPK / ERK and PI3K / AKT / mTOR pathways, stimulating cell proliferation and tumor survival. Subsequently, it became a molecular target, being identified in patients with NSCLC, myofibroblastic tumors and neuroblastoma. In NSCLC, ALK mutations occur in approximately 3-5% of adenocarcinomas, which also overexpress TTF1 (thryroid transcription factor-1) and p63: Crizotinib, Ceritinib;
- CDK4 / 6 inhibitors: CDK4 (Cyclin-dependent kinase 4) together with CDK6, with which it is closely related, are known for their important role in the transition of the G1 phase to the S phase in the cell cycle. These are in turn influenced by the activity of

type D cyclins, the expression of which may vary depending on various extracellular mitogenic signals (activation of PI3K, Ras-MAPK or β-catenin-Tcf / LEF pathways). Together, CDK4 and CDK6 form an active complex, with a role in inhibiting Rb function (tumor suppressor protein with a role in controlling the cell cycle). Selection of target patients for CDK4 / 6 inhibition is essential, frequent abnormalities of the cyclin D-CDK4 / 6 complex have been identified in mantle lymphomas, ENT, breast, NSCLC, esophageal, malignant melanoma and glioblastoma: Palbociclib, Ribociclib;

- MET inhibitors: MET is a tyrosine kinase associated with hepatocyte growth factor (HGF / SF) and secreted by mesenchymal cells (fibroblasts and smooth muscle cells) and tumors. This is correlated with an unfavorable prognosis in solid tumors, by activating the Ras / MAPK / ERK and PI3K / AKT / mTOR signaling pathways, as well as by cross-talking with other signaling pathways such as VEGFR, EGFR and WNT. MET mutations have been found in renal tumors (c-MET is required for the survival of clear cell renal tumors with Von Hippel-Lindau mutations), ENT, NSCLC, digestive and breast (5): Cabozantinib for renal cancer;
- Inhibition of angiogenesis: Angiogenesis is a complex, multistage process, with an essential role in the growth and metastasis of tumors. Endothelial cell growth factors (VEGFs) and their receptors (VEGFRs) play a central role in endothelial cell proliferation, migration, and survival. Also, the signals induced by PDGFR-β in pericytes allow the maturation, maintenance and survival of already formed neoformation vessels. Medications that block VEGF, VEGFR-1, -2, -3, and PDGFR-α and -β function are currently available, and clinical effects have shown that these receptors are important therapeutic targets;
- VEGF and VEGFR inhibitors: Bevacizumab for colorectal, breast, kidney, glioblastoma and metastatic non-microcellular bronchopulmonary carcinomas; Sunitinib for metastatic and second-line renal cancer in patients with advanced gastrointestinal stromal tumors (GIST); Sorafenib for Child-Pugh Class A and B Class A / B Local Advanced / Metastatic Hepatocellular Carcinoma, Advanced and / or Metastatic Renal Carcinoma, and

is active in imatinib-resistant GIST; Vandetanib for advanced non-microcellular bronchopulmonary cancer; Dasatinib for: CML and acute lymphoblastic leukemia (ALL) with Ph + chromosome; GIST; Pazopanib for metastatic kidney cancer; Axitinib for metastatic renal cancer refractory to cytokine, thyroid, pancreatic, non-microcellular bronchopulmonary and breast therapy; Ramucirumab for colorectal cancer and metastatic eso-gastric junction; Cediranib for microcellular or colorectal metastatic bronchopulmonary cancers; Thalidomide (Thalomid®) for refractory multiple myeloma, clear metastatic renal cell carcinoma and malignant gliomas.

PARP pathway inhibitors

- Poly (ADP-ribose) polymerases (PARP). The best represented is PARP-1, a nuclear enzyme activated by the breakdown of DNA strands that plays a key role in the repair of single-stranded lesions through the process of excision of base-pairs. Defective cell lines of the BRCA-1 and BRCA-2 genes are exclusively sensitive to inhibition of PARP compared to those with normal BRCA (wild type): Olaparib for triple negative breast cancer and ovarian cancers, with BRCA1 / 2 mutations present including resistant platinum-salt chemotherapy, Niraparib for recurrent platinum-sensitive recurrent ovarian cancer; Veliparib, Rucaparib.
- Inhibition of the proteasome: Intracellular proteolysis systems recognize and destroy poorly folded proteins, unassembled protein chains, and short half-stem regulatory proteins. The proteasome-ubiquitin pathway is the main mechanism by which catabolism of intracellular proteins (from the cytosol and nucleus) occurs in mammals. Disruption of the degradation of these proteins can have a profound effect on cell cycle control and cell growth, and leads cells to apoptosis, playing a critical role in maintaining cellular homeostasis by regulating transcriptional factors, cellular signals, and apoptosis: Bortezomib for cytostatic-resistant multiple myeloma.
- Epigenetic therapies (histone deacetylase inhibition, DNA demethylation, etc.): Demethylating agents: 5-azacitidine, Decitabine for acute myeloblastic leukemias (AML) and myelodysplastic syndromes (MDS).

- Apoptosis inducers: Bcl-2 targeting agents overexpressed in haematological, nasopharyngeal, colorectal, prostate malignancies: Oblimersen, Obatoclax mesilat.
- Differentiating agents: Cell differentiating agents can inhibit growth, induce differentiation and trigger apoptosis in different cell types. They are represented by natural and synthetic retinoids, for which there are two subfamilies of specific nuclear receptors, retinoic acid receptors (RAR) and X retinoid receptors (RXR): Isotretinoin in oral leukoplakia, Retinoic acid in Kaposi's skin sarcoma in AIDS patients; Tretinoin for acute promyelocytic leukemia.
- Other biological therapeutic approaches: Cyclooxygenase-2 inhibitors (COX-2): COX-1 plays a "guard" role in a variety of tissues, and COX-2 induces the response to a variety of stimuli and is frequently overstimulated in inflammation and tumors, and also in about 50% of colorectal adenomas. In addition to decreasing downstream prostaglandin synthesis, COX-2 inhibition also leads to reduced VEGF (antiangiogenic effect): NSAIDs and Selective COX-2 Inhibitors: sulindac, celecoxib, rofecoxib.

Extracellular matrix medications: Extracellular matrix metalloproteinases (matrix metallo-proteinases, MMPs) are a family of zinc-dependent endopeptidases synthesized as inactive zymogens (pro-MMPs) and activated by proteinase cleavage, which mediate the degradation of this tumor expressed by tumor stroma.: Vitaxin, Marimastat.

Stem cells, which maintain neoplastic proliferation and are cellular targets for future therapies.

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PALIATIVE TREATMENTS IN ONCOLOGY

Cancer patients are affected by many types of symptoms. These can range from pain, shortness of breath, constipation, nausea to many other symptoms. In oncology, palliative care focuses on combating suffering and improving the quality of life of cancer patients, their families, and those close to them.

„Palliative care is the treatment given to improve the quality of life of patients and their families who are facing problems associated with the treatment of the disease, to prevent and alleviate suffering. The areas of palliative care cover four dimensions: physical, psychological (emotional), social (relational and logistical) and spiritual / existential.

The purpose of palliative care is to:

- relieving (alleviating) the symptoms;
- maximizing the quality of life;
- potential prolongation of survival.

A. Pain is one of the most severe and common symptoms of cancer. It is a complex symptom, with an impact on the quality of life and psychology of the cancer patient.

A more practical definition: pain is what the patient says hurts, being what the patient describes and not what others think it might be.

Pain is the most prominent symptom in cancer present in 30-40% of patients at the time of diagnosis, 40-70% at the time of treatment and 70-90% in the advanced stages of the disease. In cancer patients, the pain may be a consequence of the disease itself or may result from antineoplastic treatments such as surgery, radiation therapy or chemotherapy.

ABCDE pain assessment in clinical practice (adapted after);

A - choose the analgesic therapy according to the patient, his material and intellectual possibilities; takes into account its compliance and expectations;

B - balances the therapy so that any analgesic intervention is coordinated with the rest of the treatment;

C - believes the patient and his relatives regarding the intensity of the pain and the factors that alleviate it;

D - discuss with the patient at each address about the presence of pain;
E - DO NOT hesitate to involve the patient and his relatives in the therapeutic decision.

Pain treatment is done according to the WHO „pain scale" using opioid and non-opioid medications.

Pharmacological therapy

Principles of pharmacological pain management recommended by the WHO report:

1. oral treatment (by mouth: oral route should always be preferred whenever possible - avoid painful MI injections);
2. treatment will be administered by the clock: based on fixed schemes, and not as needed. Occasional administration related to adverse events (nausea, pruritus, somnolence) and low levels associated with periods of suboptimal analgesia should be avoided; „On-demand" medication should be avoided with one exception: breackthrough pain control;
3. Three-step ladder according to WHO recommendations:

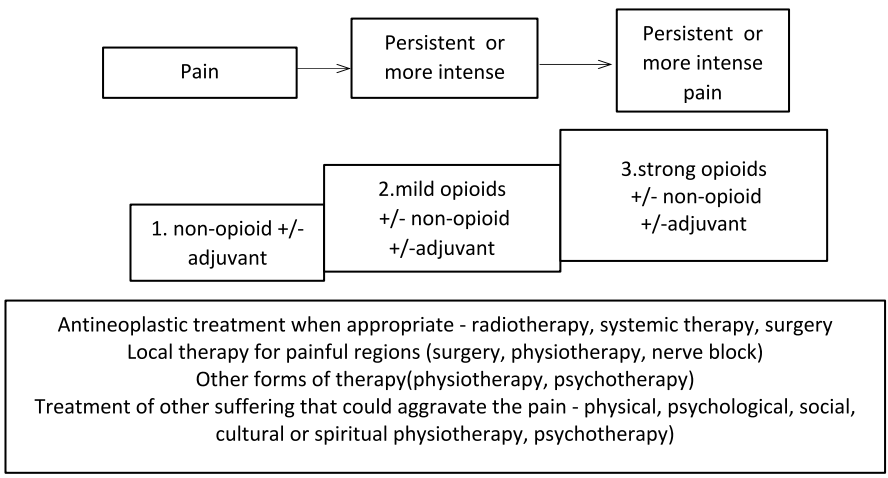

FIG. 1. *Scale of step analgesia according to WHO*

"Step" treatment of pain according to O.M.S recommendations (Table 1).

Step 1: Non-opioid analgesics (acetaminophen or NSAIDs) with or without adjuvant therapy are used in mild pain (<4 on the VAS scale).

Step 2: In moderate pain (4-7 on the VAS scale), weak opioid analgesics

will be combined with non-opioid analgesics (see table) or, alternatively, combinations with narcotic analgesics with or without adjuvant therapy.

Step 3: For severe pain, replace the weak opioid with a strong opioid (see table) in combination with a neopioid analgesic, with or without adjuvant therapy.

Table 1. Gradual approach to pain therapy

Steps of administration	Dose	Interval (hours)	Maximum doses
Step 1*			
Paracetamol	500-1000	4-6	3000
Diclofenac	25-50	4-8	200-300
Ibuprofen	300-400	6-12	2400
Metamizole	500-1000	4-6	6000
Step 2*			
Paracetamol + Codeine	1-2 tablets	4-6	1-2 tablets
Diclofenac+Codeinephosphate	1-2 tablets	6-8	4-5 tablets
Dihydrocodeine	60-120	8-12	240-360
Tramadol	50-100	2-4	600
Step 3*			
Buprenorphine	1-3 tablets	6-8	20 tablets
Morphine sulfate	10-200	8-12	no
Oxycodone	10-40	8-12	no
Hydromorphine	4-24	8-12	no
Fentanyl (patch) only in stable pain		72 hours	
Step 4*			
Stage 3 drugs in continuous administration i.v, subcutaneous,epidural/intrathecal			

* In addition, co-analgesics / adjuvant analgesics may be administered

B.Nausea and vomiting

Nausea is an unpleasant sensation that can precede vomiting and is often associated with pallor, cold sweats, salivation, tachycardia, and diarrhea. Vomiting is defined as the action of removing gastric contents from the mouth, induced by the somatic nerve pathway which includes coordinated actions in the gastrointestinal tract, diaphragm and abdominal muscles. Vomiting is a reflex act and a natural protective mechanism of the body against toxic substances. In oncological practice, most chemotherapeutic regimens cause nausea and vomiting in up to 75% of patients (24).

Treatment

The best therapeutic approach is to prophylaxis nausea and vomiting with appropriate doses of antiemetics, especially when using cytostatics with high emetogenic potential, which is why the emetogenic potential of each chemotherapeutic must be known.

Planning chemotherapy for cancer patients takes into account several basic principles:

a) the main purpose is the complete prevention of emesis;
b) in order to reduce the risk of anticipatory emesis, the initial doses of antiemetics will be adapted to the emetogenic risk of the protocol from the first cycle of chemotherapy;
c) the education of the patient in case of an episode of episodic emesis (breakthrough emesis) and the prescription of an antiemetic medication at home will be considered.

If, despite optimal treatment, emesis occurs in a patient during chemotherapy, other causes such as intestinal obstruction, intestinal dysmotility, other concomitant medications (especially opioids), metabolic disturbances (hyponatremia, hypercalcemia) and CNS metastases will be considered. .

Therapeutic classes of antiemetics:

a. dopaminergic receptor antagonists: metoclopramide
   - dose 1-3 mg i.v. 2h from 2 to 6 doses;
   - side effects: mild sedation, agitation and diarrhea. In high doses it causes extra-pyramidal effects;
   - is given in combination with corticosteroids, lorazepam and diphiphenhydramine.

b. serotonergic receptor antagonists (5HT3): ondansetron, granisetron, palonostron, tropisetron, dolasetron

- granisetron (Kytril) 0.01 mg (10μg) / kgc i.v. or 1-2 mg orally at increased risk of emesis;
- palonostron (Aloxi) 0.25mg i.v. in 30 seconds in acute and late emesis.

Side effects are: moderate headache, constipation, transient increase in transaminases.

c. NK-1 receptor antagonists: aprepitant, fosaprepitant (block substance P)
   - aprepitant (Emend) decreases late emesis by 20%.
   - CHT is administered for 3 consecutive days together with a 5-HT3 inhibitor and dexamethasone; 125 mg orally 1 hour before chemotherapy on day 1, then 80 mg orally in the morning on days 2 and 3 in high emetic risk protocols.

d. benzodiazepines: lorazepam (Ativan), dose of 1-2 mg IV or sublingual at 3-6 hours in anticipatory and refractory vomiting;

e. Corticosteroids are very effective in treating chemotherapy-induced emesis, either alone or in combination with 5-HT3 blockers. Is recommended:
   - Dexamethasone 10-20mg IV single dose or in 2 doses
   - Methylprednisolone (Solu-Medrol) 125 mg IV one or 2 doses.

C.Constipation

Constipation is the difficulty of defecating or eliminating fecal matter of increased consistency as the frequency of defecation decreases. Constipation can cause a number of secondary symptoms such as diarrhea, urinary retention or bowel obstruction.

Constipation treatment consists of:

- *General measures:*
  - changes in diet: increased food intake, increased fiber content, increased consumption of fluids / fruit juices;
  - patient mobilization. Ease of access to the toilet and its arrangement (chair to support the legs to allow easier contraction of the abdominal muscles);
  - reduce the dose or stop taking constipation drugs (eg opioids);
- *Drug treatment:* administration of laxatives: fibers (methylcellulose, mucyloids), lubricants, mineral or paraffin oil, salts (magnesium salt, sodium sulfate, sodium phosphate), osmotic agents (lactulose, sorbitol, mannitol).

D.Dyspnoea

- Dyspnoea is the subjective and unpleasant sensation of shortness of breath; In oncology, it is one of the most common symptoms, with an increased incidence of up to 70% in terminal conditions.
- Principles of treatment:
- Calming the patient's anxiety;
- Identification and therapeutic approach of organic causes of dyspnea;
- Non-pharmacological treatment;
- Pharmacological treatment;

E. Malignant ascites

Ascites is an accumulation of fluid in the abdominal cavity and is a common cause of discomfort in patients with advanced cancer. At the physical examination, the signs that support the presence of ascites are: abdominal distension, abdominal pain or discomfort, inability to sit up, early satiety, dyspepsia, gastroesophageal reflux, nausea and vomiting, edema in the lower limbs, dyspnea.

Treatment:

- Therapeutic paracentesis may cause symptomatic improvement with minimal morbidity and mortality. Paracentesis may be the only effective way to treat patients with malignant ascites and relieve pain faster than diuretics! Up to 5 liters of ascites fluid can be evacuated by paracentesis in a single session. Evacuation can be done through an i.v. cannula. or through a suprapubic catheter. Patients show an improvement in their general condition even after the discharge of only 2 liters of fluid. If diuretics fail to control ascites, paracentesis may be repeated.
- Diuretics may be a useful therapeutic modality. Spironolactone is the initial diuretic (25-50 mg in the morning) associated with furosemide after the start of spironolactone treatment. In 2/3 of patients, ascites is successfully controlled by taking Spironolactone in daily doses of 25-50 mg in the morning, up to 300 mg / day. Once a favorable effect is obtained, the dose of the loop diuretic will be reduced.

G. Terminal state

Despite the progress made in recent years, cancer remains one of the leading causes of death worldwide. When the malignant disease reaches its terminal stage, the goal of treatment ceases to be healing or prolonging

survival. Clinicians need to actively recognize the terminal condition in the evolution of the cancer patient, especially since studies suggest that terminal therapy is most commonly suboptimal. The diagnosis is suggested by the continuing deterioration of the general condition, lethargy, decreased consciousness, drowsiness, confusion, reduced spontaneous movements and respiratory changes. The main goal is symptomatic treatment, combating suffering, improving the quality of life of both the patient and his family. This involves actions in 6 directions: physical, emotional, interpersonal, cognitive, behavioral and spiritual.

In the last days of life, before death, a large number of patients have one or more of the following symptoms:

- fatigue or pain (70%);
- restlessness / agitation / delirium or noisy or wet breathing (60%);
- incontinence or urinary retention (50%);
- dyspnea (20%);
- nausea and vomiting (10%).

Terminal care is multilateral, but focuses on the medical control of physical symptoms and consists of:

- The need for optimal pain relief.
- The need to combat other symptoms of discomfort and suffering.
- The care will be applied by doctors and trained health personnel who show a positive attitude towards palliative care.
- Respect for the patient's wishes.
- Achieving a relationship of trust and open communication between doctor-patient-family, which allows overcoming anxiety and prepares the family and the patient for death.

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RESPONSE TO THE TREATMENT AND FOLLOW-UP OF THE ONCOLOGICAL PATIENT

To evaluate the quality of the results of therapeutic methods, a multitude of data are used, which must be interpreted in a clinical context. Thus, we can evaluate the effectiveness of a therapeutic method by:

- Clinical evaluation: direct measurement of palpable tumors (example: measurement of breast tumors, lymphadenopathy, skin lesions).
- Direct assessment of invasive lesions by invasive methods: evaluation of gastric tumors by upper digestive endoscopy, lung tumors by fibroscopy.
- Measurement of lesions by imaging techniques: ultrasound, radiography, computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy.
- Dynamic tracking of biochemical constants (liver samples, tumor markers).

Of this variety of ways, the easiest to standardize is tracking by high performance imaging methods (CT, MRI). In order to create a series of international criteria, the follow-up of cancer patients is currently subject to the RECIST criteria. The RECIST (Response Evaluation Criteria in Solid Tumors) system is a way of quantitative evaluation resulting from the conversion of imaging observations. Version 1.1 has been validated and its criteria are useful in all studies where objective response, disease stabilization, tumor progression, or time to progression analysis are the goal. This evaluation system can be adapted to each study and can be used in clinical practice, without being mandatory.

Molecular therapies, alone or in combination with chemotherapy, are now being used more and more. To standardize the tumor response to molecular therapies and to simplify assessment methods, Eisenhauer proposed the modification of the RECIST criteria. The new criteria, RECIST 1.1 define four main response categories for measurable lesions: complete response - RC (disappearance of all tumor lesions), partial response - RP (reduction

by 30% of the maximum measured diameters), progressive disease - BP (increase by 20 % of the sum of the maximum measured diameters and increase by at least 5 mm of at least one tumor lesion and stable disease - BS (partial response criteria or progressive disease are not met).

The major changes included in version 1.1 were:

- reduction of the total number of lesions necessary to define the tumor response from 10 to 5 and from 5 to 2 per organ;
- introduction of the option of pathological evaluation of the lymph nodes to define the complete response;
- introduction of the 5mm criterion for defining progressive disease;
- defining the size of 15 mm in the smallest axis of a ganglion in order to be considered a target lesion;
- consideration of the nodes with short axis reduced below 10 mm after treatment as normal lymph nodes.

In addition, the new guide introduced information on functional imaging evaluation (eg PET-CT). These criteria, although universally valid, can be modified and adapted to each trial.

The purpose of the initial assessment is to establish tumor or lymph node lesions and to classify them as measurable (target) or non-measurable (non-target) lesions. The criteria necessary to define the target lesions are: minimum size 10 mm for CT evaluation with maximum sections of 5 mm, 10 mm for clinically measurable lesions, 20 mm for chest evaluation by radiography and 15 mm in the short axis for lymph nodes (measured on CT). Non-measurable lesions group all tumors that do not meet the above criteria as well as truly non-measurable lesions: fluid ascites, pleurisy or pericarditis, leptomeningeal metastases, inflammatory breast cancer, carcinomatous lymphangitis, blast bone metastases. Cystic lesions or lesions previously treated by local procedures, such as radiofrequency ablation, chemoembolization, cryoablation, steam ablation, should be avoided due to the difficulty of differentiating tumor tissue from the area of necrosis induced by the therapeutic procedure and its secondary inflammation. For a correct assessment, the same imaging method as the baseline should be used during the tracking period, making it difficult to compare different methods.

The evolution of non-measurable lesions can be grouped into 3 categories:

- complete response - RC - defined by the disappearance of all lesions and reduction of the diameter in the short axis of the lymph nodes below 10 mm;
- incomplete response / stable disease –RI / BS - defined by the persistence of non-target lesions or the level of tumor markers;
- progressive disease - BP - defined by unequivocal progression.

The frequency of evaluations should be at 6-8 weeks and coincide with the end of a treatment cycle. In order to define the clinical benefit, the appearance of stable disease should be maintained for a predetermined minimum period of time (eg 16 weeks, in which case the unit of measurement is PFS16 - progression free survival 16). To evaluate the efficacy of PFS therapies, all patients included in the study must have measurable disease. In certain particular situations, evaluation of the response may be impossible: premature discontinuation of treatment due to toxicity, death, patient refusal, etc. The results of the study should be based on reporting the response to all eligible patients and not just on the selective processing of response rates to "assessable" patients.

The RECIST criteria can be adapted to a specific tumor location and to a certain therapy, in order to evaluate the effectiveness of the therapy according to the changes it produces. To be eloquent, here are the criteria for adapting to hepatocellular carcinomas. Because RECIST criteria were originally designed to assess tumor response in cytotoxic treatments, the European Association for the Study of Liver (EASL) recommends the use of modified RECIST (mRECIST) criteria in clinical trials. Thus, the measurement of lesions is done on the basis of viable tumor tissue, which captures the contrast substance in the arterial phase, excluding necrotic areas, and pleural and peritoneal effusions require cytological confirmation to declare disease progression, portal lymph nodes are considered tumors if the short axis is greater than 2 cm, portal vein thrombosis is considered a non-target lesion and a new lesion defines progressive disease if it has a maximum diameter of at least 1 cm and captures the contrast substance. The study by Ahsun Riaz et al. demonstrated a better concordance between mRECIST and the pathological response to the RECIST and WHO systems, while the combination of mRECIST with WHO is more valuable than any method taken individually. Patients previously treated by local methods should be carefully evaluated, taking into account possible lipiodol-induced artifacts (used in chemoembolization), metal clips, etc.

Ultrasound (US) is the initial examination performed on most patients suspected of having abdominal, breast, or soft tissue damage because it is fast, accurate, and non-invasive. In addition, US provides real-time imaging and can support real-time guidance biopsies. By contrast enhanced US (CEUS), focal lesions can be diagnosed based on their vascularity and specific characteristics. The main disadvantage is the dependence on the operator and the patient, in the sense that obese patients can be difficult to scan and the reproducibility is limited. Based on these disadvantages of the US, the guidelines recommend the use of CT or MRI in clinical trials. However, in the follow-up period after local treatment with curative potential, the US can be used after the first year after stopping treatment, if during this period there was no evidence of recurrence (evaluation at 3 months by CT or MRI).

In conclusion, there is no consensus on the optimal strategy for assessing tumors in clinical trials or in current practice. The choice of method is based on the requirements of the clinician, the availability of equipment, the status of patients and the experience of the imager.

Long-term follow-up of cancer patients

The success of oncology therapies has led to an increase in the number of cancer survivors. The size of this population requires effective and cost-effective means of monitoring. The post-therapeutic follow-up of the cancer patient is necessary to monitor the side effects of the cancer therapies, with attention to the long-term effects, and for the early detection of the recurrence of the disease. This attitude is justified in terms of maintaining the chances of cure at the time of early detection of recurrence and the need to monitor the long-term adverse effects of antitumor therapies as they can have a significant impact on quality of life.

Objectives of supervision

- Diagnosis of a recurrence to check that remission is maintained.
- Assessment and treatment of late complications of treatments.
- Detection of a possible second neoplasm (for example in the case of smokers who may have another neoplasm after the first cure).

Diagnosis of recurrence

The assessment of the risk of recurrence can be made by integrating the anticipated natural history of the neoplasm according to the prognostic data based on biological risk factors and the results of anticancer treatments administered. The interest in detection is weighted by the expected therapeutic options, the main goal being the early detection of a curable recurrence, accessible to the rescue treatment.

Recurrence can be local or remote. Local recurrence can occur:

- after conservative treatment (eg local recurrence after tumorectomy for breast cancer);
- after a radical treatment, sometimes rescue by radiotherapy if the initial treatment was surgical.

For all locations, it is generally recommended:

- history of recent symptoms;
- physical examination every 3-6 months, in the first 3 years and every 6-12 months for 3 years, then annually;
- blood count, biochemical examination, tumor markers (eg CA15-3, AFP, ACE);
- imaging follow-up: chest radiography, abdominal ultrasound, abdominal and chest CT scan.

The post-therapeutic follow-up of the cancer patient presents three distinct periods, depending on the time interval after the end of the treatment and the type of events revealed:

1. The immediate post-treatment period begins on the first day after treatment and lasts until the first recommended post-treatment check-up in most cases every 3 months. At the end of this period, a first objective evaluation of the response to treatment is performed, the standard interval allows the evaluation of the response and the consolidation of the cytotoxic effect on the tumor tissue.
2. The risk period is between 2 months and 5 years after the end of treatment. It represents the most important follow-up period because during this time most of the loco-regional recurrences can appear, which manifest clinically in the first 3 years as well as distant metastases.
3. The period of relative safety occurs 5 years after treatment, which reduces the risk of cancer death. The risk of developing a second neoplasm increases.

However, the follow-up interval of cancer patients differs depending on the natural history and the type of therapeutic response of the various malignancies.

Detection of long-term complications

The increase in the number of survivors has led to the emergence of a population exposed to the late side effects of cancer therapies. Late therapeutic effects include various medical and psychosocial problems

that may affect survival, physical and mental health.

The late effects of oncological therapies can be anticipated, depending on the treatment followed and its age of onset. Early detection of these side effects can be done:

• based on individualized laboratory investigations according to the problems anticipated by clinicians;

• based on the patient's disease and therapeutic history.

Developing a stable relationship with the therapist (knowledge of the history of the disease, the risks of side effects and screening recommendations) will improve the chances of detecting a possible secondary cancer in early, curable stages.

Clinicians caring for adult cancer survivors should be aware of the clinical and socio-demographic factors that predispose to the morbidity associated with neoplasia and take appropriate measures to maintain and improve health status.

The long-term follow-up of a patient after cancer therapy, especially at a young age, is very important for several reasons. The side effects of aggressive oncological therapies can be detected late in adulthood. Knowing these effects allows clinicians to develop long-term follow-up strategies and promote hygienic-dietary behaviors to minimize these complications.

The main purpose of long-term follow-up of a cancer patient, especially at a young age, is to confirm the remission of cancer and to monitor late toxicity. Late complications should include an assessment of side effects, adverse effects on various organs: brain, heart, lung, endocrine glands, gonads, bone marrow, bone and soft tissue, which are likely to affect the quality of life of children cured of cancer. Psychological effects, social inclusion, school performance, relationships with family and friends should not be overlooked.

The association of laboratory and imaging investigations will be based on the risk category conferred by the type of therapy followed (surgery, chemo-, radio-, hormone therapy, etc.) and the delayed side effects expected for them, as well as the identified clinical symptoms. on the following devices and systems: skin and muscle tissue, dentition, thyroid, gonads, pituitary gland, cardiovascular and respiratory system (pulmonary fibrosis), urogenital system (hypertension, proteinuria, hematuria) and digestive system, central nervous system.

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PRINCIPLES AND INDICATIONS OF ANTINEOPLASIC CHEMOTHERAPY

Systemic treatments that can affect the survival of cancer cells throughout the body currently include cytotoxic cytostatics (chemotherapy), hormonal agents (hormone therapy), targeted molecular agents (biological therapies), and immunotherapy.

Chemotherapy is the systemic drug treatment of cancer that is based on the use of substances that interfere with metabolism and the cell cycle, causing cell death.

Because cell multiplication is a feature of most normal and cancer cells, cytostatics exert their toxic effects on all rapidly dividing cells, including bone marrow, germ cells, or mucosal cells.

Classification of cytostatics

A.Classification of cytostatics by source and mechanism of action (Table 1).

Table 1. Classification of cytostatics currently used in oncology (3)

1.Alkylating agents	
- Nitrogen mustard	Mechlorethamine, Chlorambucil, Melfalan, Estramustin, Bendamustin
	Cyclophosphamide, Ifosfamide
- Aziridine	Triethylene Thiophosphamide (Thiotepa)
- Alkylsulfonates	Busulfan
- Triazene	Dacarbazine (DTIC), Temozolomide
- Nitrozuree derivatives	Carmustin, Lomustin, Streptozotocin
- Metal salts	Cisplatin, Carboplatin, Oxaliplatin, Satraplatin, Picoplatin
- Others	Trabectedin
2. Antimetabolites	
- Folic acid antagonists	Metitrerexate, Ralitrexed, Pemetrexed, Edatrexate, Piritrexim, Pralatrexed,

- Purine analogues	6-Thioguanine, 6-Mercaptopurine, Azathioprine, Allopurinol, Fludarabine
- Adenosine analogues	Cladribine, Pentostatin
- Pyrimidine analogues	Gemcitabine, Cytarabine, 5-Azacitidine,
- Fluoropyrimidine	5-Fluorouracil, Uracil-phtorafur, Capecitabine, Trifluridine-tipiracil
- Substituted urea	Hydroxyurea
3. Natural products	
A). Antineoplastic antibiotics	
- Antibiotics that interfere with transcription	Dactinomycin (Actinomycin D), Mitoxantron
- Anthracyclines and anthracycline analogues	Doxorubicin, Daunorubicin, Epirubicin,
Idarubicin, Amrubicin, Valrubicin, Mitoxantron	
- Antibiotics with partially alkylating action Mitomycin C	
- Radiomimetic antibiotics Bleomycin	
B) Topoisomerase inhibitors	
- Topoisomerase inhibitors I - Camptothecin derivatives Irinotecan, Topotecan	
- Topoisomerase inhibitors II- epipodophyllotoxin derivatives Etoposide, Teniposide	
- anthracyclines	
C) Compounds with action on the spindle microtubules	
- Mitotic inhibitors - Vinca alkaloids	Vincristine, Vinblastine, Vindesine,
Vinorelbine Ixabepilone, Eribulin	
- Microtubular polymer stabilizers - taxanes Paclitaxel, Docetaxel, Cabazitaxel	
D). Various enzymes, retinoids and anti-tumor agents	
- L-Asparaginase; Glucarpidase, Isotretionoin, Bexaroten; Hexamethylmelamine; Mitotan (Op'-DDP); Procarbazine	

I. Alkylating agents

Alkylating agents are a diverse group of chemical compounds capable of forming molecular bonds with nucleic acids, proteins, and numerous other low-weight molecules, and act on cells in all phases of the cell cycle, including the G0 phase.

Alkylating agents have the ability to form DNA-attached compounds (alkylating agents target the N7 position of guanine residues) through covalent bonds via an alkyl group. Bifunctional alkylating agents form cross- and inter-chain bonds in the DNA molecule by altering its double-heliocoidal structure, preventing the separation of DNA strands, and interfering with DNA replication. Bifunctional agents are more effective than monofunctional ones. The cytotoxic effect occurs due to the interaction between electronophilic radicals and DNA through substitution reactions, interchain bonds or chain breaks, ultimately with inadequate inhibition or replication, alteration of the information encoded in DNA and cell death.

II. Antimetabolites

Antimetabolites are a group of low molecular weight compounds that exert their function due to their structural or functional similarity to the metabolites involved in nucleic acid synthesis. By blocking DNA synthesis, antimetabolites are highly active on fast-growing cells and are entirely cyclo-phase S specific. Being structural analogues of metabolites involved in DNA and RNA synthesis, it acts by competing with them for a catalytic or regulatory site of key enzymes, or by substituting them and incorporating them into DNA or RNA, in the synthesis phase (S) of the cell cycle. . By inhibiting critical enzymes involved in nucleic acid synthesis or becoming incorporated into nucleic acid, they cause incorrect coding, resulting in cell death by inhibiting DNA synthesis.

III. Natural derivatives (4 subgroups):

1. Antitumor antibiotics.

A. Anthracyclines: Doxorubicin (Adriamicin®), Epirubicin (Farmorubicin), Daunorubicin, Idarubicin. The mechanism of action of anthracyclines is complex and involves:
   - intercalation between the base pairs of DNA (alkylating - like);
   - topoisomerase II inhibition: anthracyclines form a cleavable ternary complex with DNA topoisomerase II that binds to DNA strands;
   - the generation of oxygen free radicals that damage macromolecules by oxidation cycles REDOX- the peroxidation of membrane lymphoids explains the cardiac toxicity of anthracyclines.

B. Non-antracicline: Mitomicina C, Mitoxantron (Novantrone), actinomicina D (Dactinomycin), Bleomicina.

2. Topoisomerase inhibitors

Antitopoisomerases I (Irinotecan, Topotecan) act on a single DNA strand. Topoisomerase 1 is a nuclear enzyme that relaxes the twisted chain of DNA by catalyzing transient single-stranded DNA bonds by stabilizing DNA binding points.

Antitopoisomerases II (Etoposide, Tenoposide, Anthracyclines). Topoisomerase 2 releases the twisted DNA by inserting stable interchain bonds stabilizing the DNA in the helix configuration.

3. Cytostatics with action on the division spindle *(antimitotics)* by binding to microtubule proteins, preventing cell division in the M phase of the cell cycle:

a) Vinca rosea derivatives (vincristine, vinblastine, vinorelbine, vindesine sulfate): prevent the formation of microtubules by depolymerization, which results in the blocking of cells in the Gs and M phase of mitosis and the cell cycle.

b) Taxanes: paclitaxel, docetaxel, cabazitaxel, Nab-paclitaxel (1,3,4,5)

4. Enzymes, retinoids and other compounds (L-asparaginase that degrades L-asparagine in the blood thus preventing the proliferation of lymphoblasts, retinoids (eg bexarotene, isotretinoin) and other compounds with various mechanisms of action (mitotane - adrenocortical steroid inhibitor)

B. Classification of cytostatics in relation to the action in the cell cycle:

- ***I Class: ciclo-nespecifice (ciclo-independente)*** non-specific cycles (independent cycles) (eg alkylating agents) - acts in all phases of the cell cycle, including non-dividing cells (phase G0).
- ***II Class: cyclo-specific, phase-nonspecific -*** are effective only if the cells are during the active phases of the mitotic cycle, but induce cell damage regardless of the point in the cycle where the cell is at that time (eg antitumor antibiotics).
- ***III Class:*** **cyclo-specific, phase-specific** - efficacy depends on the proliferative state of the cell (not in the G0 phase), and in addition are effective only if they are present in a certain phase of the cell cycle (eg G1 [L-asparaginase], S [antimetabolites], G2 [bleomycin] or M [Vinca alkaloids, taxanes]).

Phase-nonspecific cytostatics (classes I and II) show a linear dose-response curve: the higher the amount of cytostatics administered, the greater the fraction of destroyed cells. For phase-specific cytostatics (class

III), increasing the dose beyond certain limits will not improve the antitumor effect, but prolonged exposure may increase efficacy (more cells will enter, over time, the phase in which they are sensitive to that cytostat). Thus, from the point of view of clinical practice, in the rapidly proliferating tumors the use of cyclo- and phase-dependent chemotherapeutics is justified, while in the slowly proliferative ones the use of cyclo-nonspecific cytostatics is more advantageous.

Toxicity of chemotherapy

Chemotherapy causes a large number of side effects, due to insufficient specificity for tumor cells, which limits both the dose and the rate of administration of cytostatics.

The side effects of chemotherapy depending on the time of onset are:

- *immediate toxic effects, may occur within 30 minutes of initiating chemotherapy;*
- *short-term toxic effects occur between 3 and 7 days after the start of cytotoxic therapy;*
- *Long-term toxic effects occur more than 7 days after chemotherapy and are often cumulative.*

A. *Acute toxicity*

Hematological toxicity

Myelosuppression associated with chemotherapy is the major limiting side effect of treatment tolerance. The most common is leukopenia with neutropenia, less often thrombopenia and anemia. Myelosuppression poses a vital risk for severe forms: thrombocytopenia <1000 cells / mm3 (haemorrhage), neutropenia <500 cells / mm3 (febrile neutropenia and septic shock) or total spinal cord aplasia.

Neutropenia is defined as the absolute value of neutrophils <1500 / mm3, a situation that presents a risk for infections. The risk increases when the absolute value of neutrophils falls below 500 cells / mm3. Erythrocyte (erythropoietin), granulocyte (G-CSF) and macrophage (GM-CSF) hematopoietic growth factors are used for prophylactic and curative purposes in conjunction with cytostatic treatment to reduce the symptoms of anemic syndrome and the risk of infection.

Mucosal toxicity

It is manifested more frequently as mucositis and stomatitis (after

methotrexate, 5-fluorouracil, etc.), and less frequently as a taste alteration, xerostomia, esophagitis.

Digestive toxicity

Nausea, vomiting (emesis), diarrhea and constipation are often associated with chemotherapy. To establish an effective treatment, the emetogenic potential of the cytostatics in the protocol used must be known (6,7). The classification of cytostatics according to emetogenic potential includes 3 groups:

a) *increased emetogenic risk* (emesis in> 75% of patients): cisplatin, ifosfamide, carmustin, cyclophosphamide (dose> 1500mg / m2), dacarbazine;
b) *moderate emetogenic risk* (emesis in> 50-75% of patients): cytarabine, carboplatin, oxaliplatin, ifosfamide, doxorubicin, cyclophosphamide;
c) *reduced emetogenic risk* (emesis in 25-50% of patients): topotecan, irinotecan, procarbazine, mitoxantron, paclitaxel, etoposide, methotrexate)
d) *without emetogenic potential:* bleomycin, busulfan, vincristine, hydroxyurea.

The main causes of diarrhea in advanced cancer are numerous; Chemotherapeutics such as 5-fluorouracil, mitomycin C, methotrexate, doxorubicin, etoposide, L-asparaginase may be responsible for diarrheal syndromes that often jeopardize the administration and results of therapy.

Hypersensitivity and anaphylactic reactions

Certain cytostatics may induce hypersensitivity reactions with / without anaphylactic response, usually with immediate onset. Cytostatics such as paclitaxel or asparaginase, but also some monoclonal antibodies (ibritumomab tiuxetan) have the highest risk of hypersensitivity reactions. Anthracyclines, bleomycin, cisplatin, carboplatin, docetaxel, melphalan, or humanized monoclonal antibodies (trastuzumab, rituximab) have a low / moderate risk of allergic reactions at or after administration.

Skin toxicity

Photosensitization reactions are manifested by erythema, blisters, hyperpigmentation and desquamation, which may occur after administration of dacarbazine, 5-FU, methotrexate, vinorelbine, procarbazine; bleomycin may be associated with skin hyperpigmentation, as may busulfan.

Alopecia (total after anthracyclines or etoposide, partial after taxanes, etc., but reversible) remains a reason for less physical suffering, more psychological, especially for women.

Hand-foot syndrome (palmoplantar erythrodysesthesia, PPE) occurs after 5-fluorouracil, capecitabine, classic doxorubicin or liposomal. EPP is a toxic drug reaction that begins as a scaly rash of the palms and plantar surface of the soles, associated with paresthesias, and can reach severe conditions to erosions and deep ulcerations with total functional impotence.

Cytostatic extravasation (especially doxorubicin, actinomycin D, melphalan, paclitaxel) at the site of administration results in atonic necrosis, the severity and extent of which depends on the amount extravasated and most often requires skin grafting.

Vascular toxicity

Thromboembolic disease is a problem associated primarily with neoplastic disease, but also with the administration of chemotherapy (risk of DVT of 2-30% when receiving chemotherapy). Other particular factors favoring the cancer are: prolonged bed rest, use of central intravenous or intra-arterial catheters, prolonged surgery. Thus, numerous chemotherapeutic agents frequently cause chemical phlebitis and acute venous thrombosis: mechlorethamine, anthracyclines, nitrosureas, mitomycin C, 5-fluorouracil, dacarbazine and epipodophyllotoxins; L-asparaginase inhibits protein synthesis (including coagulation factors or antithrombin III), causing either bleeding or thrombosis, especially in patients with haemostasis disorders.

Late toxicity

Agent-specific toxicity

For different agents, the detoxification and elimination pathway (hepatic, renal) or a particular affinity for a particular tissue determines a (generally chronic) dose-cumulative (total) cytostatic-dependent toxicity: hepatic (high-dose methotrexate); renal (cisplatin, methotrexate in high doses); cardiac (anthracyclines: cardiomyopathy; 5-fluorouracil: coronary spasm); pulmonary (bleomycin); neurological (vincristine, cisplatin, oxaliplatin, taxanes); otics (cisplatin) etc.

Secondary carcinogenesis (occurrence of the second cancer)

Acute myeloid leukemia may occur after concomitant chemo-radiotherapy, or as a result of chemotherapy with alkylating agents.

Secondary carcinogenesis usually occurs after variable time intervals (5-30 years) in survivors of cancer diagnosed at a young age (eg lymphomas, germline tumors).

Cardiac toxicity

It is frequently chronic (chronic alterations of the myocardial fiber, associated with congestive heart failure) and, less frequently, acute (direct injuries, with dysrhythmias).

Anthracyclines (doxorubicin, epirubicin, daunorubicin) are the most cytostatic cardiotoxic, whose pathogenesis is partially mediated by free radicals, with disruption of mitochondrial functions. The risk of developing cardiomyopathy is related to the cumulative total dose of anthracyclines, thus the risk of developing clinically significant cardiomyopathy is 7% at doses of 550 mg / m2, 15% at 600 mg / m2 and 30-40% at 700 mg / m2 of doxorubicin.

Other risk factors include *mediastinal irradiation and advanced age.*

Gonadal dysfunction

Some cytostatics (especially alkylating agents) cause altered reproductive function by:

- azoospermia (frequency of up to 100% of cases, sometimes reversible after therapy; requires prior collection and preservation of sperm in young patients);
- secondary amenorrhea (occurs 3-4 months after chemotherapy; recovery is variable and depends on the age at which cytostatic treatment was started - in young women, it can reach over 50% of cases).

No particular fetal abnormalities have been reported in children born to parents with chemotherapy-cured neoplasms.

Pulmonary toxicity

Respiratory toxicity is due to lesions (direct or indirect) both endothelial and epithelial (pneumocyte), due to cytotoxic agents such as bleomycin, mitomycin C, busulfan, nitrosurea derivatives. The clinical presentation can fall into 3 major categories: *pneumonitis / pulmonary fibrosis* (the most common), *hypersensitivity pneumonitis* and *non-cardiogenic pulmonary edema*, but these are not mutually exclusive.

Neurological toxicity

It is manifested by altered consciousness, cerebellar dysfunction, ototoxicity or peripheral neuropathy due to inflammation, injury or degeneration of neural fibers. The most common cause of neurotoxicity in neoplastic patients is chemotherapy with Vinca alkaloids, platinum derivatives, taxanes, procarbazine, high doses of methotrexate, ifosfamide, cytarabine or biological agents (bortezomib, interleukin-2, thalidomide).

Peripheral neurological toxicity may occur after administration of Vinca alkaloids and after cumulative *platinum derivatives.*

Central neurological manifestations (convulsive manifestations) observed after vincristine are rare. Administration of high-dose 5-fluorouracil and cytarabine may be responsible for sometimes irreversible cerebellar syndromes. Repeated intrathecal administration of methotrexate may be responsible for arachnoiditis, and i.v. of methotrexate simultaneously with radiotherapy sometimes causes cortical atrophy with ventricular dilation and late onset of white matter calcifications.

Endocrinological toxicity

Early menopause may occur in adjuvant patients treated for breast cancer and may be considered a sign of the effectiveness of chemotherapy. The risk is related to age, higher in women over 30 years of age at the time of treatment (9,10).

Chemoresistance is the major obstacle to therapeutic success. Chemoresistance can be:

a) ***temporary (conjunctural)*** - the cells do not have their own resistance mechanisms, but the drug cannot reach the cellular target (8). It refers to the blood-brain barrier (BHE), as well as the so-called „blood-testicular barrier" and Resistance due to the phenomenon of cell kinetics.

Bulky tumors are generally refractory to chemotherapy, mainly due to changes in cell kinetics (decreased proliferation fraction, increased number of cells in the G0 phase, reduced vascularization).

b) ***permanent*** - tumor cells have their own biological mechanisms of resistance (genetic conditioning), which can be: intrinsic (primary) - refers to the initial resistance of a tumor (eg: kidney cancer, malignant melanoma) and secondary (acquired) following mutations after effective initial treatment.

2. Permanent resistance:

Primary (general) (from first exposure to cytostatics), explained by tumor cell heterogeneity: spontaneous mutations may occur in different subpopulations of tumor cells prior to exposure to chemotherapy. Some of these subpopulations are natively resistant to medication, and their proliferation may become predominant after chemotherapy has eliminated sensitive cell lines.

Secondary (specific) (malignant cells are initially sensitive to cytostatics, chemoresistance is subsequently installed): many agents (especially antimetabolites) can cause specific unique mutational changes and, consequently, a particular resistance of the tumor to them. In other cases, however, a mutational change after exposure to a single drug may lead to resistance to others, apparently unrelated to initial exposure (cross-resistance). It can also occur after:

- production of catabolic enzymes that determine drug resistance by faster catabolism of the drug in the cell and after the action of intracellular detoxification enzymes.
- decreasing cytostatic access to target enzymes or altering their structure or activity, and increasing the rate of DNA repair.
- adaptive changes such as overproduction of transmembrane transport proteins (smaller amounts enter the cell, or increased amounts are transported out of the cell)
- induction or amplification of the MDR1 (multidrug resistance) gene, the product of which is a 170 kDa membrane glycoprotein (Pgp-170) that functions as a pump for the rapid export of hydrophobic chemicals out of the cell.
- loss of apoptosis is manifested by the frequent increase in aneuploidy in cancers that become more aggressive and have a higher frequency of mutations in the p53 suppressor gene or other genes involved in apoptosis.
- increase the repair of DNA, protein and membrane mutations, which increase the resistance to the action of cytotoxic chemotherapeutics

Indications for chemotherapy:

- to cure certain neoplasms (eg germline tumors);
- to alleviate some symptoms in patients with disseminated cancers, when the potential benefits of treatment outweigh its side effects;
- to treat the asymptomatic patient:

- when the neoplasm is aggressive and treatable
- when treatment will decrease the recurrence rate and increase the disease-free interval or absolute survival (stage III colon cancer, stage III breast cancer, osteogenic sarcomas).
- in order to allow a conservative, less mutilating surgery (eg breast cancer, larynx, esophagus, anus, osteosarcomas).

Contraindications to chemotherapy:

- *Absolute contraindications:*
  - terminal neoplastic diseases;
  - pregnant (initiated only after termination of pregnancy or after the first trimester of pregnancy);
  - malnourished, comatose patients with depressed hematopoietic function or recent spinal cord failure;
  - curable neoplasms by radical surgery or curative radiation therapy.
- *Relative contraindications:*
  - ECOG 3-4 performance index (Karnofsky <70%);
  - severe comorbidities (eg renal / hepatic / cardiac insufficiency, severe infections, coagulopathies or mental disorders), other conditions that may be aggravated by cytostatics (eg pulmonary fibrosis when bleomycin is administered), or serious disturbances in the values of haematological constants or biochemical (eg anemia <8g%, hyponatremia);
  - obvious tumor resistance;
  - children <3 months, elderly (> 75 years), debilitated or uncooperative;
  - the impossibility to evaluate the therapeutic effect and to monitor / treat the side effects;
  - reduced life expectancy to allow obtaining the tumor cytoreductive effect of chemotherapy;
  - quality of life, even in the case of prolonged survival, insufficient to claim a benefit (patients with severe disabilities);
  - slow-growing, incurable but asymptomatic tumor (chemotherapy should be postponed so that it can be used to alleviate symptoms) (5).

Clinical applications

Currently, chemotherapy is used in different therapeutic sequences:

1. ***primary treatment*** - in chemosensitive cancers as the main therapeutic modality

2. ***neoadjuvant treatment*** - in localized disease, potentially curable, before surgery, radiation therapy.
3. ***concomitant administration (most commonly with radiotherapy)***
4. ***adjuvant treatment*** - concomitantly or sequentially after surgery, radiotherapy or both);
5. ***loco-regional treatment*** - direct instillation (intrathecal) or as a direct infusion of specific sites (chemoembolization).
6. ***palliative treatment*** - in advanced tumors or for which there is no other effective treatment

Methods of administration

A. *Intravenous chemotherapy*

It is the main mode of administration of the vast majority of cytostatics, either on the peripheral vein or, more frequently at present, through the central venous catheter, with or without infusion pump.

B. *Continuous infusion chemotherapy* for 24-120 hours, with programmable pump systems that maintain long-term exposure of tumor cells to cytotoxic agents and also improve patient tolerance to the immediate side effects of cytostatics. Commonly used cytostatics in continuous infusion are 5-fluorouracil, cisplatin, cytarabine.

C. *Intraperitoneal chemotherapy*

Intraperitoneal chemotherapy (CIP) is a way to obtain an increased concentration of cytotoxic substances in direct contact with the peritoneal serosa, which has a low clearance to the systemic circulation. The cytostatics used are cisplatin (most commonly), 5-fluorouracil, paclitaxel, thiotepa, mitoxantron. Their effectiveness is increased when the peritoneal lesions are small (diameter <1cm).

D. *Intra-arterial chemotherapy*

It consists of the administration of chemotherapeutics directly into the nutrient circulation of the tumor, after the introduction of an intra-arterial catheter (CIA). This method allows to increase the intratumoral concentration of cytotoxic products and minimal systemic exposure to side effects. The most common neoplastic locations in which the CIA is used are:

- liver metastases (colon cancers): infusions of 5-fluorouracil or floxuridine (FUDR);
- primitive liver tumors: chemoembolization with doxorubicin and lipiodol;

Oral chemotherapy aims to achieve a longer duration of exposure to the drug and is a convenient way of administration in outpatient conditions to those with impaired biological status. Among the most commonly used oral cytostatics are: capecitabine, UFT, vinorelbine, temozolomide, etoposide, hexamethylmelamine, lomustin (CCNU), procarbazine.

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HORMONAL THERAPY OF CANCER

Hormone therapy is the treatment of hormone-dependent (hormone-sensitive) cancers by suppressing hormone sources or by blocking their action at the cellular level.

Hormones and cellular antagonists are active anticancer agents that include steroid derivatives (estrogens, progestins, androgens, corticosteroids and their derivatives), synthetic non-steroidal compounds with steroid activity or steroid antagonists, aromatase inhibitors, hypothalamic-pituitary analogues and hormones.

Hormones can generally be classified into two broad groups:

a) *Non-steroids* (amino acids, peptides and polypeptides) that usually act on membrane-located cellular receptors (because they are water-soluble and cannot penetrate intracellularly) that activate the second molecular messenger such as cyclic-adenoside monophosphate (cAMP) or to mediate their action. Examples: thyroid hormones, epinephrine, oxytocin.

b) *Steroids* that bind directly to intracellular receptors to mediate their action.

I. Principles of hormone therapy

Reducing or blocking the action of hormones or their binding to the specific cellular receptor results in inhibition of cell proliferation and / or promotion of programmed cell death (apoptosis).

Hormone therapies can be additive or suppressive (ablative, hormone-depriving); hormone suppression can be achieved by surgical castration (ovarectomy / orchiectomy), drug castration or radiation therapy.

Classification of anticancer hormone therapy agents by mechanism of action.

I. Hormone suppressive therapy
- surgical, radiological ovarectomy
- orchiectomy

II. Hormone additive therapy

a. competitive:

- selective estrogen receptor modulators: tamoxifen, raloxifene, toremifene
- androgen receptor inhibitors: bicalutamide, enzalutamide, flutamide, nilutamide
- estrogen receptor antagonists: fulvestrant
- antiandrogens: fluoxymesterone
- estrogen: diethylstilbestrol
- androgens: testosterone propionate
- progestins: medroxyprogesterone acetate, megestrol acetate

b. privative:

- LHRH agonists: goserelin, leuprolide, triptorelin
- GnRH receptor antagonists: degarelix
- aromatase inhibitors: letrozole, aminoglutethimide, anastrazole
- androgen biosynthesis inhibitor: abiraterone acetate.

III. Repressive hormone therapy

- thyroid hormones: levothyroxine, lyothyronine
- somatostatin hormones

somatostatin analogs: octreotide acetate, octrotide LAR

- corticosteroids: dexamethasone, prednisone.

A. Suppressive hormone therapy (ablative)

Ablative hormone therapy involves the suppression of the main source of hormones (ovary, testis) by surgery or radiation therapy. Decreasing the amount of estrogen in the bloodstream can be performed surgically by ovariectomy (laparoscopic or laparotomy), immediately and safely reducing the level of circulating estrogen in 100% of patients.

Additive hormone therapy

Additive hormone therapy involves the use of exogenous sex hormones and their synthetic derivatives or non-steroidal compounds with *competitive* or *deprivation* antagonizing effect.

Competitive hormone therapy

Competitive hormone therapy is performed with compounds that have an increased affinity for hormone receptors and is substituted for the respective hormones, causing the inhibition of the corresponding pituitary tropic hormones.

Selective modulators of estrogen receptors (antiestrogens)

Antiestrogens (tamoxifen, toremifene, raloxifene, fulvestrant) are

substances that can inhibit cell proliferation by blocking ER-mediated tumor growth or blocking growth mediated by tumor growth factors (antiangiogenic and apoptotic).

Selective estrogen receptor modulators (SERMs) bind to cytoplasmic and nuclear high-affinity receptors and then recruit co-activating and co-repressor factors of the transcription complex to bind to the estrogen response elements in the nucleus in the promoter region of estrogen-regulated genes affecting cell growth.

Tamoxifen, the best known SERM, acts as a receptor blocker in the mammary glandular tissue but as an agonist in the uterus and liver. As a result, tamoxifen is a highly effective antiestrogen in breast cancer that expresses ER but has the disadvantage of increasing endometrial proliferation and the risk of uterine cancer.

Tamoxifen continues to be an important hormonal treatment for the prevention and treatment of breast cancer.

Tamoxifen is used in the first line of treatment in patients with breast cancer with ER + and PgR +, causing response rates of 60-70%. Adjuvant treatment with Tamoxifen for a period of 5 years is associated with a reduction in the annual mortality rate of 34.0%, with an absolute decrease in mortality of 9.2% at 15 years after diagnosis. Its administration (especially for more than 5 years) was incriminated in the development of secondary endometrial adenocarcinomas and venous thrombosis.

Side effects are divided into vasomotor symptoms (hot flashes, cold sweats, night sweats, insomnia), neuro-psychic symptoms (headache, vertigo), gastrointestinal symptoms (weight gain, diarrhea, nausea), gynecological symptoms, vaginal bleeding vaginal dryness, decreased libido), musculoskeletal symptoms (osteoporosis, myalgias, arthralgias) and cognitive impairment. These side effects occur in up to 50.0% of patients.

The second generation of antiestrogens is represented by toremifene (Fareston®), raloxifene, fulvestrant (Faslodex®), etc.

Toremifene has an increased affinity for ER, but also cytostatic effects on ER cells. The side effects are similar to tamoxifen, minus the risk of uterine carcinogenesis. Adjuvant tamoxifen reduced the rate of distant recurrences by approximately 41% and the death rate by 34%.

Fulvestrant is a pure antagonist, which has a 100-fold higher affinity for ER than tamoxifen, which completely inhibits ER expression, causing

both blocking and accelerating their degradation and loss in the cell.

Antiandrogens

Antiandrogens are used in the treatment of metastatic prostate cancer, with minimal side effects: gynecomastia, diarrhea, reversible liver toxicity. They are divided into two main categories: *steroids* and *non-steroids* ("pure").

- *Steroid antiandrogens* (**cyproterone acetate** [Androcur®]) suppress gonadotropins by feedback and lower testosterone levels and are also strong inhibitors of nuclear androgen attachment.
- *Non-steroidal antiandrogens* (**flutamide, bicalutamide** [Casodex®]) are progestational compounds that exert dual effects: blocking the cytosolic androgen receptor.

Enzalutamide is a new non-steroidal antiandrogen. Enzalutamide binds 7 times higher to the androgen receptor than the antiandrogens bicalutamide and flutamide. This new inhibitor blocks the nuclear transcription of AR, negatively influences the binding of AR to androgen response DNA elements, and blocks the recruitment of co-activators (3).

Estrogens

Estrogens have long been used in the treatment of metastatic breast cancer in postmenopausal women (diethylstilbestrol [DES], estradiol, chlorotrianisen [Tace®]), and in metastatic prostate cancers (chlorotrianisen, polyestradiol [Estradurin®], Estramustin [Estracyt® , combination of estrogen with alkylant]). Their use is currently restricted, primarily due to cardiovascular side effects.

Progestins

Progestin exerts an indirect action (inhibition of pituitary gonadotrophin prohormones) and a direct action (inhibition of cell proliferation) on the hypothalamic-pituitary axis. They have shown important activity in breast (lines II and III treatment) and endometrial cancers (5) and also have some results in ovarian and prostate tumors; have been used, but with modest response rates (16%), in the treatment of metastatic renal cancer. The usual preparations are medroxyprogesterone acetate (Farlutal®, Provera®) and megestrol acetate (Megace®).

Androgens

The mechanism by which high doses of androgens inhibit breast cancer is unknown, although experimental and clinical evidence shows inhibition of pituitary gonadotrophin hormones and increased estrogen production,

as well as blocking ER (but at 1000 times higher concentrations than estrogen). Available agents are testosterone propionate (Testosterone®), methyltestosterone (Oreton®), fluoxymesterone (Halotestin®).

Deprivation hormone therapy

Deprivation hormone therapy blocks hormone sources by suppressing pituitary stimuli (GnRH analogues) or by blocking adrenal hormone synthesis (aromatase inhibitors). It is considered that there are four mechanisms of action of GnRH analogues on ovarian function:

1) the hypoestrogenic state induced by GnRH analogues decreases blood perfusion in the ovaries;
2) the hypogonadotropic environment induced by GnRH analogues decreases the number of primordial follicles;
3) reduction of ovarian cell apoptosis by activating GnRH receptors;
4) protective effect of GnRH analogues on ovarian stem cells.

Pituitary and gonadal function inhibitors (GnRH analogues / GnRH antagonists)

GnRH analogues (practically LH-RH) cause a form of chemical castration, which can be reversible if applied for a limited period of time (usually less than one year) (6). Indications for GnRH analogues are advanced prostate cancer and advanced breast cancer in premenopausal women. Available LH-RH analogues are: Lucrin Depot 3.75 mg (active substance - leuprorelin) with intramuscular administration once every 28 days for 2 years; Dipheriline 3.75 mg (active substance - triptorelin) with intramuscular administration once every 28 days for a period of 2 years; Zoladex 3.6 mg (active substance - goserelin acetate) administered subcutaneously to the anterior abdominal wall every 28 days for a period of 2 years; 10.8 mg subcutaneously every 12 weeks.

GnRH receptor antagonists: **degarelix** have the advantage of inhibiting the hypothalamic-pituitary axis without the occurrence of the "flare-up" phenomenon.

Adrenal inhibitors and aromatase inhibition

Circulating androgens secreted by the adrenal glands are converted to estrogen under the action of the enzyme aromatase, which is found not only in the adrenal glands, but also in other tissues (ovary, mammary gland, muscle, adipose tissue). Aromatase inhibitors (AIs) can be steroids or non-steroids; causes a chemical adrenalectomy and, at the same time, blocks the peripheral aromatization of estrogen.

Non-steroidal AIs of I generation (aminoglutethimide) block the conversion of cholesterol to δ5-pregnenolone (an early stage in adrenal steroidogenesis) by competitively inhibiting cytochrome P450, affecting the production of aldosterone, cortisol and androgens; it also blocks the aromatization of androgens to estrogen. It is used as a second-line hormone treatment in metastatic (especially bone) breast cancers; should be given in combination with hydrocortisone and electrolyte monitoring is required.

Non-steroidal AIs of generation II (fadrazole) and **generation III** (anastrazole, letrozole) operate a more selective inhibition of aromatase and do not require concomitant administration of hydrocortisone.

Generation II (formestan) and **generation III** (exemestane) steroids cause skin rash, drowsiness, dizziness, ataxia, leukopenia, fever.

Repressive hormone therapy

Thyroid hormones

It is administered after thyroidectomy for thyroid carcinoma, in order to inhibit pituitary secretion of TSH (which is a growth factor for thyroid carcinomas) and also for substitution purposes (7).

Somatostatin analogues

Somatostatin analogues (octreotide, lanreotide, pasitreotide) are used in the treatment of neuroendocrine tumors (based on the identification of somatostatin receptors in 80-90% of them), especially those manifested by carcinoid syndrome; is the treatment of choice for patients with carcinoid tumors (8).

Corticosteroid therapy

Corticosteroids have multiple indications in oncology, such as:

- inclusion in cytostatic treatment protocols in leukemias and lymphomas (lympholytic effect)
- palliation of paraneoplastic febrile syndromes (anti-inflammatory effect)
- palliation of brain metastases and superior vena cava compression syndrome (antiedematous and analgesic effect)
- improvement of neoplastic and paraneoplastic hypercalcemia (bone metastases)
- prevention and treatment of nausea and vomiting (antiemetic or potentiating effect of antiemetic medication)
- supportive treatment (anabolic effect)

Hormone resistance

One of the major obstacles to the effectiveness of hormone therapy is the phenomenon of hormone resistance. Resistance to hormone therapies

is of 2 types: de novo / intrinsic hormone resistance and acquired hormone resistance. Hormone resistance means no response to an initial hormone therapy, disease progression after hormone treatment, or disease progression after an initial response.

Primary resistance mechanisms:

- Mutations in tumor-independent tumor proliferation pathways with or without loss of hormone receptors
- The hormone-dependent pathway exists but is unresponsive to treatment due to mutations in the receptors
- Stimulation of tumor growth by other hormone-independent signaling pathways.

Mechanisms of acquired resistance:

- Clonal selection
- Increasing the production of hormone receptors
- Increasing the affinity of the hormone receptor
- Alteration of hormone-receptor interactions
- Induction of metabolic enzymes that reduce the intracellular level of antagonist hormone.

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CERVICAL CANCER

Cervical cancer is becoming more and more common among women around the world, although it is one of the most preventable malignancies.

As early as 450 BC Hippocrates made a reserved prognosis of cervical cancer. By the time of the Renaissance, there were low references to cervical cancer. John Clarke (1812) stated the vegetative form of cervical cancer, Rudolf Virchow, R. Hooper (1832), and J.H. Bennet (1845) described the benign and malignant cervical lesions. E. Wertheim (1898) developed a surgical technique named after him. In 1925, Von Hinselmann first described colposcopy, and in 1943 Papanicolaou and Traut introduced exfoliative cytology.

Despite important advances in the prevention, diagnosis and treatment of cervical cancer worldwide, it is currently the fourth most common malignancy in women. There are 530,000 new cases annually with 270,000 deaths worldwide. There are about 85% of deaths caused by cervical cancer worldwide in underdeveloped or developing countries, and the death rate is 18 times higher in low-income and middle-income countries compared to highly developed countries. The highest incidence is recorded in Central and South America, the Caribbean, Sub-Saharan Africa and South Asia.

The incidence of cervical cancer in the Republic of Moldova reached 17.1% 000 in 2019, while the mortality rate was 8.7% 000, accounting for 160 deaths.

Cervical cancer usually develops in middle age and is most commonly diagnosed in women between 35 and 44 years. It rarely develops in women under 20 years and is detected only in 15% of women over 65 years.

Etiopathogenesis

Numerous studies on the epidemiology of cervical cancer have shown direct associations with religious, marital, and sexual patterns. It is well established that women with multiple sexual partners and young age (up to 16 years) at first sexual contact are at high risk, supporting the hypothesis about a vulnerable period of the cervix and the need for repeated exposure to an infectious agent.

Harald zur Hausen, a German scientist, established the correlation between HPV and cervical cancer, for which he received the Nobel Prize

in Medicine in 2008. This is a great achievement of modern medicine. Most cases of cervical cancer result from human papillomavirus infection (HPV), which is part of the Papovaviridae family (figure 2). The HPV infection is transmitted by direct and sexual contact (traditional or non-traditional) in the case of the cervix or by skin and / or mucous membrane contact, being considered the most common sexually transmitted infection in most people.

There are more than 100 known HPV genotypes. Depending on the oncogenic risk, the HPV types can be divided into low oncogenic risk and high oncogenic risk groups. The association between certain (high-risk) oncogenic strains of HPV and cervical cancer is well established. The most common types of HPV involved in the development of cervical cancer in a decreasing prevalence are such as HPV 16, 18, 45, 31, 33, 58, 52, 35, 59, 56, 6, 51, 68, 39, 82, 73, 66 and 70 (figure 3).

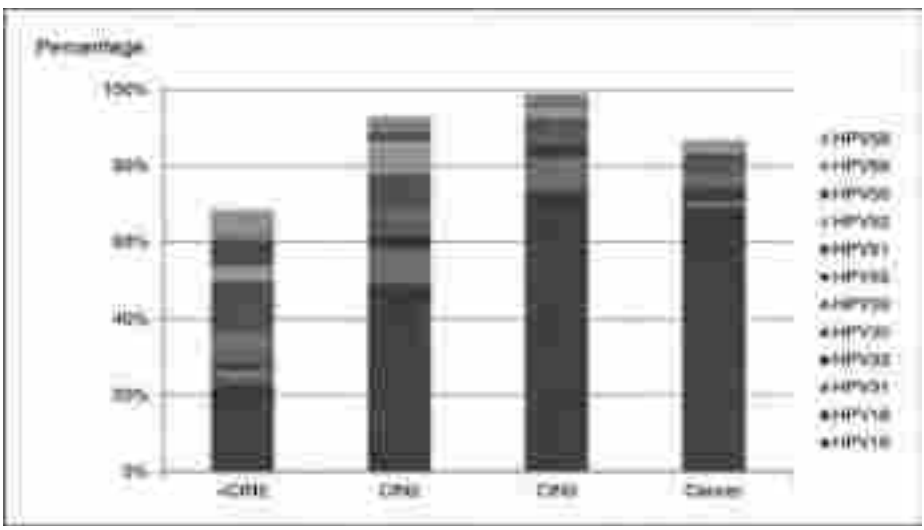


Figure 1. *HPV types and associated risk*

Among high-risk types, HPV 16 and 18 are the most common, causing about 70% of cervical cancer worldwide. About 80% of HPV infections are transient and can cease spontaneously without developing dysplasia. However, in a significant minority of cases, the infection becomes persistent.

Other risk factors for cervical cancer are:

- Socio-economic factors. Socially vulnerable women and the lack of health insurance.

- Smoking. Women with a long history of cigarette smoking. In 1977, Winkelstein reported the correlation between smoking and cervical cancer.
- Diet. Numerous studies have shown the protective role of vitamin C against cervical cancer (Romney and Basu-1985). Marschall et al. highlighted the protective role of beta-carotene. Other researchers have found reverse associations between blood retinol levels and cervical cancer. The protective effect of folic acid against cervical cancer has also been established.
- Weight. Overweight women are more likely to develop cervical adenocarcinoma.
- Age. Most epidemiological studies report unanimous views on a high incidence of cervical cancer in age groups 20-29 years, with the peak incidence between 45 and 54 years, after which it decreases slightly.
- Weakened immune system.
- Administration of immunosuppressants.
- Use of oral contraceptives (birth control pills) for over 5 years.
- Multiparity - three or more full-term gestations.
- Age under 17 years at first full-term pregnancy.
- Chlamydia trachomatis infection.
- Family history of cervical cancer.
- Sexual history of the male partner. Male promiscuity has been associated with cervical carcinogenesis.

Precancerous conditions

Precancerous cervical changes are quite common. Cervical dysplasia can occur in 1 to 5% of women in the general population. It is estimated that approximately 69,000 new cases of mild dysplasia and 15,000 cases of moderate and severe dysplasia occur in Europe each year.

Dysplasia is an acquired abnormality of the malpighian epithelium and an increased number of basal cells. Moderate and severe disturbances of cell differentiation and maturation are associated with more or less marked nuclear atypia.

They can be reversible for a long time, but are potentially malignant, describing several degrees of dysplasia - Mild (CIN I), Moderate (CIN II) and Severe (CIN III).

If left untreated, CIN2 or CIN3 (collectively referred to as CIN2 +) can progress to cervical cancer. Precancerous changes of the cervix usually do not cause any pain or symptoms. They can be detected by pelvic exam or Pap test.

Atypical squamous cells:

- Low-grade squamous intraepithelial lesion - LSIL.
- High-grade squamous intraepithelial lesion (moderate or severe dysplasia) - HSIL.

Atypical glandular cells:

- AGC-NOS (atypical glandular cells not otherwise specified).
- AGC-FN (atypical glandular cells - favor neoplasia).
- AIS - adenocarcinoma in situ, cancer in situ (non-invasive cancer, stage 0 cancer) derived from endocervical or endometrial glandular cells.

Table 1. Correlation between cytological versus histological investigations

Natural history model	Histology			Cytology	
	Dysplasia nomenclature	CIN nomenclature	LAST nomenclature	Papanicolaou classification	The Bethesda system
				I	NILM
				II	ASC-US
Infection					
		CIN1	LSIL	III	LSIL
Persistence		CIN2	HSIL		HSIL
		CIN3		IV	
Cancer	Carcinoma	Carcinoma		V	Carcinoma

Atypical leukoplakia (from Greek λευκός - "white" and πλάξ - "patch") is an area of keratinized and thickened epithelium of the cervix of varying severity (such as hyperkeratosis, parakeratosis, acanthosis) that is associated with an increased risk of malignant transformation of ***the cervical epithelium.***

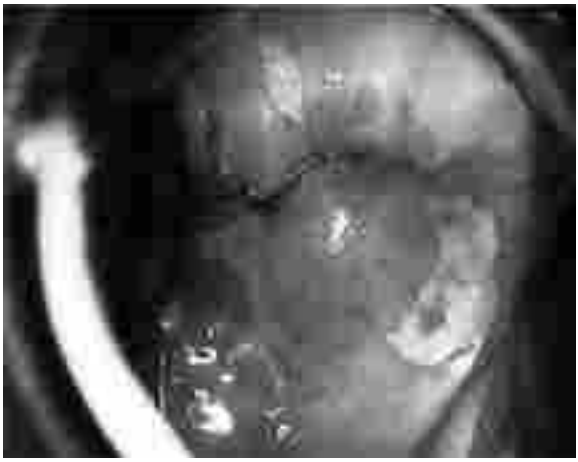


Figure 3. *Leukoplakia with atypia*

Erythroplakia - is characterized by atrophy of the superficial epithelial layer of the cervix.

From Greek, the term means "red patch". It can develop both in women of childbearing age and during menopause or postmenopause.

Figure 4. *Erythroplakia*

Embryological, histological and anatomical-functional features of the cervix

Prior to examining cervical neoplasia, it is necessary, both clinically and surgically, to study the notions of embryology, anatomy, physiology and histology of the female genital organs, especially the cervix. The development of the external genital organs involves the undifferentiated stage and, after the third month of embryonic development, the stage of

sexual differentiation ensues. In some cases, this migration is incomplete and causes the squamous-columnar junction to locate in the upper part of the vagina.

The cervix continues into the uterine body and the isthmus in the lower part of it. It is cylindrical in shape like a barrel and has an average length of 3 cm. The insertion of the upper extremity of the vagina at the level of the cervix bounds three parts, namely the supravaginal, vaginal and intravaginal. The cervical canal is inside the cervix, being bounded below by the external cervical orifice, which connects with the vaginal cavity, and above by the internal cervical orifice, which continues into the uterine cavity. Histologically, the cervix is made up of muscle fibers originating from the fibers of the outer and inner layers of the myometrium and elastic fibers, and is lined with glandular and squamous epithelium. The lining of the cervix covers both the endocervix and the exocervix. The endocervical mucosa consists of simple columnar epithelium, while the cells contain a clear cytoplasm with vacuoles of mucus and basal oval nucleus. Within the exocervix, the columnar epithelium of the mucosa continues, **without any transition**, with a non-keratinized stratified squamous epithelium.

The epithelium may show some changes depending on the woman's age and physiological condition. **At this level** there are no glands, and the musculoelastic arranged in three layers forms the external cervical orifice. The squamous-columnar junction of the cervix defines the boundary between the stratified squamous epithelium and the secretory columnar epithelium within the endocervix. The arterial blood is supplied to the cervix by the descending branches of the uterine artery, the cervico-vaginal artery as well as multiple branches with a sinuous trajectory originating at its level.

The lymphatic drainage of the cervix involves rich plexuses that merge into 3 pedicles:

- preurethral;
- retrouretral;
- posterior.

Nerve supply to the cervix is via both sympathetic and parasympathetic vegetative branches originating in the terminal part of the presacral plexus (Frankenhauser), which are responsible for innervating the deep areas of the endocervix and exocervix.

Diagnosis of cervical cancer

Clinical and anamnestic diagnosis

Cervical cancer is a "silent" disease, as early stages of the disease are completely asymptomatic. Clinical manifestations occur only after precancerous changes become malignant and invade adjacent tissues. Given that, the most common symptom triad can be determined:

A. Bleeding which occurs during the menstrual flow, becoming much more abundant (menometrorrhagia) in the interval between two menstruations, after a sexual contact or pelvic exam. Postmenopausal bleeding can also be a symptom of cervical cancer.

B. Leukorrhea - abnormal vaginal discharge present in large quantities and sometimes mixed with fine streaks of blood, is a common symptom in many gynecological conditions, being abundant premenstrually, clear out of an infection.

C. Pain in the lumbar region and during sexual intercourse **(**dyspareunia**).**

Advanced cervical cancer has the following symptoms:

- anemia due to abnormal blood loss;
- pelvic pain, lower limb pain and edema;
- frequent urination;
- painful urination;
- constipation;
- marked weight loss.

Most women with dysplasia or pre-invasive cancer do not have any clinical manifestations, so screening tests are very important.

Physical examination

The cervix is an organ which can be easily examined both clinically and paraclinically, through a gynecological exam using the following methods:

- speculum examination of the cervix;
- bimanual examination of the internal genital organs (pelvic exam);
- rectal examination of the internal genital organs and rectovaginal septum may reveal other pelvic metastases and / or cervical tumor growing into the intestine;
- physical examination may detect edema of the legs (due to impaired parameters), hepatomegaly (liver metastases), pleural exudate (lung metastases);
- palpation of the inguinal supra- and subclavicular lymph nodes.

Paraclinical and laboratory investigations

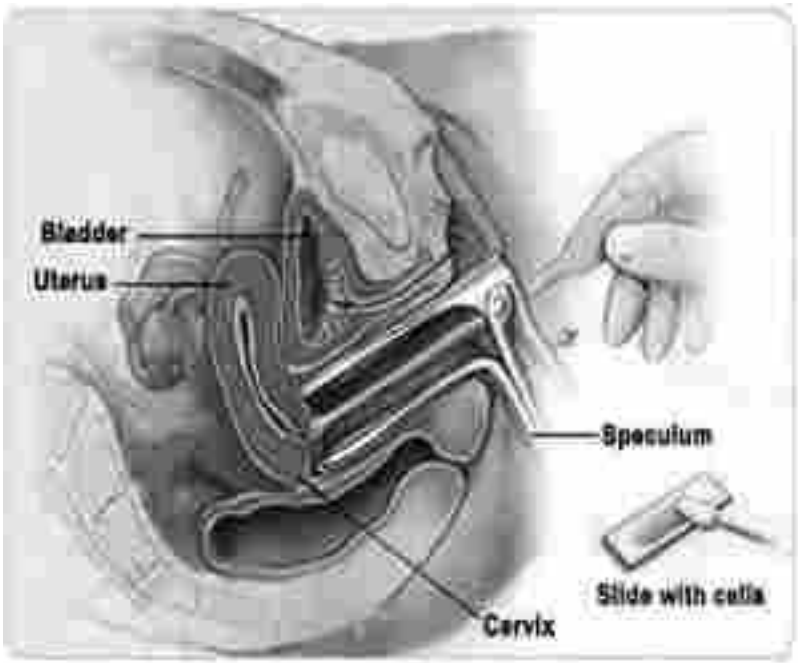


Figure 5. Pap test

Sampling the cytological exo- and endocervix smear. The Pap test (Papanicolau smear or cytological examination) was introduced in 1943 to detect abnormal cells in the cervix and is most often used in screening for cervical cancer.

There are three techniques for harvesting cervical material: cervical brushing, using a spatula or combining the spatula with the endocervical brush.

Viral genotyping by HPV DNA testing. Targeted DNA amplification by PCR technique and nucleic acid hybridization for individual qualitative HPV detection (genotyping) in cervical cells collected in the liquid medium.

The purpose of the test is to select patients positive for HPV 16 or 18 who should be referred immediately for colposcopy, and negative patients should be subjected to repeated cytology and HPV DNA-detection for oncogenic types over 12 months.

Colposcopy is a method of investigating not only the cervix, but also

the vagina and vulva, its effectiveness being unanimously recognized in the examination of neoplastic disease (Figure 13). During colposcopy, an instrument called colposcope is used, which is an optical device consisting of a light source and a magnifying glass that enlarges the image 2 to 60 times, allowing it to detect abnormalities that would not have been detected with the naked eye. At the first stage (simple direct colposcopy) the colposcope is positioned at the entrance to the vagina, without the device touching the patient's body; the surface of the vaginal mucosa and the cervix being examined without any prior preparation. At the second stage, it will be examined after applying acetic acid to the surface, thus any premalignant lesion should appear "acetowhite". The last step (Lahm-Schiller test) involves examination of the cervix and vagina after applying Lugol's solution to the cervix and vagina, which causes a dark brown homogeneous staining of the normal epithelium (Figure 14, 15).

There are other methods of tissue sampling:

• *Endocervical curettage*

• *Diagnostic conization*

Cytological and histological examination of the samples obtained. Histopathological examination is the gold standard for diagnosing neoplastic disease and precursor lesions (figure 16). Tissue biopsy can be taken (either by colposcopy or not), by endocervical curettage, after excising a portion of the cervix (conization, amputation of the cervix, loop electrosurgical excision procedure) or after total hysterectomy.

A minimal assessment of blood, liver and kidneys of patients with cervical cancer is indicated, namely complete blood count, blood biochemical test (glucose, urea, creatinine, bilirubin, ALT, ASAT, amylase, total protein) and urinalysis.

Genomic profiling of cervical tumors is a new era in the implementation of genomic medicine to detect actionable mechanical mutations. The most common finding is the determination of phosphatidylinositide 3-kinase (PI3K) abnormalities, PIK3CA and KRAS mutations in 17.5% of adenocarcinomas, but none of squamous cell carcinomas, thus suggesting that these tumor subtypes require different types of targeted therapies.

New somatic mutations have been identified in profiled squamous cell carcinoma, including E322K substitutions in the MAPK1 gene, inactivated HLA-B gene mutations, and EP300, FBXW7, TP53, and ERBB2

mutations. Somatic ELF3 and CBFB mutations have been determined in cervical adenocarcinoma.

Tumor extension can be investigated by the following methods:

- chest X-ray;
- ultrasound of the abdominal cavity, especially the retroperitoneal space;
- pelvic USG ;
- nuclear magnetic resonance;
- contrast-enhanced computed tomography;
- positron emission tomography (PET/CT);

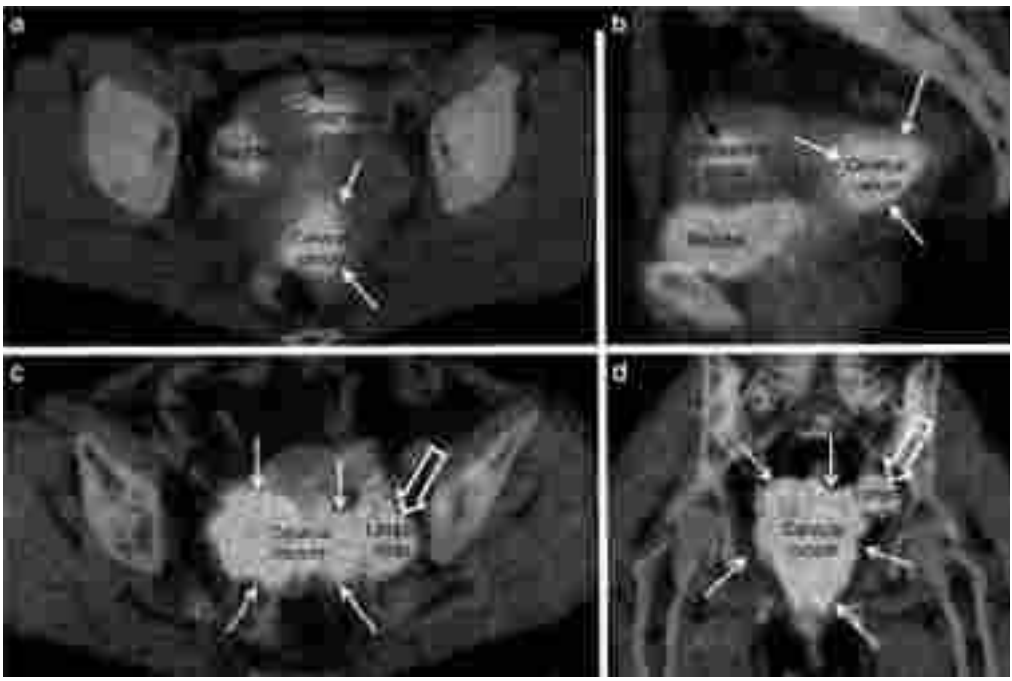
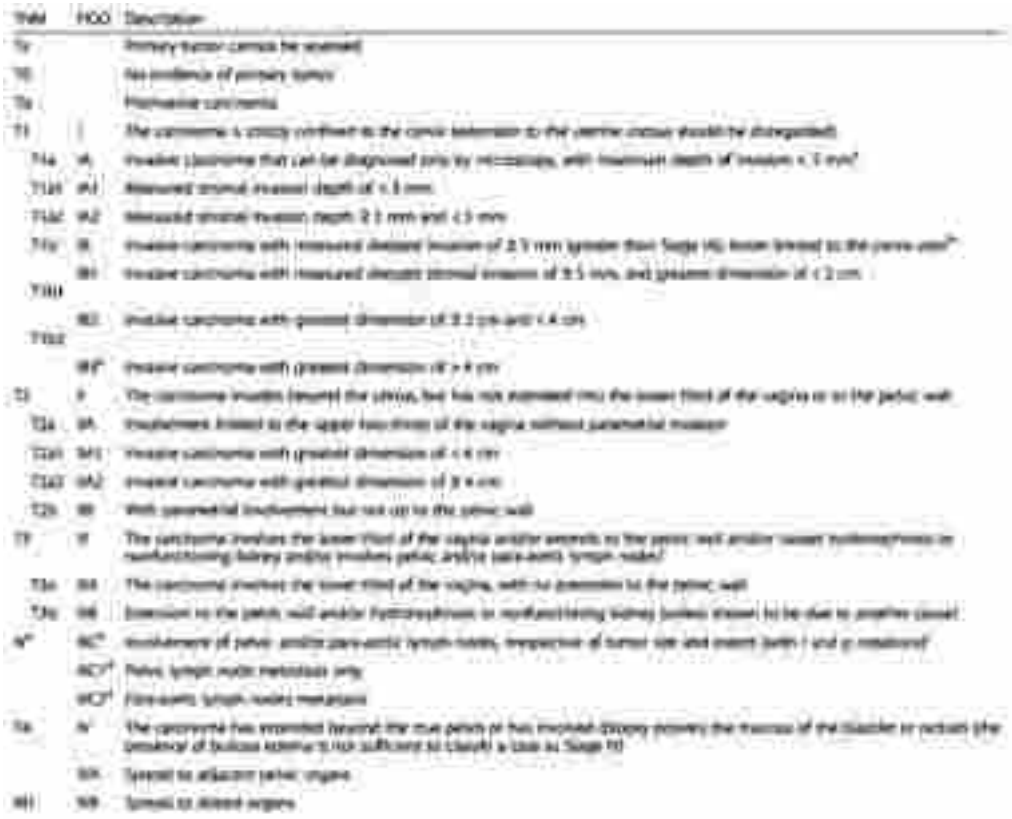


Figure 6. *FDG PET-CT in a 41-year-old woman with squamous cell carcinoma, clinical FIGO stage 1B1 cervical cancer (a, b; same patient as in Fig. 1f, g and Fig. 2), and a 70-year-old woman with squamous cell carcinoma, clinical FIGO stage 3B cervical cancer (c, d). The primary cervical cancer lesions are typically highly FDG-avid (white arrows).*

- intravenous urography;
- cystoscopy;
- rectoromanoscopy and colonoscopy.

TNM / FIGO Staging for Cervical Cancer, AJCC, 8th Edition



WHO histological classification of tumors of the uterine cervix

- **epithelial tumors**
  - **squamous tumors and precursors**
    - squamous cell carcinoma, not otherwise specified - 8070/3
    - keratinizing - 8071/3
    - non-keratinizing - 8072/3
    - basaloid - 8083/3
    - verrucous - 8051/3
    - warty - 8051/3
    - papillary - 8052/3
    - lymphoepithelioma-like - 8082/3
    - squamotransitional carcinoma of cervix - 8120/3
    - early invasive (microinvasive) squamous cell carcinoma - 8076/3

- squamous intraepithelial neoplasia of cervix
- cervical intraepithelial neoplasia (CIN 3) - 8077/2
- cervical squamous cell carcinoma in situ - 8070/2
- benign squamous cell lesions
- condyloma acuminatum
- squamous papilloma of cervix - 8052/0
- cervical fibroepithelial polyp

- **glandular tumors and precursors**
  - adenocarcinoma of cervix - 8140/3
  - mucinous adenocarcinoma of cervix - 8480/3
  - endocervical - 8482/3
  - intestinal - 8144/3
  - signet-ring cell - 8490/3
  - minimal deviation - 8480/3
  - villoglandular - 8262/3
  - endometrioid adenocarcinoma of cervix - 8380/3
  - clear cell adenocarcinoma of cervix - 8310/3
  - serous adenocarcinoma of cervix - 8441/3
  - mesonephric adenocarcinoma of cervix - 9110/3
  - early invasive adenocarcinoma of cervix - 8140/3
  - cervical adenocarcinoma in situ - 8140/2
  - glandular dysplasia
  - benign glandular lesions
  - Müllerian papilloma of cervix - 8560/3
  - endocervical polyp - 8015/3
  - other epithelial tumors - 8015/3
  - adenosquamous carcinoma of cervix
  - glassy cell carcinoma variant of cervix
  - adenoid cystic carcinoma of cervix - 8200/3
  - adenoid basal carcinoma of cervix - 8098/3
  - neuroendocrine tumors
  - carcinoid - primary cervical - 8240/3
  - atypical carcinoid - primary cervical - 8249/3
  - small cell carcinoma of the cervix - 8041/3
  - large cell neuroendocrine carcinoma of cervix - 8013/3
  - undifferentiated carcinoma of cervix - 8020/3

- **mesenchymal tumors and tumor-like conditions**
  - leiomyosarcoma of cervix - 8890/3

- endometrioid stromal sarcoma, low grade - 8931/3
- undifferentiated endocervical sarcoma - 8805/3
- sarcoma botryoides - 8910/3
- alveolar soft part sarcoma of cervix - 9581/3
- cervical angiosarcoma - 9120/3
- malignant peripheral nerve sheath tumor of cervix - 9540/3
- cervical leiomyoma - 8890/0
- genital rhabdomyoma - 8905/0
- postoperative spindle cell nodule - cervix

- **mixed epithelial and mesenchymal tumors**
  - carcinosarcoma of cervix (malignant Müllerian mixed tumor) - 8980/3
  - adenosarcoma of cervix - 8933/3
  - cervical Wilms tumor - 8960/3
  - cervical adenofibroma - 9013/0
  - cervical adenomyoma - 8932/0
- **melanocytic tumors**
  - primary cervical malignant melanoma - 8720/3
  - blue nevus of cervix - 8780/0
- **miscellaneous tumors**
  - tumors of germ cell type
    - yolk sac tumor of cervix - 9071/3
    - dermoid cyst of cervix - 9084/0
    - mature cystic teratoma of cervix - 9080/0
- **lymphoid and haematopoetic**
  - malignant lymphoma - cervical lymphoma (specify type)
  - cervical leukemia (specify type)
- **secondary tumors**

Macroscopic aspects of cervical cancer:

There are three common types of malignant cervical lesions:

1. *Exophytic* (vegetative) lesion. It is found in the exocervical area, forming a large, friable, polypoid mass that presents spontaneous or contact bleeding.
2. *Infiltrative* form of cervical carcinoma. It gives the cervix a "barrel-shaped"appearance. This form is detected late and has an insidious evolution.
3. *Ulcerative* tumor is a lesion that causes erosion of the cervix and upper region of the vagina. The ulcerative lesion of the cervix

presents excavated ulcers with central necrosis and irregular, hard and infiltrated edges.

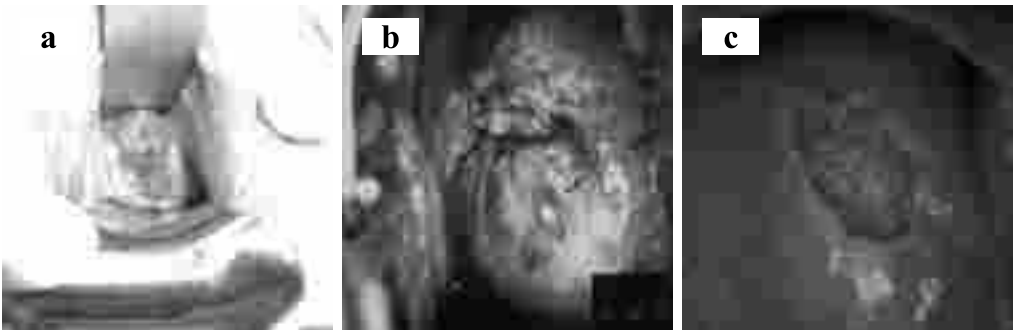


Figure 7. *Macroscopic forms of cervical cancer: a) exophytic; b) infiltrative; c) ulcerative.*

In clinical practice, mixed exophytic-ulcerative forms are also common.

Metastatic pathways

- **Per continuitatem** - in the form of an "oily patch". It most commonly develops by extending to the vaginal mucosa, paracervical tissue, cardinal ligaments, utero-sacral ligaments, paracervical ligaments, and uterine body. Bladder and rectal invasion occurs relatively late.
- **Lymphatic**. Due to a rich lymphatic network of the cervix, early metastasis can occur as the disease evolves. The cervix is supported by the parametric, cardinal, and uterosacral ligaments in the following groups of regional lymph nodes (Table 2, figure 8).

Table 2. Regional lymph nodes of the cervix

I station	*II station*
- Parametrial lymph nodes - Paracervical, urethral lymph nodes - Obturator lymph nodes - Hypogastric lymph nodes (internal iliac) - External iliac lymph nodes - Sacral lymph nodes	- Common iliac lymph nodes - Inguinal lymph nodes - Para-aortic lymph nodes

- **Hematogenous** dissemination is uncommon, but relatively

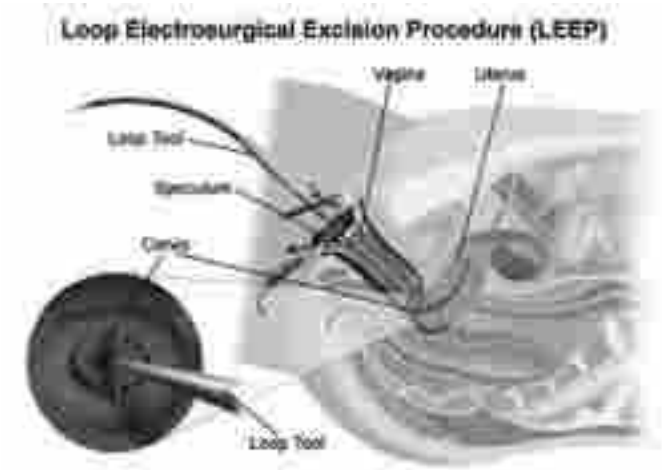
characteristic in the advanced stages. Lungs, bones and liver are the most common places of metastases, while the brain, adrenal glands and pancreas are less common.

Treatment of cervical cancer according to stages

Cervical cancer can be detected in a biopsy taken during colposcopy after obtaining an abnormal PAP-smear. In advanced stages it can be seen with the naked eye when the cervix is examined with the speculum.

After the diagnosis of cervical cancer is established, the stage of the disease is determined according to the degree of invasion in the basement membrane of the cervix or outside it, which will determine the subsequent treatment and prognosis. The therapeutic management depends on the patient's age, the desire to preserve fertility, and tumor aggressiveness.

The correct anatomopathological diagnosis of the horizontal and deep tumor extension, the lymphovascular invasion and the condition of biopsy edges are crucial to establishing the therapeutic strategy.



Treatment of pre-invasive cancer

- Loop electrosurgical excision procedure (LEEP)
- Laser surgery. Conization. Cryodestruction.
- Total hysterectomy with or without salpingo-oophorectomy should be performed in case of multicenter lesions, localization of the process in the cervical canal, association with uterine fibroid or ovarian cyst (when fertility preservation is not desired).

Stage IA1

The risk of metastatic ganglion spread in stage IA1 is less than 1%, while the risk of invasive local recurrence is 2%. A correct anatomopathological diagnosis of horizontal and deep tumor extension, lymphovascular invasion and biopsy status is crucial to establishing the therapeutic strategy.

Treatment includes:

- *without lymphovascular space invasion, when fertility preservation is desired*
  - Conization / Radical trachelectomy (removal of the cervix)
- *without lymphovascular space invasion, when fertility preservation is not desired*
  - Total hysterectomy with or without salpingo-oophorectomy

Bilateral adnexectomy should be performed in the following cases:

- menopausal patients;
- associated adnexal diseases;
- the patient does not want to keep the uterine appendages.
  - Total hysterectomy with or without salpingo-oophorectomy, removal of the pelvic lymph nodes (Wertheim surgery).
  - Radiotherapy.

- *lymphovascular space invasion in patients wishing to preserve fertility* - Trahelectomy + Pelvic lymphadenectomy is indicated, along with sentinel node biopsy.
- *lymphovascular space invasion in patients who do not want to preserve fertility*- hysterectomy with pelvic lymphadenectomy is recommended (sentinel node technique/biopsy can be performed.

Stage IA2

The risk of lymph node metastasis is > 5%,while the risk of local invasive recurrence is 3.6%.

Treatment includes:

- Total hysterectomy with or without salpingo-oophorectomy;
- Total hysterectomy with salpingo-oophorectomy, removal of pelvic lymph nodes ± sentinel node (Wertheim surgery) is the treatment of choice at this stage.
- Conization / Radical trachelectomy (removal of the cervix) + pelvic lymphadenectomy ± sentinel node- when fertility preservation is desired.

Inoperable patients or those who refuse surgery must be referred for radiation therapy. Radiation therapy is an alternative treatment when surgical treatment is not possible.

Stage IB1

In stage IB1, radical hysterectomy with pelvic lymphadenectomy should be performed, the surgery having the advantage of a correct post-surgical staging, which will be reflected in an adequate adjuvant therapy.

Treatment includes:

- Associated radiotherapy is an alternative treatment when surgical treatment can not be applied.
- Radical trachelectomy + pelvic lymphadenectomy, in tumors <2 cm, *when preservation of the reproductive function is desired.*
- Conization ± neoadjuvant chemotherapy, in tumors <2cm, without LVSI.
- Antineoplastic therapy with schemes containing platinum compounds.

Positive pelvic lymph nodes and increased tumor size place the patient in the intermediate risk group. The combination of postoperative radiation therapy results in a significantly high disease-free interval and low mortality.

Stage IB2

Treatment includes:

- Combination treatment - chemotherapy and radiotherapy.
- Total hysterectomy with salpingo-oophorectomy, removal of the pelvic lymph nodes (Wertheim surgery), followed by radiotherapy and chemotherapy.
- Associated radiotherapy and monochemotherapy (if there are no contraindications).

Stage IIA1

Treatment includes:

Combination treatment - radiotherapy and monochemotherapy (unless contraindicated)

Total hysterectomy with salpingo-oophorectomy, removal of the pelvic lymph nodes (Wertheim surgery), followed by radiotherapy and chemotherapy.

Chemotherapy with schemes containing platinum compounds.

Radiation therapy and chemotherapy may have the same cure rate as

primary surgery and may be indicated for inoperable patients or patients who accept radiotherapy rather than surgery.

Stage IIA2

In locally advanced stage IIA2, the multidisciplinary team may opt for:

- chemotherapy (cisplatinum) combined with definitive radiotherapy (external and brachytherapy)

or

- total hysterectomy with salpingo-oophorectomy, removal of the pelvic lymph nodes (Wertheim surgery) with or without para-aortic lymphadenectomy

or

- external beam radiotherapy, radiosensitizing chemotherapy (cisplatinum) and brachytherapy, followed by adjuvant hysterectomy.

Stage IIB

Treatment includes:

- Radiotherapy combined with monochemotherapy (if there are no contraindications).
- Polychemotherapy along with Cisplatin.

Stage IIIA / IIIB

Concomitant radiotherapy (external radiotherapy and utero-vaginal endocavitary brachytherapy, combined with cisplatin-based chemotherapy) is the treatment of choice. Stage III is an advanced stage of the disease, primary surgical treatment being excluded.

Pelvic exenteration may be an option of surgical treatment for stage III. It is an ultra-radical surgical procedure that can be applied to a very small number of patients with recurrent disease after primary therapy of cervical cancer. Rigorous selection of patients is mandatory, without para-aortic lymphadenopathy.

Stage IVA

Concomitant radiotherapy with chemotherapy should be applied, according to the individual treatment plan.

Stage IVB - advanced (metastatic) cancer, being considered incurable.

The pre-therapeutic evaluation (in order to establish the disease extent and comorbidities) and weighing the benefits and risks associated

with any therapeutic strategy chosen by the multidisciplinary board are recommended. Platinum salts-based chemotherapy, whether or not combined with anti-angiogenic therapy (Bevacizumab), is the treatment of choice at this stage.

Palliative radiotherapy for primary tumor or distant metastases (bone, brain, etc.) or radiochemotherapy should be used in some selected cases. In stage IVB, the treatment aims, in most cases, only to improve the quality of life, without ruling out the likelihood of survival increase.

Cervical cancer prevention

Due to the discovery of the HPV infection as the main cause of cervical cancer and the development of prophylactic vaccination in the 1990s, there are now ways to take a more comprehensive approach to prevention via prophylactic vaccination. Vaccination can be considered as a primary prevention, screening being rarely a secondary prevention.

The concept behind prophylactic vaccination is to get high levels of specific HPV neutralizing antibodies that are able to prevent cervical infections. The discovery that led to the development of vaccines is that the major capital HPV protein, L1, could self-assemble into so-called virus-like particles, which have proved to be extremely immunogenic.

Two vaccines were produced, both based on virus-like particles obtained from HPV types 16 and 18, each having a different adjuvant. One was bivalent (types 16 and 18) and the other vaccine was quadrivalent to include the types responsible for genital warts (types 6 and 11).

Both vaccines had a high efficacy (> 95%) in the prevention of HPV infection and similar efficacy in the prevention of cervical intraepithelial neoplasia, as well as vaginal and vulvar lesions. However, research data have shown that vaccines are ineffective in women with an established HPV infection. Most developed countries have introduced vaccination programs for prepubescent girls and there has been early evidence of a public health benefit, with a low incidence of high-risk infections, cervical abnormalities and even genital warts in unvaccinated men.

Recent achievements in prophylactic vaccination. An achievement in this regard has been the production of a nonavalent vaccine that adds types 31, 33, 45, 52 and 58 to the vaccine containing types 6, 11, 16 and 18. The nonavalent vaccine has been approved in some countries, including the United States and United Kingdom and may well replace bivalent and

quadrivalent vaccines in the next few years. Prophylactic vaccination can save hundreds of thousands of lives, but it requires some state policies to ensure the implementation of vaccination programs in resource-poor countries.

Cervical cancer screening

Cervical cancer screening programs aim to detect precursor or invasive cervical lesions in order to perform an effective treatment. Given the fact that cervical cancer develops slowly in the form of precancerous lesions, their detection and treatment is an extremely effective measure to prevent invasive cervical cancer.

All women aged between 25 and 61 years not subjected to a Pap test over the last 3 years should undergo cervical screening.

Prognosis

The physician's prognosis of the patient's illness is based on the data obtained. The prognosis of cervical cancer is closely correlated with the disease extension upon diagnosis. The main prognostic factors are:

- tumor stage and volume;
- pelvic and para-aortic lymph node invasion;
- histological type and degree of malignancy;
- vascular and lymphatic invasion.

The chances of five-year rate survival, after the diagnosis of cervical cancer has been established, are as follows:

- stage I - 80-99%
- stage II - 60-90%
- stage III - 30-50%
- stage IV - 20%.

In about 80% of cases, cervical cancer recurs in the first 2 years after diagnosis. There are unfavorable prognostic factors, such as involvement of the lymph nodes, deep stromal cervical invasion, large tumor diameter and volume, marked parametrial extension, undifferentiated squamous or non-squamous histological type.

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ENDOMETRIAL CANCER

The endometrium is a type of tissue with an exceptionally dynamic potential, being under the hormonal influence of the hypothalamic - pituitary - ovarian axis. Apart from its complex physiology, the endometrium can be the site of various diseases, of which malignant neoplasm is one of the most common.

The first account of endometrial conditions originated in India, ancient Egypt, and Greece. Ambroise Parré (1510-1590) made significant references to the assessment of uterine diseases. In 1973, Matthew Baillie described endometrial cancer in detail.

Epidemiological features

Endometrial cancer is ranked sixth among women and fifteenth among the general population in the structure of global cancer morbidity. The global incidence of endometrial neoplasm in 2018 accounted for over 380,000 cases.

The highest incidence of 24.9 cases per 100,000 population was recorded in Belarus, in 2018, while the lowest rate was recorded in Puerto Rico with 17.4 cases per 100,000 population.

Although endometrial cancer generally develops in menopausal women aged 45 years or older, 30% of women with endometrial cancer are under 40 years. In the Republic of Moldova, according to the National Cancer Registry, the incidence of uterine cancer (including uterine sarcoma) in 2018 was 19.6% ooo, and the mortality rate made up 6.7% ooo.

Etiopathogenesis

The growing incidence of endometrial cancer worldwide is mainly due to an increase in the average life expectancy of the female population, given that the highest incidence of endometrial cancer targets the age group 61-70 years, as well as some risk factors such as the use of unantagonized estrogen_as a replacement therapy in menopausal women and a high incidence of obesity, which tends to become “epidemic”, diabetes, high blood pressure, and improved methods of investigation.

Factors that increase the risk of endometrial cancer include:

• ***Obesity*** - Obese women are more likely than normal-weight women to develop endometrial cancer because their body has higher levels of estrogen. The risk of endometrial cancer is higher in women with diabetes and/or high blood pressure, which are common conditions in many obese women. Thus, the carcinogenesis of endometrial carcinoma involves the "triad" of major risks such as obesity, hypertension and diabetes.

• ***Chronic anovulation*** - polycystic ovary syndrome (Stein-Leventhal).

• ***Estrogen therapy*** - women receiving estrogen therapy without gestagenic protection have an increased risk of developing endometrial cancer.

Tamoxifen treatment - women taking tamoxifen to prevent or to treat breast cancer have an increased risk of developing endometrial cancer.

• ***Family history of endometrial cancer***

• ***Genetic factor*** - Lynch syndrome increases the risk of endometrial, ovarian, and intestinal cancer.

• ***Nulliparity*** (a condition in which a woman has never given birth to a child, or has never carried a pregnancy).

• ***History of pelvic radiation therapy.***

Types of endometrial cancer

According to the literature, there are two pathogenic types of endometrial cancer, namely estrogen-dependent and estrogen-independent.

Table 1. Pathogenic types of endometrial cancer

Classification	
TYPE 1	TYPE 2
• Associated hyperestrogenism. • Associated with hyperplasia. • Patients usually peri-menopausal. • Estrogen & progesterone receptors common. • Usually endometrioid & mucinous subtypes. • Favourable prognosis.	• Not related to hyperestrogenism. • Usually atrophic endometrium. • Postmenopausal patients. • Estrogen & progesterone receptors uncommon. • Usually serous or clear cell subtypes. • Aggressive, poor prognosis.

The high cancer risk group of premalignant lesions may be synonymously referred to as either "EIN" or "atypical endometrial hyperplasia," although supportive molecular and clinical literature underlying the two-group classification is predominantly published under EIN.

EIN is a clonal proliferation of architecturally and cytologically altered premalignant endometrial glands, which are prone to malignant transformation to endometrioid (type I) endometrial adenocarcinoma. EIN lesions are noninvasive, genetically altered neoplasms that arise focally and may convert to a malignant phenotype on acquisition of additional genetic damage. Diagnostic criteria for EIN have been developed by histopathologic correlation with clinical outcomes, molecular changes.

The 2014 revised WHO classification simply separates endometrial hyperplasia into two groups based upon the presence or absence of cytological atypia, hyperplasia without atypia and atypical hyperplasia. The risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up. The risk of developing endometrial cancer is highest in atypical hyperplasia is about 30% (22-57%). Women with atypical hyperplasia should undergo a total hysterectomy because of the risk of underlying malignancy or progression to cancer. Fertility-sparing therapy has been advocated for women who desire future fertility or who have medical comorbidities precluding surgical management. However, women need careful counselling of the risks involved with this option: co-existent or progression to endometrial cancer.

Topographic anatomy, physiology and vascularization of the uterus.

The uterus, originally derived from the Muller canals, is a pear-shaped hollow organ with an upward-facing base and a downward-pointing apex. It is 6.5 cm long in nulliparous women and 7.8 cm long in multiparous women. The uterus base has a transverse diameter of 5 cm and 3 cm in the middle part of the cervix and an antero-posterior diameter of 2.5 - 3 cm. The middle part of the uterus, called the uterine isthmus, is narrow and semicircular. It divides the uterus into:

- The corpus (body) is a cone flattened antero-posteriorly with two faces and two edges.

- The cervix is narrower and less bulky than the body, being barrel-shaped with two convex faces and two thick rounded edges.

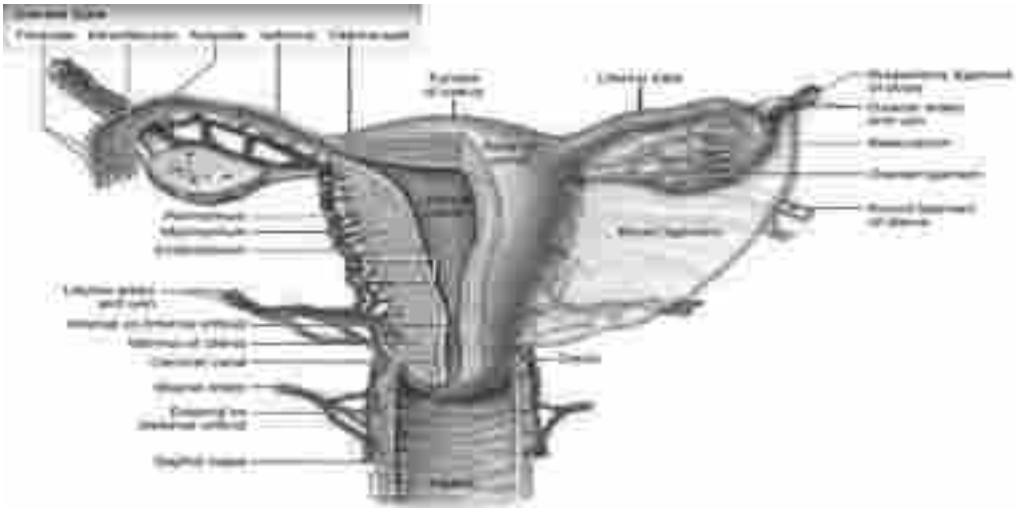

Figure 1. Anatomy of the uterus

The uterine wall is considerably thick, being made up of three tunics, namely the serous coat, the myometrium and the endometrium.

The uterus is attached by means of *suspension* and *support*.

The suspension means which anchor the uterus to the walls of the pelvic excavation include:

A. the broad ligaments of the uterus

B. the round ligaments of the uterus

The means of support of the uterus are the structures that attach it to adjacent organs, as well as to the sacro-recto-genito-pubic lamellae and the perineum.

1. The uterus is attached to adjacent organs by the following structures:
   - the supravaginal portion of the cervix and the isthmus is adherent to the bottom of the bladder through the uterine-bladder septum.
   - the sacro-recto-genito-pubic ligaments attach it indirectly to the rectum.
2. Attachment to the sacro-recto-genito-pubic lamellae:
   - these are condensations of the pelvic-subperitoneal tissue
   - it adheres to the rectum, the cervical-isthmic part of the uterus, to the vaginal fornix and the fundus (base) of the bladder, by means of:
     a) the utero-sacral ligaments;

b) the pubo-uterine ligaments;
c) the cardinal ligaments.

3. Attachment to the perineum: - this is the most important means of supporting the uterus.

Arterial blood supply of the uterus:

- uterine artery originating in the internal iliac artery which gives off collateral and terminal branches;
- ovarian artery originating in the inferior epigastric artery.

Venous blood supply of the uterus

Uterine venous blood is collected in the uterine sinuses in the uterine venous plexus. Veins forming the uterine venous plexus leave from here. Venous blood is driven from the uterine plexus:

- through the uterine veins;
- the internal iliac vein;
- the vein of the round ligament which enters the inferior epigastric vein.

The lymphatic collectors of the uterine body are made of three pedicles:

a) the main pedicle;
b) the transverse accessory pedicle (external iliac);
c) the anterior accessory pedicle (of the round ligament of the uterus).

Uterine innervation

- Parasympathetic innervation originates in the pelvic parasympathetic nucleus.
- Sympathetic innervation is provided by the uterovaginal plexus (from the inferior hypogastric plexus) and the ovarian plexus (from the abdominal aortic plexus).

Methods used to diagnose endometrial cancer

In case of postmenopausal and abnormal perimenopausal bleeding, in order to determine the specific therapeutic tactics the following steps are essential:

Clinical anamnesis

History of unusual intermenstrual or menopausal bleeding, vaginal lymphorrhea or bloody vaginal discharge, pelvic pain, as well as associated risk factors. The clinical pathognomonic signs of endometrial cancer (> 90%) are as follows:

- Postmenopausal bleeding. Thus, 1/3 of women with postmenopausal bleeding have endometrial cancer. Abnormal intensity and frequency of menstrual flow in perimenopausal women is alarming. Although

this clinical manifestation is early and unexpected, many patients ignore it and do not show up immediately for investigations.

- Abnormal leukorrhea is another clinical sign of endometrial neoplasia. Initially it is serous, then it becomes seromucous and purulent in the advanced stages of the disease. The clinical signs which occur late in the disease evolution and are associated with the involvement of the adjacent anatomical structures are as as follows:
  - pelvic pain
  - dyspareunia
  - difficult and painful urination
  - hematuria
  - constipation

Physical examination

- Speculum examination of the cervix can determine pathological changes of the cervix and bloody discharge.
- Bimanual examination (pelvic exam) of the internal genital organs can find a normal cervix. If the epithelium and stroma of the cervix are involved, the affected parametrium may be stiffer and more painful, while the vaginal fornices are shorter.

If there are metastases in the uterine appendages, adnexal masses can be palpated.

- Rectal examination of the internal genital organs and rectovaginal septum enhances the information obtained, completing the data of the bimanual examination and detecting data suggestive of pelvic metastases and / or the cervical tumor growing into the intestine.
- Physical examination can detect hepatomegaly (suggestive of liver metastases), pleural exudate (suggestive of lung metastases). The mammary glands, the supra- and subclavicular lymph nodes, as well as the inguinal lymph nodes can also be palpated.

Paraclinical and laboratory investigations

A minimal assessment of blood, liver and kidneys of patients diagnosed with endometrial cancer should be made, such as general blood test (anemia secondary to menometrorrhagia / metrorrhagia), biochemical analysis of blood (glucose, urea, creatinine, bilirubin, ALT, AST, amylase, total protein), general analysis of urine, in order to assess the organic function and to rule out comorbidities or secondary foci, which can crucially change the therapeutic strategy and help to select a personalized treatment.

Cytological smear - exo- and endocervical sampling (view cervical cancer)

- *"Endometrial biopsy"* is a minimally invasive surgery that can be performed by hysteroscopy or uterine curettage. Both methods aim to get a small portion of the endometrium.
- *Dilation and curettage (D&C).* Prior to the procedure, local or general anesthesia is administered and the vagina is disinfected. The cervix is examined and dilated with dilators, gradually increasing in size. The cavity is scraped and the endometrial tissue is removed. The extracted tissue is sent to the laboratory for histopathological examination.

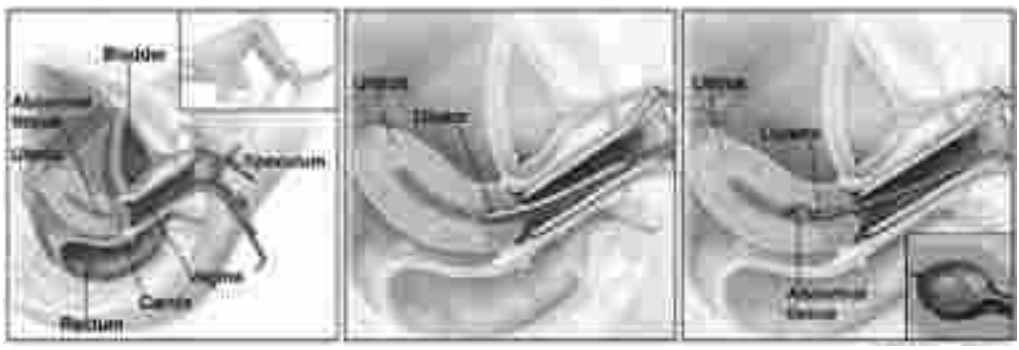

Figure 2. *Dilation and curettage (D&C)*

• *Cytological and histological examination of biopsy samples.*

Hysteroscopy is a minimally invasive gynecological procedure in which a fiber-optic endoscope is inserted into the uterine cavity through the cervix to examine the uterine cavity and to take tissue samples.

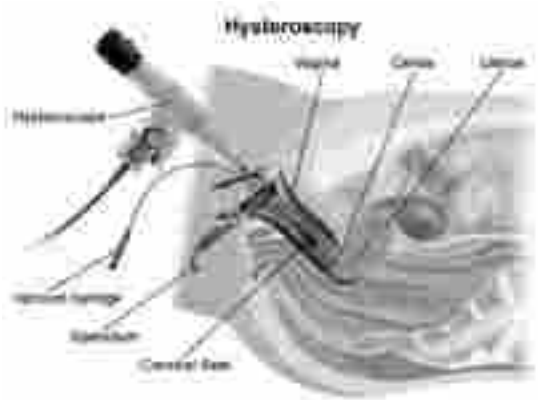

Figure 3. *Hysteroscopy*

Transvaginal ultrasound is a procedure used to examine the uterus and to measure the endometrial thickness. A thickened endometrium (more than 4 mm) raises suspicions and further investigations are required.

The tumor spread can be investigated by the following methods: chest X-ray, abdominal USG, especially retroperitoneal USG, pelvic USG, Nuclear Magnetic Resonance Imaging, Contrast Computed Tomography, Positron Emission Tomography (PET), Intravenous Urography, Cystoscopy and Rectoromanoscopy, bone scintigraphy. Laparoscopy or exploratory laparotomy, with biopsy, if necessary, can confirm the absence of extrauterine involvement by the carcinoma.

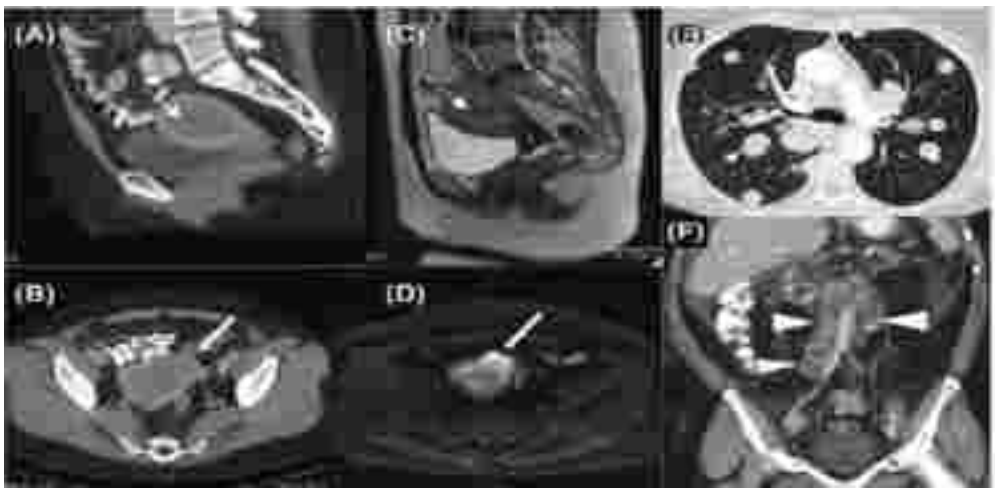

Figure 4. *Computed tomography (A: sagittal plane, B: axial plane) and MRI (C: sagittal T2, D: axial diffusion-weighted) in the same patient with endometrial carcinoma distending the endometrial cavity (dotted arrows) and deep myometrial invasion (solid arrows). E: Axial CT chest with multiple "cannonball" pulmonary metastases (dashed arrows). F: Coronal CT abdomen demonstrating multiple para-aortic necrotic lymph node metastases (arrowheads).*

Histopathological classification of uterine tumors (WHO)

Endometrial epithelial tumors and precursors

- precursor lesions
  - endometrial hyperplasia without atypia

- endometrial atypical hyperplasia / endometrioid intraepithelial neoplasia
- endometrial carcinomas: most common of all uterine malignancies (>90%)
  - endometrioid carcinoma: most common histological subtype
  - serous carcinoma: ~10%
  - clear cell carcinoma: <10%
  - undifferentiated and dedifferentiated carcinomas: ~2%
  - mixed carcinoma: ~10%
  - other endometrial carcinomas: rare (includes mesonephric adenocarcinoma (~1%), mesonephric-like adenocarcinoma, squamous cell carcinoma (<5%), mucinous carcinoma)
  - carcinosarcoma: previously known as a malignant mixed Müllerian tumor (~5% of all uterine malignancies)

Tumor-like lesions

- endometrial polyp
- endometrial metaplasia
- Arias-Stella reaction

Mesenchymal tumors of the uterus

- smooth muscle tumors
  - uterine leiomyoma
  - intravenous leiomyomatosis
  - smooth muscle tumor of uncertain malignant potential (STUMP)
  - metastasizing leiomyoma
  - uterine leiomyosarcoma
- endometrial stromal and related tumors
  - endometrial stromal nodule
  - low-grade endometrial stromal sarcoma
  - high-grade endometrial stromal sarcoma
  - undifferentiated uterine sarcoma
- miscellaneous mesenchymal tumors
  - uterine tumor resembling ovarian sex cord tumor

- perivascular epithelioid cell tumor (PEComa)
- inflammatory myofibroblastic tumor
- other mesenchymal tumors of the uterus: rare (includes vascular tumors, lipomatous tumors, alveolar soft part sarcoma, solitary fibrous tumor, nerve sheath tumors, NTRK sarcomas, giant cell tumor)

Endometrial cancer biomarkers

The biomarkers of endometrial cancer are as follows: K-ras, HER2/neu, epithelial growth factor receptor (EGFR), catalytic subunit phosphatidylinositol 3-kinase (PI3KCA), growth factor receptor 2 (FGFR2), phosphatase and tensin homologous (PTEN), p53, p21, Ki-67 (cell proliferation index), protein X (BAX) associated with BCL2, apoptosis gene promoter, Bcl-2 apoptosis suppressor, estrogen and progesterone receptors (ER and PR), and vascular endothelial growth factor A, known as VEGF-A.

The immunohistochemical expression of p14 ARF antibody is inversely proportional to the degree of histological endometrial lesions. The Ki-67 proliferation index may be an important indicator for assessing the proliferation and differentiation of endometrial carcinoma, having an essential biological and clinical significance for its onset, progression, and diagnosis.

Molecular genetic changes in endometrial adenocarcinoma (type I) differ from those in serous carcinoma changes (type II). Thus, type I is associated with mutations of PTEN, PIK3CA, K-RAS and CTNNB1 genes. Type II is characterized by p53 changes, chromosomal instability, and other molecular changes (STK15, p16, E-cadherin, and C-erbB2).

Recent molecular findings and new histopathological parameters have given new concept on risk stratification. The Cancer Genome Atlas Research Network (TCGA) of tumours have brought new insights into endometrial cancer management. Four molecular subgroups have been described: *POLE* ultramutated (*POLE* mut), p53 mutant (p53abn), mismatch repair deficient (MMRd) and non-specific molecular profile

(NSMP). This new subdivision has been recently introduced in the European risk stratification system.

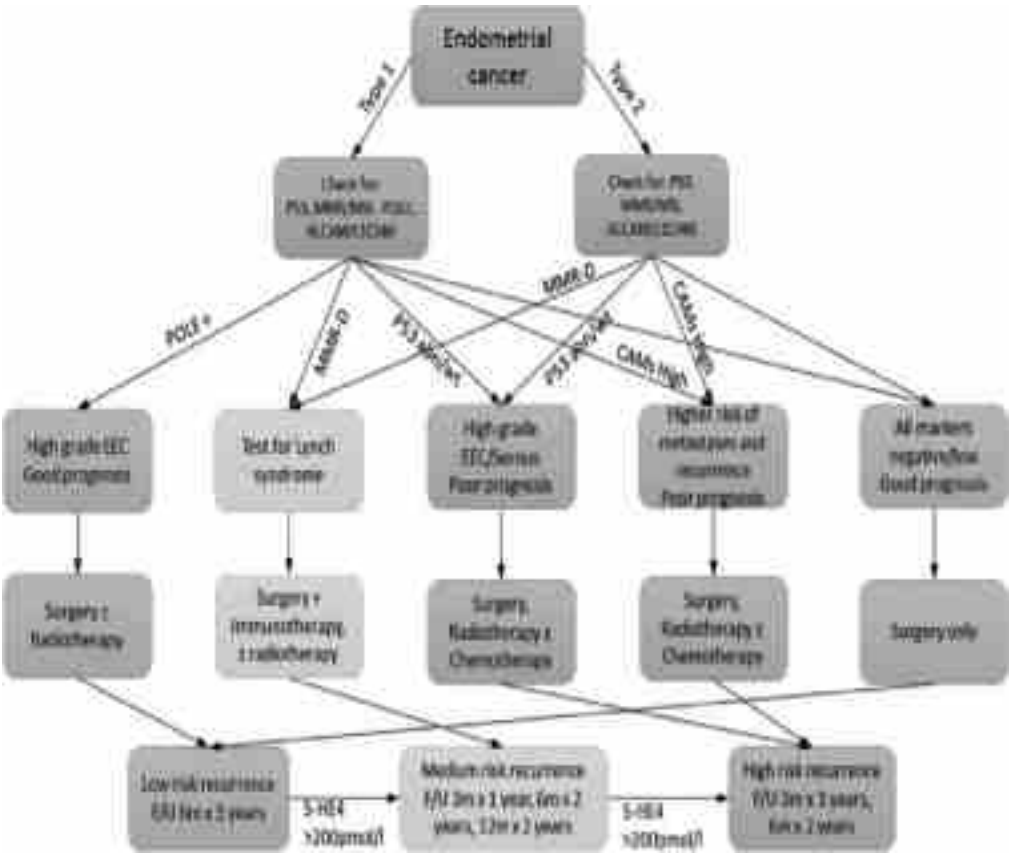

Figure 5. *Endometrial cancer biomarkers*

Endometrial cancer staging

The stage of the disease upon diagnosis determines the prognosis and a specific therapeutic strategy is necessary. In 1971, FIGO established the clinical staging criteria for endometrial neoplasia. Given the fact that the preoperative clinical staging can substage the disease, in 1988 FIGO revised the staging criteria for endometrial cancer and adopted the post-operative staging criteria for endometrial neoplasia. The latest TNM / FIGO classification of endometrial cancer was revised in 2017.

Endometrial cancer staging, TNM - AJCC classification, 8th edition

TNM	FIGO	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1	**I**	Tumour is growing inside the uterus. It may also be growing into the glands of the cervix, but not into the supporting connective tissue of the cervix
T1a	**IA**	Tumour is in the endometrium (inner lining of the uterus) and may have grown less than halfway through the underlying muscle layer of the uterus (the myometrium)
T1b	**IB**	Tumour has grown from the endometrium into the myometrium. It has grown more than halfway through the myometrium, but has not spread beyond the body of the uterus
T2	**II**	Tumour has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix (called the cervical stroma). But it has not spread outside the uterus
T3	**III**	Tumour has spread outside the uterus, but has not spread to the inner lining of the rectum or urinary bladder
T3a	**IIIA**	Tumour has spread to the outer surface of the uterus (called the serosa) and/or to the fallopian tubes or ovaries (the adnexa)
T3b	**IIIB**	Tumour has spread to the vagina or to the tissues around the uterus (the parametrium)
T4	**IVA**	Tumour has spread to the inner lining of the rectum or urinary bladder (called the mucosa)
	IVB	Tumour has spread to inguinal (groin) lymph nodes, the upper abdomen, the omentum, or to organs away from the uterus, such as the lungs, liver, or bones (M1). Tumour can be any size (Any T) and it might or might not have spread to other lymph nodes (any N).

Metastatic pathways

Endometrial cancer spreads in several ways. The most common ways are such as the direct extension (invasion) in the neighboring structures, lymphatic spread, hematogenous spread and transtubal dissemination.

Localized metastasis refers to the invasion of the myometrial and cervical canal. The regional lymph nodes of the uterine body include paracervical, parametrial, hypogastric (internal iliac, obturator), common

iliac, external iliac, presacral, and lateral sacral lymph nodes. Invasion of the paraaortic lymph nodes is classified as distant metastasis.

Lymphatic invasion of the isthmus occurs in the hypogastric, external and common iliac lymph nodes, and for the toumors localized in the fundus-in the paraaortic lymph nodes.

Hematogenous dissemination results in pulmonary, skeletal and hepatic metastases, while the transtubal one is responsible for peritoneal dissemination.

Treatment

The treatment algorithm must be customized, the patient's individual parameters being paramount. It is essential to take into account risk factors, the general condition of the body and tumor characteristics.

In case of fertility preservation, conservative therapy is an option for patients with well differentiated endometrial carcinoma (or adenocarcinoma) stage IA and for women who want to procreate. It is absolutely necessary to explain and warn the patients about the high likelihood of disease recurrence or progression even after conservative treatment, thus rigorous monitoring being mandatory.

Fertility preservation therapy is contraindicated in patients with low-grade endometrioid adenocarcinoma, uterine papillary serous carcinoma, clear cell carcinoma or carcinosarcoma.

Conservative treatment should be initiated only after confirming the absence of myometrial invasion and ovarian metastases by ultrasonographic examination and nuclear magnetic resonance. The absence of extrauterine manifestations of carcinoma can be confirmed by diagnostic laparoscopy, with biopsy, if necessary. Hysteroscopy is also mandatory. Continuous oral administration of Megestrol acetate 160 mg/day or Medroxyprogesterone acetate 200 mg/day for about 3 months is the first-line medication. Ultrasound examination, hysteroscopy and endometrial biopsy should be performed in 3 months. Pregnancy is allowed only after a thorough disease restaging.

Given the high likelihood of recurrence after conservative therapy, surgical treatment should be performed after childbirth.

Surgical treatment is the therapy of choice in the early stages of endometrial cancer. Total hysterectomy with bilateral salpingo-oophorectomy +/- lymphadenectomy is the basic treatment for most

patients with endometrial cancer, enabling the physician to adequately assess the disease stage and spread, as well as the need for an appropriate adjuvant therapy.

Total hysterectomy is the surgical removal of the entire uterus (the uterine body and the cervix), without removing the vagina or lymph nodes. Considering the high likelihood of metastasis of tumor cells in the uterine appendages, both fallopian tubes and ovaries must be removed (bilateral salpingo-oophorectomy). The uterus is removed under general anesthesia, through an incision in the abdomen (abdominal hysterectomy) or vagina (vaginal hysterectomy), or laparoscopically (laparoscopic hysterectomy). Infertility is the consequence of total hysterectomy. Complications such as infection, excessive bleeding, involvement of the urinary system or intestines can rarely develop.

Radical hysterectomy. In 1898, E. Wertheim developed the surgical technique called Wertheim's hysterectomy. It involves removing the uterus, the cervix, the parametrium, the upper third of the vagina, and the regional lymph nodes (regional radical lymphadenectomy).

Laparoscopic and robotic-assisted surgery

Pelvic exenteration is an ultraradical surgical procedure of removing all pelvic organs such as the bladder, the uterus, appendages, and the rectosigmoid junction. It is extremely rarely performed and must be well justified, since it is associated with a high rate of severe complications, low cure rate and a severe change in the quality of life.

In some cases, even in patients with advanced incurable endometrial cancer, interventional treatment can be applied (hysterectomy for hemostatic reasons, "debulking" - complete removal of tumor masses), which can improve the subsequent palliative care.

If preoperative histological results following the fractional diagnostic curettage are indicative of serous or clear cell carcinoma, omentectomy should be performed.

The role of sentinel node mapping in endometrial cancer should be evaluated. Sentinel node mapping is performed as in the case of cervical cancer using the same tracers (blue dye, technetium-99 [99Tc], green indocyanine [ICG]).

Radiation therapy

Radiation therapy is an important treatment option for endometrial

cancer, depending on the patient's clinical condition. Radiation therapy is administered as a postoperative or stand-alone adjuvant therapy. when surgical treatment is contraindicated, or in combination with chemotherapy, as decided by the multidisciplinary board.

There are 2 types of radiation therapy:

- *External radiation therapy* (telegammatherapy, distance, TGT) is a form of radiation therapy, which acts on the pelvic area, metastasis pathways (the retroperitoneal lymph nodes and the parametrial tissue), using a special radioactive device *Terabalt* Co-60, 1.25mV photon energy; Clinac DHX accelerator, 6-15 mV photon energy. Irradiation technology with 2 opposite fields (anterior AP and posterior PA) or 4-field technology (box technology - anterior AP + posterior PA and 2 lateral fields) is used for the treatment of endometrial cancer.
- *Internal radiotherapy* (intracavitary or brachytherapy, BT) delivers high energy. The radioactive sources are introduced directly into the metastatic pathways, the uterine cavity and the vagina, using the "afterloading" method and a special device. BT is a form of radiation therapy that acts on tissues through a closed contact. During the procedure, the radioactive sources are placed on special applicators, namely intrauterine and vaginal ones, being in contact with the tumor.

In low-dose-rate brachytherapy (LDR), the applicator with the radiation source is kept for about 1 - 4 days. In high-dose-rate brachytherapy (HDR), the radiation is higher. Each treatment session usually takes less than an hour, and irradiation is only performed for 10-20 minutes.

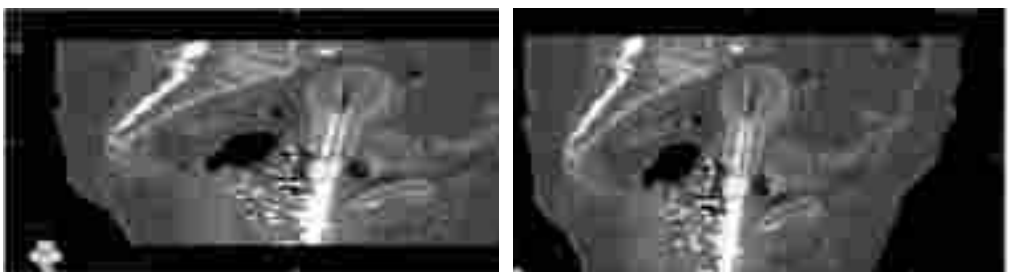

Figure 6. *Sagittal images from treatment plans for HDR brachytherapy (A) and Tomotherapy SBRT (B) approaches for a single patient with medically inoperable endometrial cancer. Both treatment plans were performed with goal of delivering 8.5 Gy per fraction to the uterus.*

Types of radiation therapy:

• Postoperative radiation therapy;

• Independent radical or palliative radiation therapy;

• Symptomatic radiation therapy depends on prognostic factors (tumor stage, size, histological type, age, hemoglobin level). It can be performed in 2 stages, with a 2-week break, if there are side effects during radiation therapy according to the Karnofsky index <60%.

Chemotherapy

The specific antineoplastic treatment can be applied in stage III after the surgical and radiotherapeutic stage, and in stage IV after or concomitantly with the hormonal treatment in patients with undifferentiated fast progressing and recurrent tumors.

Table 2. Combination chemotherapy protocols

AP	Doxorubicin 60mg/m² i.v. 1day; Cisplatin 60mg/m² i.v. 1day, every 3 weeks.
AC	Doxorubicin 60mg/m² i.v. 1 day, Cyclophosphamide 600mg/m² i.v. 1 day, every 3 weeks.
CAP	Cyclophosphamide 600mg/m² i.v. 1 day; Doxorubicin 50mg/m² i.v. 1 day; Cisplatin 100mg/m² i.v. 1 day, every 3 weeks.
PC	Paclitaxel 135-175mg/m² i.v. 1 day; Carboplatin AUC5-7 i.v. 1 day, every 4 weeks.
DP	Doxorubicin 50mg/m² i.v. 1 day, Paclitaxel 135-175mg/m² i.v. 1 day, every 3 weeks.
CAF1	Cyclophosphamide 400mg/m² i.v. 1, 8 day; Doxorubicin 30mg/m² i.v. 1, 8 day; 5-Fluorouracil 400mg/m² i.v. 1, 8 day, every 3-4 weeks.
PAC	Doxorubicin 45mg/m² i.v. 1 day; Paclitaxel 135mg/m² i.v. 1 day; Cisplatin 60mg/m² i.v., every 3 weeks.
PV	Cisplatin 80mg/m² i.v. 1 day; Vinorelbine 25mg/m² i.v. 1, 8 day, every 3-4 weeks.
PD	Carboplatin AUC5 i.v. 1 day; Doxorubicin liposome 40mg/m² i.v. 1 day, every 4 weeks.
Monochemotherapy:	
Topotecan 1,5 mg/m² i.v. 1-5 day, every 3 weeks.	
Ifosfamide 1200mg/m² i.v. 1-5 day (+Uromitexan), every 3-4 weeks.	
Oxaliplatin 130mg/m² i.v. 1 day, every 3 weeks.	

Hormone therapy

Hormone therapy is indicated in:

- stage IV, in older patients with well-differentiated slow-growing tumors (G1);
- recurrences.

The protocols for hormone therapy are as follows:

- Medroxyprogesterone acetate 150mg orally for a long time;
- Depo-provera 1000mg i.m. weekly no.4, then twice a week for a long time;
- Megestrol acetate 160mg orally daily for a long time;
- Tamoxifen 40mg daily, for a long time.

Chemotherapy toxicity is assessed by physical examination, complete blood count + platelets, urinalysis, biochemical blood test, echocardiography.

Treatment effectiveness is assessed by physical examination, ultrasound, radiography, computed tomography, magnetic resonance imaging, and bone scintigraphy.

Targeted therapy for endometrial cancer

Lenvatinib is a medicine known as kinase inhibitor. It helps suppress tumor growth and targets some proteins in cancer cells that normally help them grow. It can be used in combination with pembrolizumab, the immunotherapeutic drug, to treat advanced endometrial cancer, usually after at least one attempt of antineoplastic treatment.

Bevacizumab belongs to a class of medicines called angiogenesis inhibitors. It is a monoclonal antibody that blocks the vascular endothelial growth factor (VEGF), involved in tumor neovascularization. Bevacizumab is often administered in combination with chemotherapy, but also as monotherapy, usually after other treatments have been tried.

mTor inhibitors (Everolimus, Temsirolimus) are drugs that block a cellular protein known as mTOR, which is normally involved in cell growth and division. They can be administered alone or in combination with chemotherapy or hormone therapy to treat recurrent / metastatic endometrial cancer.

The VEGF, PI3K/AKT/mTOR, and Ras/Raf/MEK signal transduction pathway and therapeutic interventions. After ligand binding, the receptors initiate the signaling cascade reaction, which is overactive in

cancer cells. The figure shows the main elements in those pathways and the therapeutic agents.

Table 3. The five-year survival rate according to disease stage Evolution and prognosis

Stage	Five-year survival rate
I-A	90%
I-B	88%
I-C	75%
II	69%
III-A	58%
III-B	50%
III-C	47%
IV-A	17%
IV-B	15%

The main prognostic factors are as follows: the disease stage at diagnosis, the histological grade, the depth of myometrial invasion and the lymph node status. The histological grade and the depth of myometrial invasion have a high predictive value of the disease spread, correlating with the risk of lymph node metastases and patients` survival rate. The depth of myometrial invasion is an important prognostic factor for lymph node involvement and five-year survival rate.

Patients with myometrial invasion higher than 50% have a 5-7-time higher prevalence of pelvic and aortic lymph node involvement, being in an advanced stage compared to patients with myometrial invasion of less than 50%.

The prevalence of para-aortic lymphatic metastases varies between 3% in patients with tumors limited to the endometrium and / or myometrial invasion below 50%, and 46% in patients with myometrial invasion above 50%. Patients with lymphatic metastases have a lower five-year survival rate, than those without lymphatic invasion. Therefore, patients with myometrial invasion above 50% should undergo a much more aggressive therapy.

Primary, secondary and tertiary prevention of endometrial cancer

The majority of gynecological conditions can generally be prevented by a regular routine gynecological check-up.

Primary prevention entails avoiding the development of the triad, namely obesity, diabetes, and hypertension. Active and healthy lifestyle, sports, consumption of low levels of fats and carbohydrates, vegetables and fruits are essential.

Secondary prevention involves the treatment of precursor conditions of endometrial cancer. In premenopausal hyperplasia without atypia, in which the risk is 1-3%, cyclic administration of gestagens may be recommended, which results in regression in 60-80%. In patients with polycystic ovary syndrome, the administration of oral contraceptives is rational.

In atypical hyperplasia, hysterectomy is indicated in premenopausal and menopausal women because the risk of carcinoma is 30%. Conservative therapy, similar to endometrioid carcinoma without myometrial invasion, should be undertaken in patients who want to preserve the reproductive function and women at high surgical risk. If atypical hyperplasia persists, hysterectomy is indicated.

In order to prevent occurrence or recurrence of distant metastases (tertiary prevention), rigorous patient monitoring is required.

Table 4. The risk of recurrence in endometrial cancer

Low	Intermediate	Intermediate-high	High	Advanced	Metastatic
- stage IA - G1 or G2 - LVSI negative	- stage IB - G1 or G2 - LVSI negative	- stage IA - G3 - regardless of LVSI or - stage I - G1 or G2 - LVSI positive unequivocally	- stage IB - G3 - regardless of LVSI – stage II – stage III lack of signs of residual disease – non- endometrioid cancer	- stage III with residual disease - stage IVA	- stage IVB

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OVARIAN CANCER

History - the first descriptions of ovarian cancer

Cancer is not a modern disease, it has certainly existed for thousands of years, although today it is much more common than in the past. The earliest description of human cancers refers to eight cases of breast tumors described in the Egyptian papyrus Edwin Smith (ca. 3000-1500 BC), and Egyptian mummies have been diagnosed with ovarian and nasopharyngeal cancers. Several interventions in tumors were generally amputations. More modern ways of surgery have been described since the 19th century: for example, in 1809 a very large ovarian tumor was successfully excised.

Epidemiological and geographical features of ovarian cancer

Ovarian cancer (CO) is one of the most serious current gynecological pathologies. As an international frequency, it varies greatly between different geographical regions and ethnic groups. In Northern Europe and the United States the incidence is high, while in Japan the incidence is low and is only about 3/100,000 inhabitants. Globally, more than 225,000 women are diagnosed at various stages and almost 140,000 die each year. Of the total number of cases, about 90-95% are ovarian epithelial carcinomas that include borderline tumors. 5% of tumors of germ cells and stroma of germ cells.

The diagnosis rate of ovarian cancer patients has been constant for the last 20 years. The risk of developing ovarian cancer in a lifetime for the general population is 1.39% and the risk of dying is 1.04%. In the US (American Cancer Society) SAC in 2014 estimated a diagnosis of ovarian cancer of 21,980 new cases and 14,270 deaths.

Data from the Oncological Institute of the Republic of Moldova show in 2018, 208 patients found out that they have ovarian cancer. Every year the number is growing. For example, in 2015 the diagnosis was established in

142 women. In 2016 - there were 173 new patients detected, and in 2017 - 187 women found out that they have this aggressive form of cancer.

Topographic anatomy of the ovaries, physiology and vascularization

The ovaries border with the pelvic organs and are located on either side of the uterus, close to the lateral pelvic wall behind the broad ligament. During pregnancy they move, then return to their original position. They are located in a space called the ovarian fossa which has dimensions of 4 cm x 3 cm x 2 cm., Space delimited by the external iliac vessels, umbilical artery and ureters. The ovary has two extremities. The tubal extremity that is attached to the fallopian tube through the infundibulo-pelvic ligament and the uterine end connected to the uterus through the ovarian ligament. Each ovary is attached along the anterior edge to the posterior edge of the broad ligament, by a double fold of the peritoneum called the mesovarium, which stabilizes their position. The median pole is connected to the uterine horn by the ipsilateral ovarian ligament (uterine-ovarian ligament) and the upper pole is connected to the lateral pelvic wall by the infundibulo-pelvic ligament (suspensory ligament).

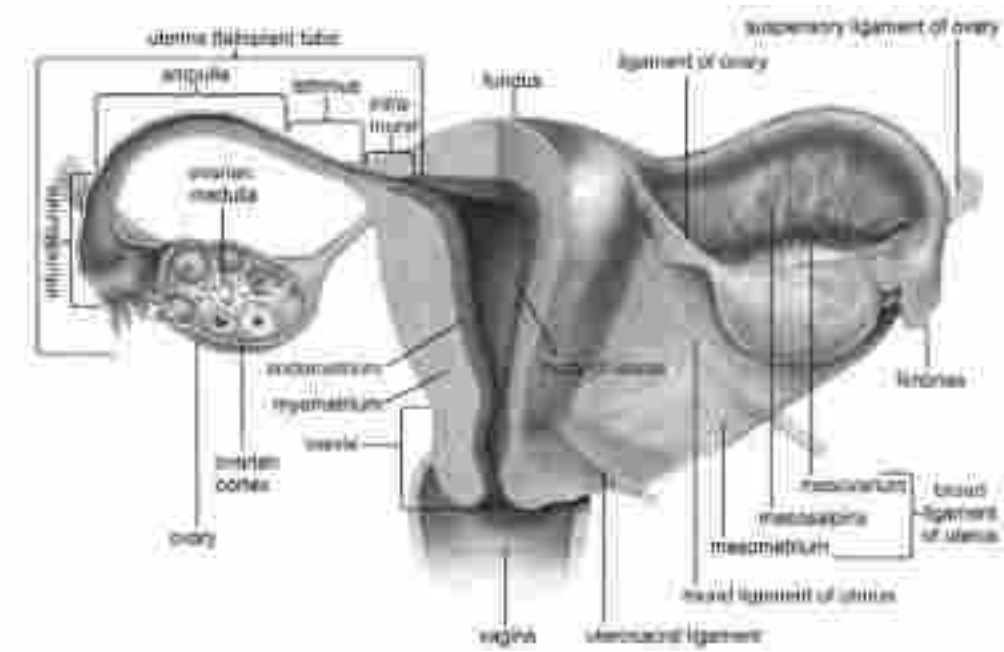

Figure 1. *Anatomy of the internal female genitals*

The infundibulum-pelvic ligament contains the main blood vessels, the artery and the ovarian vein, which enter the ovarian hilum. The mesoovarian boundary is straight, facing the umbilical artery, while the free boundary of the ovaries is convex and facing the uterus. The arches of the fallopian tubes over the ovary run up and in relation to the mesovarian border, then bend at the tubal pole and finally pass down to the free border and the medial surface of the ovaries.

The ovaries in the adult female represent a solid, ovoid, gray-pink structure, the size and shape of an almond. They have dimensions of about 3-5 cm x3 cm, and a weight of 5-8gr. The outer surface is usually smooth during the early reproductive period, then becomes more and more irregular as a result of repeated ovulation. There are three areas on the vaguely defined section surface: the cortex on the outside, the medulla, and the hilum on the inside. They are visible as usual in the ovarian cortex and medulla, follicular structures such as cystic follicles, corpus luteum and albicans that are in varying degrees of development. The ovaries reach about half to a quarter of the size observed during the reproductive period after menopause. At menopause the ovaries have a withered, giriform appearance while others are smooth and uniform.

The vascularization of the ovaries is through the uterine artery, a branch of the aorta, it has its route along the infundibulo-pelvic ligament and the mesovarian limit of the ovary, where it anastomoses with the ovarian branch of the uterine artery. About ten arterial branches detach from this arch that penetrate the ovarian hilum, where they branch and become helical arteries. The medullary arteries and arterioles form at the cortico-medullary intersection from a plexus where the cortical arterioles detach, straight and small, which penetrate radially the ovarian cortex, perpendicular to the surface of the ovary.

The cortical branch of the arterioles anastomoses several times and forms sets of interconnected vascular arches that generate capillaries and form dense networks in the thecal layers of the ovarian follicles. Intraovarian veins accompany the arteries and flow to the left into the left renal vein and into the right vena cava on the right, respectively.

The lymphatics of the ovary come predominantly from the thecal layers of the follicles. The layer of granular cells of the mature follicle is devoid of lymph, while the yellow body possesses a rich network of lymph. They pass through the ovarian stroma and join into larger trunks that form a

plexus at the hilum. Leaving the plexus, the lymph nodes decrease in number and size, and pass along the free edge of the infundibulo-pelvic ligament, along the ovarian veins. From there they accompany the ovarian vessels and flow into the upper paraaortic lymph nodes, at the level of the lower pole of the kidney.

Ethiopatogenesis

The risk of developing ovarian cancer seems to be influenced by several factors and the incidence of this disease is associated with genetic, environmental and reproductive factors.

Risk factors that may promote ovarian epithelial cancer are: nulliparity, premature menarche, late menopause, race (white women are more exposed), advanced age, family history, personal history of breast cancer, colorectal cancer.

Genetic factors

The most important role can be considered the family history and the incidence of breast or ovarian cancer among family members, causing a certain inherited genetic predisposition that is found in 5-10% in patients diagnosed with ovarian cancer. If in the general population the risk of developing ovarian cancer is 1.6%, it increases to 4-5%, when a first-degree relative is affected, so it triples among patients with a history of oncology in first-degree relatives: sister, mother, daughter.

Nulliparity

Patients without children develop a double risk of developing ovarian cancer, being associated with long periods of repeated ovulation as well as those with infertility. The risk of ovarian cancer decreases with each natural birth, stagnating in women over 5 births. An interesting theory in this regard explains the protective effect and the fact that repeated births induce rejection of premalignant ovarian cells.

Early menarche and delayed menopause

There is an increased risk of ovarian cancer, early menarche and delayed menopause. Repeated ovulation without breaks can lead to malignant ovarian tumors. By preventing ovulation in this context it is breastfeeding that has a protective effect due to the prolongation of amenorrhea. Long-term oral contraceptives reduce the risk of ovarian cancer by more than 50% and the duration of protection against the carcinogenic process lasts up to 25 years from the last use.

Race

Racial classification has a higher incidence of white women in all ethnic ranks by 30-40% than black women. The exact causes of racial discrepancies are unknown.

Age

As you get older, your risk of developing ovarian cancer increases. It is less common in young women. The age of 50-65 is the peak incidence and the growth rate is lower after that. Under the age of 45, the presence of this malignancy is relatively unusual.

Endometriosis

Histological and epidemiological arguments accumulated in recent years suggest that ovarian endometriosis may give rise to malignant ovarian tumors, especially of epithelial origin. Endometriotic implants may be associated with malignant ovarian disease. Atypical endometriosis has intermediate proliferative activity between typical edometriosis and ovarian carcinoma.

Diet

There is a correlation between the consumption of animal fats, proteins, caloric intake and the increased incidence of ovarian cancer. A low risk is given by the consumption of vegetables, carbohydrates, vitamin A, C and fiber.

Obesity

Weight gain is associated with an increased risk of developing several cancers, including epithelial ovarian cancer. Obesity with ovarian cancer has been linked to postmenopausal women by the IARC working group. In another recent study, an increase in body mass index gives an increased risk of ovarian cancer mortality in women over the age of 50.

Smoking

According to recent studies, the association between cigarette smoking and ovarian cancer has shown a high incidence only in mucinous tumors.

Asbestos exposure

Studies have shown an increased incidence of ovarian cancer in occupational „family" exposure to asbestos. The association between ovarian cancer risk and asbestos exposure was addressed by the International Agency for Research on Cancer (IARC) working group, which concluded that the evidence was sufficient for a causal association between occupational asbestos exposure and ovarian cancer.

Diabetes

Insulin resistance characteristic of type II diabetes coexists in clinical syndromes with hyperestrogenism and hyperandrogenism, suggesting that the ovary may be sensitive to the effects of insulin. Insulin-like growth factors (especially IGF-1) have receptors in the ovary and control cellular activity.

Pathogenesis of ovarian epithelial cancer

There are at least three pathways in the genesis of epithelial ovarian cancer. Malignant transformation of benign ovarian cysts is explained by the accumulation of genetic alterations caused by mutations in genes that control cell division: - **EGFR and HER2 / neu** - expressed in normal ovarian surface epithelium and overexpressed in 35-70% of ovarian cancers.

Precancerous conditions

Unlike other malignancies involving the female genital tract, precursor lesions of ovarian cancer are not well characterized and have led over time to a failure to develop effective screening programs. One of the problems in elucidating the pathogenesis of ovarian carcinomas is that it is a heterogeneous disease, consisting of different types of tumors, which have very different clinical and pathological characteristics and behavior.

Histological forms

The classification of ovarian tumors is complicated by the existence of a wide range of morphological types and subtypes, which in turn include several varieties that may have overlapping different histological features. (refer to)

AJCC Cancer Stagiung Manual, Eighth Edition. Editor-in-Chief Mahul B.Amin, MD, FCAP; American Joint Committee on Cancer 2017. page 689.

Metastatic pathways

Ovarian carcinoma spreads predominantly by exfoliation (intraperitoneal), lymphatic, retroperitoneal and diaphragmatic, hematogenous and by continuity. Ovarian epithelial cancer metastasizes predominantly by exfoliation. In necropsy examinations, metastases are located most frequently peritoneally (90%).

TNM Classification, Geneva 2017 (refer to)

AJCC Cancer Staging Manual, Eighth Edition. Editor-in-Chief Mahul B.Amin, MD, FCAP; American Joint Committee on Cancer 2017. pp. 688-689.

Diagnosis of ovarian cancer

The diagnosis of ovarian cancer is based on: clinical examination (general examination, digestive disorders, chest examination, examination of the abdomen and pelvis), laboratory tests (tumor antigen CA-125, CA-19-9, CEA), imaging examination (USG gland breast, abdominal and pelvic floor, CT of the abdomen and pelvis, MRI of the abdomen and pelvis, lymphography, chest X-ray, irigography-scopy, cystography), endoscopic examination (laparoscopy with biopsy, FCS with biopsy, RRS with biopsy, FEGDS with biopsy)

The clinical picture

Ovarian cancer is often described as a hidden, mute and silent killer due to the lack of symptoms in the early stages, this being evident only in the advanced stages.

The symptoms most often happen to be present from the very first stages, but frequently co-founded with the monthly female physiological events. Abnormal abdominal circumference, abdominal distension, enlarged abdomen, urinary urgency and pelvic pain are often constant.

Figure 2. *Increased abdomen due to large ovarian formation.*

The anamnesis will highlight the personal pathological antecedents: the first and last menarche, the flow and regularity of the menstrual cycle, the menopausal status, the number of pregnancies, hereditary collateral personal history. Women with symptoms of ovarian disease should be evaluated by clinical examination, abdominal, pelvic, and rectovaginal

examination, and palpation of the supaclavicular and inguinal lymph nodes.

On physical examination, an abdomino-pelvic or pelvic mass can be frequently felt, where the malignant tumors have a solid, nodular, fixed consistency but without finding pathognomonic details that distinguish them from the benign ones.

Rectovaginal examination is recommended in all patients with ovarian tumors to assess tumor mobility, consistency, examination of the recto-vaginal space to exclude implants.

The presence of intra-abdominal fluid suggests the presence of severe ascites. Present ascites is synonymous with the possibility of cirrhosis or other primary malignancies such as gastric or pancreatic cancer.

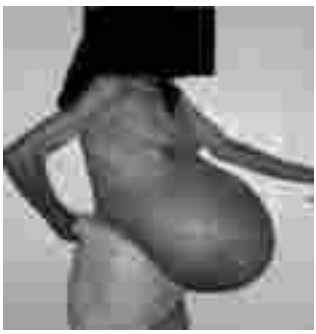

Figure 3. *Patient with a relaxed abdomen caused by ascites.*

In advanced stages, examination of the upper abdomen reveals a central mass equivalent to the neoplastic infiltration of the large omentum. Chest auscultation is included to detect malignant pleural effusions.

Paraneoplastic syndromes associated with ovarian disease include: polyneuritis, dermatomycositis, hemolytic anemia, disseminated intravascular coagulation, acanthosis, or nephrotic syndrome.

Paraclinical methods

Laboratory tests

In guiding subsequent treatment, routine biochemical tests and a blood count are performed on patients with different stages of ovarian cancer.

Tumor markers involved in ovarian cancer. Antigenic markers: CA 125, CA15-3, CA19-9, CEA (carcinoembryonic antigen), AFP (alpha-protein), TPA (polypeptidicular antigen) Enzyme markers: Alkaline phosphatase (Regan isoenzyme), LDH (lactate dehydrogenase)

Hormone markers: HCG is normally secreted by the placenta; increases during pregnancy and ovarian tumors; β-HCG (human chorionic gonadotropic hormone fraction β) - is used as a tumor marker in tumors with germ cells (embryonic) of the ovary or testicular tumors. In the case of mucinous tumors, serum levels of the tumor marker type CA19-9, carcinoembryonic antigen - CEA, prove to be more informative indicators. Immunohistochemical tests may suggest or support a specific diagnosis.

Instrumental diagnostic methods

Radio imaging methods

Ultrasonography

Transvaginal ultrasonography is used in the early stages to differentiate benign tumors from ovarian cancers. Malignant tumors are generally described as multilocular, solid, echogenic, large, have thick septa with nodular areas, locally showing papillary projections and neovascularization, all these features are identified using Doppler ultrasound. In the case of the patient in advanced stages, ultrasonography loses its usefulness.

Radiography

Patients suspected of ovarian cancer are referred for a chest x-ray to detect lung effusions or, less commonly, lung metastases. Under the conditions of ovarian cancer, irigography is used to exclude colorectal tumors.

CT

CT scans are the preferred way to stage ovarian cancer.

Laparocentesis

The role of laparocentesis is to establish the presumptive diagnosis of ovarian cancer until surgical confirmation. Its place is found in cases where the ovarian tumor mass is accompanied by ascites.

Figure 4. *Performing laparocentesis of a patient with ovarian cancer*

Endoscopic methods

In the advanced stages, the diagnosis of cancer cannot be sustained without histological confirmation, where the role of laparoscopy is major and consists in obtaining tumor tissue for histopathological examination. A morphological confirmation of ovarian disease is useful for stages III and IV of ovarian cancer, in making decisions to perform neoadjuvant treatment, polychemotherapy.

Diagnostic laparotomy

Diagnostic laparotomy in the last decade is less and less used, giving way to minimally invasive techniques. However, there are situations in which diagnostic laparotomy is essential for staging and aims to identify lymph node lesions.

Differential diagnosis

In adult women, the differential diagnosis is made with: intrauterine pregnancy; hydatidiform mole; ectopic pregnancy; functional ovarian cysts; uterine fibroids; pregnancy-related cysts; endometriosis; uterine malformations (double uterus); ectopic kidneys; intraperitoneal tumors (colon, rectum, mesentery); retroperitoneal tumors; pelvic bone tumors; tubal infectious pathology; appendicitis; abscess; wide ligament or pelvic phlegmons; intraperitoneal hydatid cyst.

Intraoperative differential diagnosis is based on the following criteria:

Intraoperative examination benign appearance /malignant appearance

- Bilateral tumor is rare.
- The capsule is rarely intact
- Vegetation on the surface is rare.
- Ader. In neighboring org rarely.
- Ascites rarely common.
- Solid areas are rare.
- Peritoneal implants are rare.
- Heme areas and necrosis rarely frequent.
- Cystic appearance quite frequent.
- Intracystic vegetation is very common.

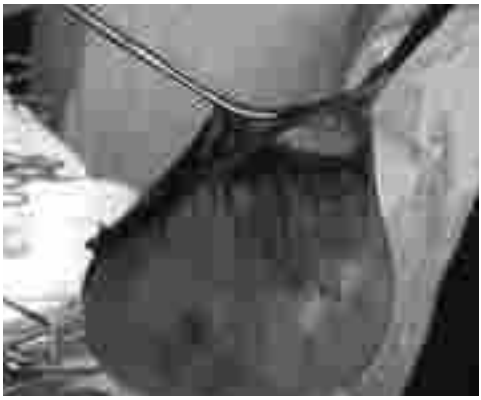

Figure 5. *Macroscopic appearance of a benign tumor*

Figure 6. Macroscopic appearance of a malignant tumor

Treatment methods

Treatment of ovarian cancer includes the following methods: surgical method (total hysterectomy with bilateral annexectomy, infrared resection of the omentum and paraaortal and pelvic lymphadenectomy), chemotherapy method (mainly polychemotherapy with platinum preparations), radiotherapy method in the case of radiotherapy small pool).

Surgical treatment

Treatment for all stages of ovarian cancer is surgical. Cytoreductive surgery is the basis of ovarian cancer therapy. Total extrafascial hysterectomy with salpingoophorectomy together with dissection of the pelvic and paraaortic lymph nodes is the standard procedure for staging ovarian carcinomas.

Chemotherapy treatment

The main purpose of treatments with chemotherapeutic agents is to prevent the multiplication of cancer cells, the invasion and metastasis, and finally the destruction of cancer cells. Neoadjuvant chemotherapy refers to the use of chemotherapy as an initial treatment prior to loco-regional therapy in patients whose surgery, radiation therapy, or both are less or incompletely effective. Its use is to reduce the extent of resection required and to obtain loco-regional control of the tumor.

The administration of preoperative chemotherapy (3 cycles), followed by surgical resection and postoperative chemotherapy is a behavior applicable to potentially resectable local-advanced tumors.

Adjuvant chemotherapy is applied in ovarian cancer after radical loco-regional treatment with curative purpose. The aim is to eradicate the remaining cells and / or micrometastases in order to reduce the incidence of local and systemic recurrence and thus improve patient survival. Platinum-based chemotherapy is the main method of treatment for systemic treatment of most types of ovarian cancer.

In women with epithelial ovarian cancer who require first-line chemotherapy, the standard intravenous regimen uses platinum and taxane agents. Although Cisplatin and / or Docetaxel may be used, the use of Carboplatin and Paclitaxel is preferred. One regimen may be Carboplatin + Paclitaxel which is widely used and administered intravenously over 6 cycles of 3 weeks apart (21 days).

Radiation therapy

Radiation therapy in ovarian cancer is usually used as a palliative method in case of resistance to polychemotherapy or recurrences in the small pelvis that do not respond to cytostatic treatment. Radiation therapy can also be used as a method of symptomatic treatment in incurable patients with ovarian cancer.

Hormone treatment

Hormonal agents that can be used to treat ovarian cancer: Tamoxifen 40 mg daily; Anastrozole 1 mg daily; Letrozole 2.5 mg daily; Megestrol acetate 160 mg daily.

Immunotherapy (types of immunotherapy)

Immunotherapy involves the use of biological agents that act on the body's natural defense mechanisms against tumors, and / or substances involved in the differentiation, proliferation and activity of immune cells. The range of modalities used in cancer immunotherapy includes cytokines, cell therapies, tumor vaccines, checkpoints, „connector" bi-specific antibodies (also known as bi-specific T cellengagers), dual-specific antibodies, molecules. small, oncolytic viruses and immune adjuvants.

Immunotherapeutic agents, for example, are: *Bevacizumab* belongs to a class of angiogenesis inhibitors. *Olaparib* is known as a PARP inhibitor (poly-ADP-ribose-polymerase).

Complications of ovarian cancer

Complications in ovarian cancer, usually occur in the past stages III and IV where depending on the damage to adjacent organs are manifested in

terms of constipation, intestinal obstruction, frequent urination, hematuria. In some cases, both vaginal and rectovaginal, vesicovaginal fistulas may occur as the malignant process progresses.

Immediate and remote results of ovarian cancer treatment. Forecasts

After all stages of ovarian epithelial cancer, the survival rate is only 45% much lower than that of uterine cancer (84%) or cervical cancer (73%). To a large extent, the survival rate depends on the level of metastasis associated with the FIGO stage. Favorable prognostic factors for ovarian cancer are young age, positive evolution, cell types other than clear and mucinous cells, well-differentiated tumors, low tumor volume after surgery, absence of ascites, smaller residual tumors after primary surgery cytoreducational.

Primary, secondary and tertiary prophylaxis of ovarian cancer

Primary prevention aims to reduce the incidence of ovarian cancer by identifying and possibly eliminating risk factors such as ovarian cysts, including lifestyle, eating habits (eating foods high in fiber, carotene and vitamins has a protective effect) , environmental, occupational, hormonal and genetic factors (identification of patients with a family history - breast cancer, colon cancer). Secondary prevention involves the identification and treatment of precancerous lesions such as ovarian tumors or early ovarian cancer. Tertiary prevention can be applied to invasive ovarian cancer tumors. In the case of patients at high risk of developing ovarian cancer, the only way to prevent it is surgical surgery by ovarectomy (the condition that the ovaries are normal) and removal of the fallopian tubes.

Tumors with a low potential for malignancy (bordeline)

Of the ovarian epithelial cancers, they account for about 10-15% and are called borderline tumors with problem management. They can develop at any age and are not considered hereditary. The average age of onset of these tumors was 40 years, in contrast to invasive ovarian carcinomas that began 15 years later.

Histologically, these tumors have characteristics such as: atypical nucleus, epithelial stratification, formation of microscopic papillary projections, cell pleomorphism or intense mitotic activity and do not show stromal invasion.

The treatment is based on surgery and surgery planning varies depending on the circumstances (age, fertility) and for postmenopausal women resort to total hysterectomy with bilateral annexectomy, resection of the uterus.

Benign tumors of the ovaries, diagnosis and treatment

Epithelial tumors of the ovary are a wide variety and can be: serous, mucinous, endometrioid, clear cell, seromucinous and transitional. Of all epithelial tumors, 60% are benign, followed by malignant with 35% and only 5% borderline tumors.

The diagnosis is based on clinical examination (patient's history, gynecological examination), laboratory (biochemical, immunological, cytological, histological), imaging (USG of the abdominal cavity and small pelvis, CT, MRI) and endoscopic (laparoscopy with biopsy, FCS, RRS, cystoscopy). Treatment of benign ovarian tumors in most cases can be surgical.

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BREAST CANCER

Geographical-epidemiological features

Breast cancer (BC) is the most common form of cancer in women, and is a major problem with a global impact, caused by high morbidity and mortality. The disease occurs as a result of malignant cell proliferation of the epithelium that delimits the galactophore ducts or lobules of the mammary gland. According to WHO statistics, approximately 1.7 million new cases of BC and 627,000 deaths are detected worldwide each year. In the US, in 2018, about 231,840 women were diagnosed with breast cancer in 2018, of which 40,290 died from this disease. The lowest mortality rate is in the Southeast Asia region (about 16 per 100,000) and the highest in the South African region (20 per 100,000). It is also estimated that one in 9 women will be affected by this severe disease in their lifetime. Breast cancer can also affect the male sex. The ratio between men and women is 1: 150.

In the Republic of Moldova, there are about 10,000 patients with BC. According to the National Cancer Registry (2018), breast cancer ranks first in the structure of morbidity from malignant tumors in women, accounting for 10.7% of the oncological structure in the female population, with about 1,000 new cases registered annually. The prevalence of breast cancer in 2018 was 522.5 per 100 thousand population, and the incidence was 61.0% ooo or 1125 patients, of which 241 patients were registered during the reproductive period, which is 21.4%.

Ethiopatogenesis

Breast cancer is a hormone-dependent disease. In women with dysfunctional ovaries who have never received hormone replacement therapy, breast cancer is very rare. Factors with a major impact on the incidence of breast cancer are:

I. Reproductive function factors:

1. Menstrual function:

- *early menarche* (earlier than 12 years). Women who have menarche

at age 16 have a 50-60% lower risk of developing cancer in their lifetime than women who have menarche at age 12.

- *late menopause* (later than 55 years). Menopause that occurs 10 years before middle age (52 years), whether it occurs naturally or is surgically induced, reduces the risk of cancer by about 35%.
- *irregular menstrual cycle.* The duration of the menstrual cycle - especially in the period before the first birth - is a substantial component of the total risk of developing breast cancer.

2. Reproductive function:

- *nulliparity*. Women who become pregnant around the age of 18 have just 30-40% risk of developing breast cancer during their lifetime compared to nulliparous women.
- *the age of birth of the first child.* The birth of the first child after the age of 30 has an increased risk of developing breast cancer.

II. Lactation function factors:

Breast cancer is more common in women who are not breastfeeding or breastfeeding for a short time. As a result, there is a disorder in the levels of prolactin, progesterone, estrogen, glucocorticoids, and growth hormone.

III. Genital function factors:

- *abortions* – produce irreversible hormonal disorders, which affect the mammary glands, ovaries, thyroid gland, endometrium, etc.

All of these factors contribute to the proliferation of mammary glandular tissue and estrogenic hyperstimulation.

IV. Exogenous factors are represented by:

1. ***Physical agents -*** *ionizing radiation, ultraviolet radiation, trauma (acute or chronic) of cancer of the mammary glands.*

*Radiation***.** The magnetic field, the action of radioactive substances and sources contribute to the damage of the cell genome, which causes the appearance of neoplastic processes.

Acute and chronic mental trauma contributes to severe hormonal and immune disorders, which increase the risk of breast cancer.

Physical trauma to the mammary gland decreases the amount of IgA on the glandular cell membrane, reducing anticancer tissue immunity.

2. ***Chemical agents***- smoking, alcohol, air pollution, water, soil, food. *Smoking* – tobacco contains more than 4,000 toxic substances, including carcinogens.

Alcohol abuse affects the liver, reducing its metabolic function and eliminating hormones.

Food. Diet rich in fats, proteins and refined sweets enriched with chemicals from processing with pesticides and hormonal preparations. Animal fats also contain a high amount of cholesterol, which is an additional source of steroid hormones.

Administration of hormonal preparations for a long time without a doctor's prescription. The most credible meta-analyzes for oral contraceptives given without a gynecologist's prescription suggest that they increase the risk of breast cancer.

V. Endogenous factors are represented by:

1. ***The genetic factor.*** About 10% of mammary gland cancers are directly related to a mutation in the germ line. The first mutations identified were those that affect the germline of the p53 tumor suppressor gene. The disease caused by these mutations - called Li-Fraumeni syndrome - leads to an increased incidence of mammary gland cancer, osteogenic sarcoma and other malignancies. Numerous scientific studies have shown that mutations in the BRCA1 and BRCA2 genes, which affect the germ line, are responsible for the vast majority of hereditary breast and ovarian cancers. BRCA1 (located on chromosome 17q21) and BRCA2 (located on chromosome 13q12-q13) are tumor suppressor genes that encode proteins involved in DNA repair processes. More than 1,200 mutations in the BRCA1 gene and more than 1,300 mutations in the BRCA2 gene have been reported. Women who inherit a mutant allele of this gene from a parent (whatever it is) have a 85-90% lifetime risk of getting the disease, and also a 33% risk of developing ovarian cancer. Men with a mutant allele have a higher incidence of prostate cancer.
2. ***The hereditary factor****:* Presence of an increased risk in the offspring of mothers with breast cancer (2 times higher risk, especially when the cancer was bilateral); there is also an increased risk if there are several 1st and 2nd degree relatives in the family with mammary gland cancer.
3. ***Pathologies of the organs of the genital system -*** uterine fibroids, endometriosis, ovarian polycystosis, inflammatory processes of the ovaries, which are characterized by hormonal levels disruption.

4. History of benign conditions and precancerous conditions of the mammary gland

- Benign tumors (fibroadenoma, adenoma, phylloid tumor)
- MFC non-proliferative forms - increases the risk 3-5 times, than in women who do not have this disease.
- MFC proliferative forms with rapid evolution - the risk of cancer is about 30 times higher than in the healthy population.

VI. Endocrine-metabolic factors defined by concomitant pathologies

Obesity. Obesity increases the risk of breast cancer by 3 times. In the peripheral adipose tissue, aromatization of testosterone (its transition to estrone) takes place, therefore, obese women have an additional source of estrogen, which increases the risk in both benign and precancerous and malignant processes of the mammary glands. Obesity after menopause (when the abundance of adipose tissue causes an increase in estrogen levels), greatly increases the risk of breast cancer. The frequent association of obesity with diabetes is one of the important risk factors for both breast and endometrial and ovarian cancer.

Acute and chronic liver diseases. It is characterized by various variants of degenerative disorders in hepatocytes, which can promote the appearance of cirrhosis. The metabolic and hormonal function of the liver is disturbed by steroid hormones: 17-β estradiol, thyroxine, triiodothyronine, even in the normal functioning of hormone-producing organs. These conditions lead to hyperestrogenemia, which in turn increases the risk of breast cancer.

Diseases of the thyroid gland. It is already established that there is a direct pathogenic mechanism between the endocrine thyroid status and the genesis of breast cancer. Diseases of the thyroid gland (autoimmune thyroiditis, pituitary adenoma, Hasimoto's goiter) have a favorable role in the appearance and development of breast cancer. A special role in the genesis of breast cancer is the hypofunction of the thyroid gland, which initiates the "thyroid form of breast cancer" or "cancer of young women" (18-35 years).

Topographic anatomy, physiology and vascularization of the breast

The mammary gland is located in the parietal thoracic region and is bounded superiorly by the third rib, inferior by the sixth or seventh rib,

medially by the edge of the sternum and laterally by the anterior axillary line. In depth, it reaches the fascia of the pectoralis major muscle (see Fig. 1).

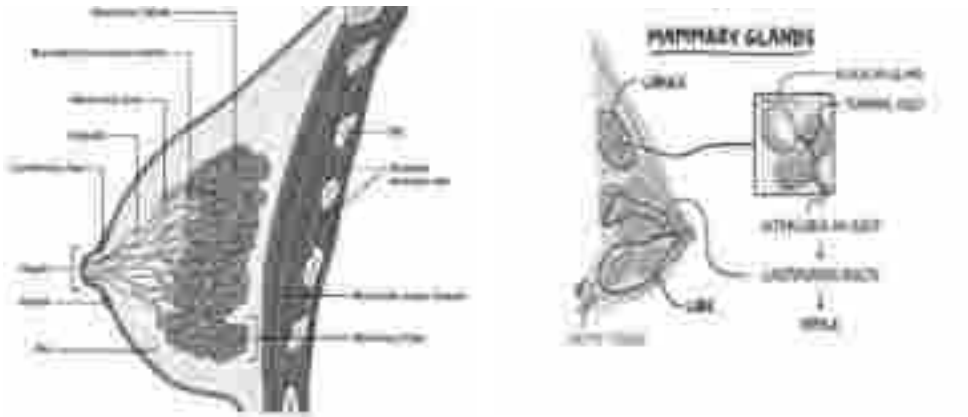

Fig. 1 *Topographic anatomy and structure of the mammary gland*

The mammary parenchyma consists of 10-20 glandular lobes (lobus glandulae mammariae). The lobes are separated from each other by dense connective tissue and adipose tissue. In turn, the lobes are divided by conjunctive septa into lobules. The lobes have a pyramidal shape, with the tip towards the papilla and the base towards the periphery. Each lobe represents a branched tubulo-acineal gland, from which the secretion product accumulates in a main collecting duct called the lactiferous duct or the galactophore duct. The ducts do not anastomose with each other, so the tip of the nipple is "sieved" by these pores (sieve area). The milk duct collects secretions from the interlobular ducts, and these, in turn, from the intralobular ducts. The mammary papilla, or nipple, is a cylindrical or conical protrusion, rounded, located in the center of the areola. The nipple has an irregular surface, on the top of which 15-25 milk ducts open through small holes. The stroma of the mammary gland is made up of connective and adipose tissue, crossed by numerous blood and lymph vessels, nerves and a rich capillary network.

Anatomical regions *(see fig. 2):*

1. Nipple.
2. The central quadrant.
3. The upper medial quadrant.
4. The upper side quadrant.
5. The lower side quadrant.
6. The lower medial quadrant.

7. Axillary tail - the accessory lobe of the mammary gland.

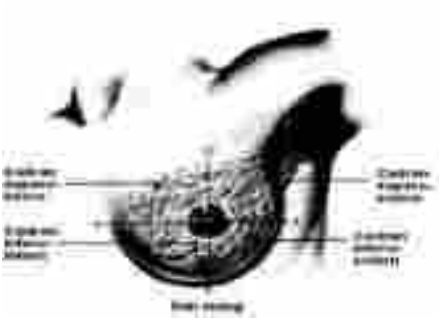

Fig. 2.*Anatomical regions*

Vascularization and innervation. The arteries come from the internal thoracic artery, the lateral thoracic artery, the superior thoracic artery and the posterior intercostal arteries of the 2nd, 3rd and 4th ribs. In the mammary gland, the arterial vessels have a radial distribution, which is why the incisions are always made radially. Their mammary branches form a superficial network in the premamarous adipose tissue and a periacinous network. The veins start from the periacinous network, reach the superficial network (very visible during lactation), called the Haller network. From here, the veins flow into the axillary vein, into the internal thoracic vein, into the superficial veins of the neck and anterior abdominal wall (see Fig. 3). The nerves come from the supraclavicular branches of the cervical plexus, from the thoracic branches of the brachial plexus and from the intercostal nerves II, III and IV. There is also a nice innervation of fibers provided by the arteries. Gland secretion is regulated by hormones.

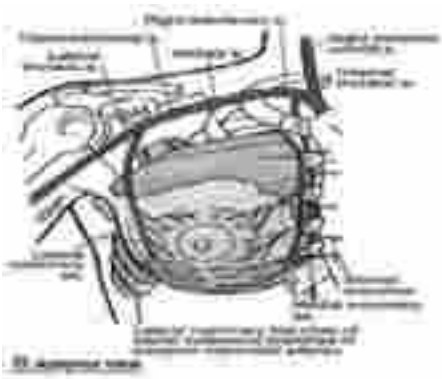

Fig. 3. *Vascularization of the mammary gland*

Diagnostic methods

Clinical investigations:

Accusations - the presence of the breast tumor can be the first symptom of the disease in 80-90% of cases. Depending on the clinical manifestations, breast cancer is divided into the following forms:

The nodular form (nodosis) *has 2 stages of development:*

1. **Preclinical stage -** is characterized by the presence of non-palpable tumor, which is usually detected occasionally by one of the instrumental investigations (USG and / or mammography).
2. **Clinical stage** - is manifested by the presence of a hard formation, usually immobile, adheres to the skin of the mammary gland and / or soft tissues, has an uncertain outline, erased, with serrated edges. Breast pain is not characteristic of breast neoplasms, they can be present only in 5-8% of cases. It usually occurs in the advanced stages of the disease, when the tumor compresses or adheres to the blood vessels and nerves near the tumor.

Skin fixation often occurs, forming skin symptoms:

- ***the symptom of the field*** appears when the skin is slightly tightened above the tumor. The result is a retraction of the skin in the form of a field.
- ***The symptom of umbilical cord*** occurs in cases when the tumor adheres to the skin, resulting in a skin retraction in the form of a funnel.
- ***symptom of "orange peel" -*** lymphostasis occurs as a result of clogging of the lymphatic vessels with cancerous emboli, the skin having the appearance of an orange peel (see Fig. 4).

Fig. 4. *Skin signs in breast cancer, nodular shape*

- ***Krauze symptom -*** *hardening of the skin of the nipple and areola.*

Diffuse forms - are detected in 3-5% of cases. It is characterized by the absence of the tumor in the breast, the infiltration of the glandular tissue with unclear contours, edema, hyperemia, ulcer disorders (result of the disorder of the blood supply of the tumor). The disease progresses rapidly, metastasizing early in both lymphogenic and hematogenous ways. It is more common in young women, often during pregnancy, lactation or after abortions.

The diffuse form is manifested in the following forms:

1. **The infiltrative form -** edematous - the mammary gland is enlarged, hard, edematous, infiltrated, with reduced mobility. Due to the current edema, the breast increases two to three times in just a few weeks. The neoplastic invasion of the lymphatics of the skin also causes the appearance of the skin with the appearance of "orange peel". The onset is sudden, the evolution is rapid, and the prognosis is severe. The regional lymph nodes are usually metastatically affected, often forming a conglomerate.
2. **The mastitis form -** also called inflammatory carcinoma or carcinomatous mastitis, has a share of 6% of breast cancer. The mammary gland is enlarged, edematous. The skin is intensely hyperemic, with local hyperthermia and mastodynia, the symptom of "orange peel" may be positive, the nipple may be flat, edematous (see Fig. 5). It is often confused with acute mastitis.
3. **Erysipeloid form** - is characterized by hyperemia of the skin without well-defined borders, in the form of "tongues of fire", which sometimes pass on the rib cage. It is a cancer with a very aggressive evolution. The differential diagnosis is made with erysipelas.
4. **"Armor" or "shell" shape -** is characterized by a decrease in breast volume, crease formation, nipple retraction. Tumor infiltration of both breast tissue and skin covering the mammary gland is present. The skin becomes hard, with difficult mobility. Gradually, the process exceeds the limits of the mammary gland and extends to the chest wall, the other mammary gland, the neck. Tumor infiltration compresses the chest wall in the form of a "cuirass" and, in effect, "suffocates" the patient. The "cuirass"

form of cancer evolves most torpidly and is rebellious to treatment (see Fig. 6).

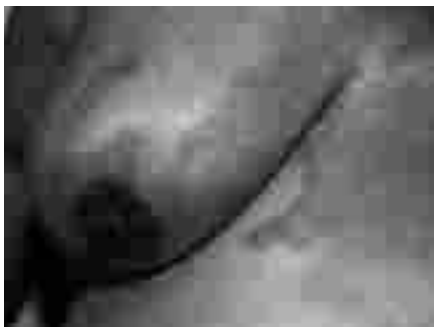

Fig. 5. *The mastitis form*

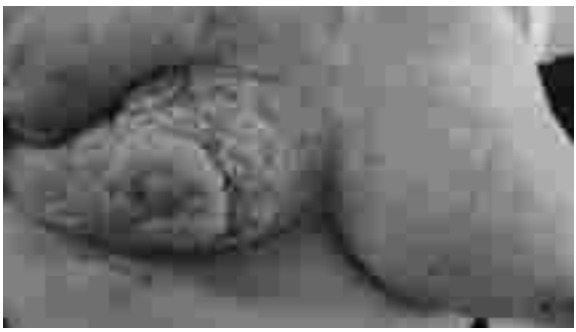

Fig. 6. *The erysipeloid (a) and "cuirass" (b) shape of the mammary gland*

Paget's disease – it is a rare form (4-7%) of breast neoplasia clinically manifested by an eczematous, pruritic lesion, which affects the areola-nipple complex. In rare cases (10%), when only the nipple epithelium is affected. The crusts are sticky and recover quickly if they are removed, much later in the place of the crusts occurs a painless itchy ulceration and sometimes bloody leaks from the nipple and the underlying tissues become hardened.

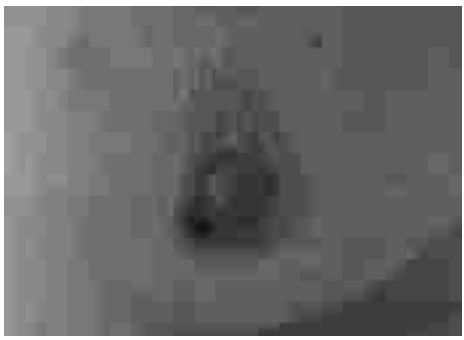

Fig. 7. *Paget's disease of the breast*

The condition gradually destroys the nipple and extends beyond the boundaries of the mammary areola. After a variable evolution, sometimes after several years, the tumor appears in the mammary gland. The location of the tumor also varies: sometimes it is close to the skin, other times - at a distance in the mammary gland. The diagnosis of Paget's disease is clinical and paraclinical by ultrasound, mammography, MRI of the mammary glands, fingerprint smear of the mammary glands and skin biopsy of the areola-nipple complex (punch biopsy).

Anamnesis - must include data on the presence of risk factors, hereditary-collateral history of both benign and malignant diseases of the mammary glands and other hormone-dependent organs. The time of onset

of menstruation and its character, the time of menopause, the number of births, abortions, including spontaneous, as well as diseases of the genitals, thyroid gland, liver, kidneys, etc. will be elucidated. We have to know the time of the first symptom when it appeared, to understand the subsequent evolution of the disease.

Inspection of mammary glands – it will be performed in a good light, sitting or standing. The patient's position will initially be with her arms on her hips, then raised above her head. Attention will be paid to the symmetry of the breasts, the external appearance, the condition of the areola and the nipple and, of course, to the deviations from the skin tissue: hyperemia, erythema, cyanosis, dilation of the subcutaneous veins. The areola and nipple are then examined for abnormalities in the form of nipple secretions, ulcers, and thickening of the skin.

Palpation of the mammary glands - it is performed in the vertical and horizontal position, in the "clockwise" direction. The mammary gland is pressed lightly towards the chest wall with the fingertips and in circular movements, starting from the base of the gland to the nipple, it is carefully palpated without omitting a segment of the mammary gland. Palpation of the breast ends in the upper-outer quadrant. The axillary, subclavicular and supraclavicular regions, the main lymphatic drainage areas, are further examined for possible lymphadenopathy. At the end, lightly press on the nipple to see if there are any secretions.

If we find a formation in the mammary gland, the examiner must first determine its location, size, then other characteristics.

The examination will be done, preferably, 5-7 days after menstruation, when the breasts are no longer painful and swollen, so as not to create discomfort. Menopausal women can be examined at any time.

Paraclinical investigations:

- Investigation of organs involved in hormone synthesis and purification (liver, thyroid gland, adenohypophysis, as indicated - adrenal glands)
- Peculiarities of hormonal homeostasis (PRL, LH, FSH, TSH, T3, T4, Cortisol, ES, PG)
- tumor markers CA 15-3, CEA.

Instrumental investigations:

Breast Ultrasound can be performed at any age, including pregnant women. It is performed to detect any pathology located in the mammary glands or once a year for prophylactic purposes. The entire mammary area is examined, including the regional ganglion regions. It has a number of undeniable advantages over mammography, and is useful regardless of the patient's age. The result of the ultrasound is not influenced by the structure of the breasts, does not have ionizing radiation, is not painful and can be repeated as many times as necessary.

ECO DOPLLER allows the analysis of the vascularization of a formation and of the regional lymph nodes, the malignant tumors being intensely vascularized.

Mammography is one of the most effective methods of detecting BC. This method can detect tumors that cannot be detected on clinical examination. The effectiveness of this method in detecting breast cancer depends on the size of the tumor and the density of the mammary gland tissue. Mammographically, the cancer has a spiky (stellate) appearance with / without numerous grouped microcalcinates, skin thickening and axillary lymphadenopathy (see fig. 8). The mammographic examination is performed strictly after the age of 35, it is indicated by the family doctor or oncologist to detect the pathology located in the mammary glands. It has a sensitivity of 85-90%, detecting breast pathology about 2 years before the perception of any clinical sign. Various mammography techniques are used, including the classical and digital method, which is the most commonly used.

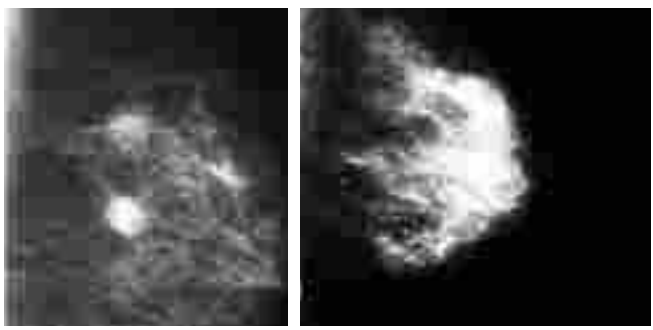

Fig. 8. *BC mammographic appearance: speculative character and grouped microcalcinates*

Nuclear magnetic resonance (MRI) of the mammary gland represents a method of superior informativeness to other diagnostic methods indicated in:

- non-informative mammographic images
- primary axillary lymphadenopathy without detection of mammary gland formation by other methods of investigation
- screening of high-risk young patients (mutations in BRCA 1 and BRCA 2 tumor suppressor genes)
- suspicion of postoperative recurrence
- staging of multiple tumors: multifocal (in the same quadrant), multicenter (in different quadrants) or bilateral (both mammary glands).

Fine needle aspiration (FNA) aims to extract cells or cell groups from various lesions. The method involves inserting the needle to the level of the lesion. In the case of small tumors, the method can be ultrasound guided, in which the examining doctor constantly visualizes the needle, it has the following advantages:

- safety of the approach of the lesion - no important structures are concerned, especially vascular;
- safety of tissue extraction from the formation

Fine needle aspiration from solid formations involves minimal discomfort and after performing the procedure the patient can perform normal daily activities.

Fingerprint smear with cytological examination in case of nipple removal or ulceration of the nipple and areola.

Core needle biopsy presents an informativeness of over 90% in establishing the diagnosis (see fig. 9). Efficient in performing morphological and immunohistochemical analysis of patients with cytologically confirmed diagnosis or established clinically and paraclinically without cytological confirmation. If necessary (small tumors, difficult to palpate, deep located in the glandular tissue) the biopsy will be performed under ultrasound or mammography guidance.

Fig. 9. *Core needle biopsy*

Ductography is performed in case of suspected pathological secretion from the nipple. It is carried out by introducing into the galactophore ducts about 0.5-2 ml of contrast medium. Subsequently, by radiological examination, the formation is detected.

To determine the spread of the process:

Mandatory:

- Chest R-graph
- USG of the thyroid gland, abdominal organs, retroperitoneal, small pelvis
- Scintigraphy of the skeleton in "whole body" mode
- CT brain - contrast, liver - angio CT plus 3 phases (in case of suspicion at secondary process)
- Tomosynthesis of chest organs, bones in case of uncertain diagnosis of secondary processes (Mt in the lungs, liver, bones, etc.)
- CT with or without contrast will be performed in case of uncertain diagnosis of secondary processes (metastases in the brain, lungs, liver, bones, etc.).
- MRI of internal organs - to assess the spread of the process (in case of exhaustion of the possibilities of other diagnostic diagnostic methods)
- Determination of BRCA1 / BRCA2 mutations in patients with breast cancer with aggravated hereditary collateral history (2 and more relatives of grade 1-2).

CLINICAL CLASSIFICATION OF BREAST CANCER - TNM

TNM International Classification, 8th edition (revised in 2017 by the International Anticancer Center)

T- primary tumor
Tx - insufficient data to assess the extent of the primary tumor.
To - nonpalpable tumor in the mammary gland
Tis - pre-invasive carcinoma ("in situ" carcinoma)
Tis (DCIS) carcinoma "in situ" ductal
Tis (Paget) - Paget's disease of the nipple without tumor in the glandular tissue.
Paget's disease with the presence of the tumor in the mammary gland is

classified according to the size of the tumor.

T1- tumor up to 2 cm.

T1mi- tumor smaller than 0.1 cm.

Tla- tumor of at least 0.1 cm, but not more than 0.5 cm.

Tlb - tumor of at least 0.5 cm, but not larger than 1 cm.

T1c - tumor whose diameter does not exceed 2 cm.

T2 - tumor with a diameter greater than 2 cm but not exceeding 5 cm.

T3 - tumor larger than 5 cm.

T4 - tumor of any size with direct damage to the chest wall or skin. The chest wall includes the ribs, the intercostal muscles, the anterior dentate muscle and not the pectoralis muscle.

T4a - spread on the chest wall.

T4b - edema (including the "orange peel" mark), skin ulceration and the presence of intracutaneous metastases on the surface of the mammary gland.

T4c - described signs at T4a and T4b.

T4d - infiltrative-edematous form of mammary gland cancer.

N - regional lymph nodes (clinical)

Nx - insufficient data for the assessment of regional lymph nodes.

N0 - there are no regional metastases.

N1 - metastases in the ipsilateral axillary lymph nodes.

N1mi- micrometastases from 0.2 to 2.0 mm

N2 - metastases in the ipsilateral axillary lymph nodes attached to each other.

N2a - axillary metastases with ganglia adhering to each other or to other adjacent tissue structures.

N2b - metastases in the intramammary lymph nodes with no clinical manifestations of axillary metastases.

N3 - metastases in the ipsilateral subclavian lymph nodes with or without impairment of the axillary lymph nodes or intramammary, ipsilateral axillary lymph nodes, or supraclavicular and axillary metastases with or without metastatic impairment of the ipsilateral intramammary lymph nodes.

N3a - metastases to the subclavian lymph nodes (a lymph node or group of lymph nodes may be affected).

N3b - metastatic damage to the intramammary and axillary lymph nodes.

N3c - metastases in the supraclavicular lymph nodes.

M - distant metastases
Mx - insufficient data to assess the presence of distant metastases.
M0 - there are no signs of distant metastases.
M1 - there are distant metastases.

CLASSIFICATION OF BREAST CANCER ACCORDING TO STAGE

0 Stage describes non-invasive mammary gland cancer (for example, "in situ" ductal carcinoma). At this stage, there is no clear evidence of the likelihood of atypical cells spreading to adjacent normal tissues.

I Stage includes the situation in which the tumor is not larger than 2 cm in size and is not extended outside the mammary gland (thus not affecting the lymph nodes).

II Stage is divided into two subcategories:

IIA -is the invasive type of mammary gland cancer in which the tumor cannot be detected in the breast, but atypical lymph nodes are present in atypical cells. Another situation may be when a tumor whose size does not exceed 2 cm and which has spread to the axillary lymph nodes is identified or when the presence of a tumor between 2 and 5 cm in size has been detected but has not metastasized to the lymph nodes. axillary lymphatics;

IIB – invasive neoplasm with a size between 2 and 5 cm, which has extended to the axillary lymph nodes, but may also be the case if the tumor is larger than 5 cm, without metastases in the lymph nodes.

III Stage is divided in:

IIIA - the tumor was not detected in the mammary glands, but the malignant cells are present in 4-9 axillary lymph nodes, or when the tumor is over 2 cm, with damage from 1-3 to 4-9 axillary lymph nodes;

IIIB –tumor extending to the chest wall or to the skin, or inflammatory carcinoma affecting 4-9 of the axillary lymph nodes;

IIIC – the absence of the primary tumor or the presence of a tumor of any size, without affecting the neighboring organs, but with the invasion of more than 10 axillary ganglia or the invasion of the subclavian ganglia.

IV Stage – any stage of the tumor, any degree of lymph node invasion, but with distant metastases.

INTERNATIONAL HISTOPATHOLOGICAL CLASSIFICATION OF BREAST CANCER

(World Health Organization Classification of Tumors of the Breast Lyon: IARC, 2016)

- Epithelial tumors
  - o Microinvasive carcinoma
- Invasive carcinoma
  - ♦ Non-specific invasive carcinoma (NST)
    - ▪ Pleomorphic carcinoma
    - ▪ Giant cell osteoclast-like carcinoma
    - ▪ Carcinoma with choriocarcinomatous component
    - ▪ Carcinoma with melanotic component
  - ♦ Invasive lobular carcinoma
    - ▪ Classical lobular carcinoma
    - ▪ Solid lobular carcinoma
    - ▪ Alveolar lobular carcinoma
    - ▪ Pleomorphic lobular carcinoma
    - ▪ Tubulo-lobular carcinoma
    - ▪ Mixed lobular carcinoma
  - ♦ Tubular carcinoma
  - ♦ Carcinoma sieves
  - ♦ Carcinoma mucinos
  - ♦ Carcinoma with medullary component
    - ▪ Medullary carcinoma
    - ▪ Atypical medullary carcinoma
    - ▪ NST invasive carcinoma with medullary component
  - ♦ Carcinoma with apocrine differentiation
  - ♦ Carcinoma with seal ring differentiation
  - ♦ Invasive micropapillary carcinoma
  - ♦ NST metaplastic carcinoma
  - ♦ Rare types
    - ▪ Carcinoma with neuroendocrine changes
    - ▪ Well-differentiated neuroendocrine carcinoma
    - ▪ Poorly differentiated neuroendocrine carcinoma (microcellular carcinoma)
    - ▪ Carcinoma with neuroendocrine differentiation
    - ▪ Secretory carcinoma

        - Invasive papillary carcinoma
        - Acinar carcinoma
        - Mucoepidermoid carcinoma
        - Polymorphic carcinoma
        - Oncocytic carcinoma
        - Lipid-rich cell carcinoma
        - Glycogen-rich cell carcinoma
        - Sebaceous carcinoma
        - Tumors of the sebaceous glands / skin appendages
        - Cylindrome
        - Clear cell hydenoma
- Epithelial-myoepithelial tumors
    - Pleomorphic adenoma
    - adenomyoepithelioma
        - Adenomyoepithelioma with carcinoma
    - Cystic adenoid carcinoma
- Precursor lesions
    - Ductal carcinoma in situ
    - Lobular neoplasia
    - In situ lobular carcinoma
    - Classical lobular carcinoma in situ
    - Pleomorphic lobular carcinoma in situ
    - Atypical lobular hyperplasia
- Intraductal proliferative lesions
    - Ductal hyperplasia
    - Columnal lesions with fatty epithelial atypia
    - Atypical ductal hyperplasia
- Papillary lesions
    - Intraductal papilloma
    - Papillary intraductal carcinoma
    - Encapsulated papillary carcinoma
- Benign epithelial proliferations
    - Sclerotic adenosis
    - Apocrine adenosis
    - Microglandular adenosis
    - Radial sclerotic lesions
    - Adenoma

- Mesenchymal tumors
  - Nodular fascia
  - Myofibroblastoma
  - Desmoid fibromatosis
  - Inflammatory myofibroblastic tumor
  - Benign vascular lesions
    - hemangioma
    - Angiomatosis
    - Atypical vascular lesions
  - Benign tumors of the peripheral nerve endings
    - Neurofibroma
    - Schwannoma
  - Lipoma
    - Angiolipoma
  - Liposarcoma
  - Angiosarcoma
  - Rhabdomyosarcoma
  - Osteosarcoma
  - leiomyoma
  - Leiomyosarcoma
- Fibroepithelial tumors
  - Fibroadenoma
  - Phyllodes tumor
    - Benign
    - Borderline
    - Malignant
    - Low-grade periductal stromal tumor
  - Hamartoma
- Nipple tumors
  - Nipple adenoma
  - Paget's disease of the nipple
- Metastatic tumors
- Tumors of the mammary gland in men
  - Gynecomastia
  - Carcinoma
    - Invasive carcinoma
    - in situ carcinoma

- Other clinical types
  - Inflammatory carcinoma
  - Bilateral mammary gland cancer

THE MORPHOPATHOLOGICAL DEGREE OF DIFFERENTIATION OF BREAST CANCER

GX - degree of differentiation impossible to establish
G1 - high degree of differentiation
G2 - average degree of differentiation
G3 - low differentiation
G4 - undifferentiated tumor

MOLECULAR CLASSIFICATION OF BREAST CANCER

(St. Gallen International Breast Cancer Conference, 2015)

Luminal subtype A ER + and / or PR≥20%, HER-2 / neu- and Ki-67 <20% (negative)

Luminal subtype B:

- ER +, any PR, HER-2 / neu + and any Ki-67
- ER + and / or PR- / <20%, HER-2 / neu- and high expression Ki-67 ≥20% (positive)

Subtype HER-2neu/+ ER-, PR-, HER-2/neu+

Subtype TNBC (triple negative)/basal-like ER-,PR-, HER-2/neu-

Normal-like subtype ER-,PR-, HER-2/neu-, EGFR+, CK 5/6+

Metastatic ways

Lymphatic circulation. Lymphatics are of particular importance because they are the main route of spread of neoplastic cells. They are divided into:

1. Superficial - collects lymph from the skin, areola and nipple.
2. Deep - collects lymph from the glandular lobes and converges to a circumareolar collector (Sappey lymphatic plexus).

From here there are three directions of lymph flow: external (axillary), internal (parasternal) and inferior (submammary, transpectoral). The main lymphatic pathway (75% of the lymphatic flow) of the breast has an external direction, represented by 2-3 thick trunks that start from the areolar lymphatic plexus, surrounds the lower edge of the pectoralis major (where there is a Sorgius paramamar ganglion), perforates the axillary fascia and reach the axillary ganglia. The internal lymphatics originate

from the inner part of the gland, follow the lymphatic collectors that accompany the internal thoracic vessels and flow into the subclavicular, supraclavicular ganglia or directly into the jugular trunk. The lower or submammary lymphatics originate from the deep surface of the gland. Some of them run along the aponeurosis pectoralis muscle and flow into the axillary ganglia. Others cross the pectoralis major and run between it and the pectoralis minor, flowing into the subclavian ganglia. Between the large and small pectorals is the interpectoral ganglion group (Rotter).

Regional lymph nodes:

a. **Superficials:**

b. **Axillary:**

- Level I (basal / inferior area of the axillary fossa) includes the lymph nodes located laterally at the edge of the pectoralis minor muscle;
- Level II (middle area of the axillary fossa) includes the lymph nodes located under the small pectoralis muscle between its lateral and medial edges and the interpectoral lymph nodes (Rotter);
- Level III (apical area) includes the ganglia located medially by the pectoralis minor muscle (see Fig. 10).

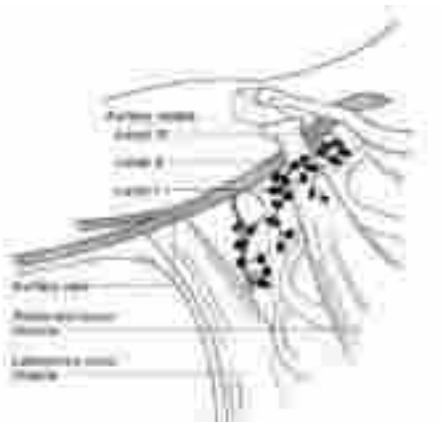

Fig.10. *Axillary lymph nodes*

a. **Subclavicular (ipsilateral)**

b. **Subscapular (ipsilateral)**

1.Profounds:

a.Intramammary (retrosternal) located in the intercostal region (at the level of ribs IV-V) at the edge of the sternum in the endothoracic fascia.

Tumors located in the lateral quadrants usually spread in the superficial lymph nodes, in the medial quadrants - in the deep lymph nodes, and with central location - radially, in all lymph nodes.

The Gerota accessory pathway is the lymphatic pathway that affects the lymph nodes of the heart and the sickle ligament.

Sentinel lymph node - is the first lymph node to drain lymph from the tumor. Its identification allows to establish the diagnosis with precision

regarding the lymph node status, being considered also "the mirror of the condition of the remaining regional lymph nodes".

Dissemination (metastasis) of the processes can take place by blood and / or lymphatic route. Virtually all organs can be affected by blood, but the most common are: bone system, liver, ovaries (Krukenberg tumors), lungs, brain, pleura (sero-hemorrhagic pleurisy), spleen, etc.

Dissemination of malignant cells by lymphogenesis can occur in both regional and distant lymph nodes.

TREATMENT OF BREAST CANCER

The treatment of mammary gland cancer has a complex character, which includes surgical treatment, with cytostatics, radiotherapy and hormone therapy. The treatment strategy is developed based on the following criteria: age of the patient, stage of the tumor process, morphopathological type, level of lymphovascular invasion, degree of tumor differentiation, expression of tumor markers (ER, PR, HER-2 / neu, Ki- 67), the number of affected regional lymph nodes, the presence of distant metastases, concomitant pathologies (cardiovascular, hepatic, renal, pulmonary, diabetes, etc.), as well as the patient's consent to the proposed method.

Surgical treatment

Types of mastectomy

1. ***Radical mastectomy (Halsted-Maier).*** At the end of the 19th century, in 1894, William Halsted
2. laid the foundations for modern treatment of breast cancer and implemented the technique of enlarged mastectomies to which he linked his name. The proposed technique involves removal of the mammary gland, small and large pectoral muscles and total lymphadenectomy (axillary, subclavicular, subscapular and interpectoral). Halsted mastectomy offers advantages of enlarged lymph node dissection, but at the same time has disadvantages for the patient: the presence of severe sequelae (upper limb lymphedema, plexalgia, unsightly appearance of the anterior part of the thorax, etc.). cases when the tumor invades the large and / or small pectoral muscles.

2. *Modified radical mastectomy:*

a. Modified radical mastectomy (Patey-Daisen) - the large pectoralis muscle is preserved, with satisfactory aesthetic and functional effects.

It consists in the ablation of the breast together with the fascia of the pectoralis major, and the ganglion highlighting (level I-III and interpectoral) is performed after the sectioning of the pectoralis minor muscle. By maintaining the pectoralis major, the functionality of the upper limb is more satisfactory than after the Halsted mastectomy, but this procedure cannot provide enough space for the correct dissection of the inter- and subpectoral area (see Fig. 11).

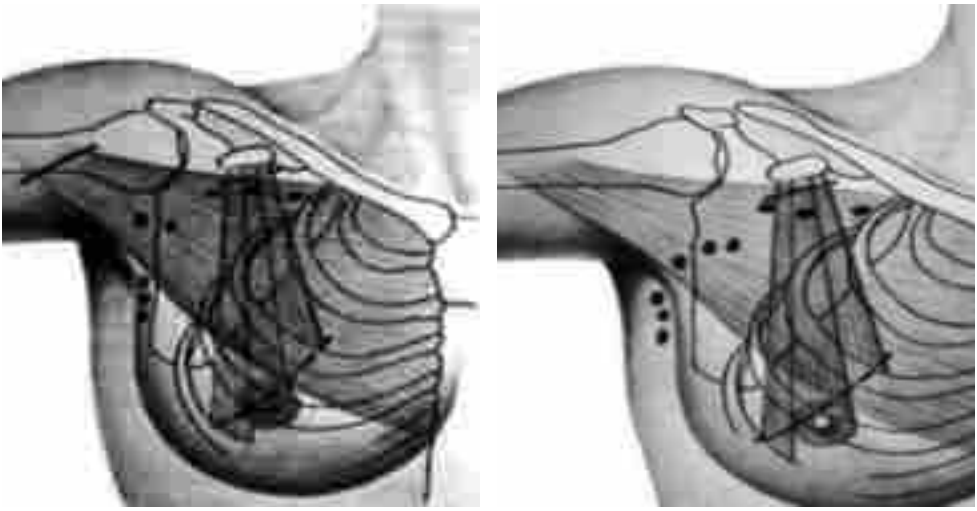

Fig.11. *Halsted-Maier radical mastectomy (a) and modified radical mastectomy Patey-Daisen (b)*

b. Modified Radical Mastectomy (Madden) - is a surgical technique currently practiced more frequently, in which the ablation of the breast is performed together with the fascia of the pectoralis major, with wide axillary (level I-III) and interpectoral, but with the preservation of both pectoralis muscles: large and the little one. The method has undeniable advantages, being aesthetic and functional, less common lymphostasis complication of the ipsilateral upper limb.

c. *Pirogov mastectomy* – is a surgical technique, which is rarely used, only in cases of decompensated concomitant pathology (severe cardiovascular disease, hepato-renal, decompensated diabetes, etc.), which limits the possibility of radical surgery. Pirogov mastectomy consists of removal of the mammary gland with the dissection of axillary lymph nodes only level I.

d. Holdien-Urban or Handley Mastectomy - for neoplasms located in

the inner quadrants of the mammary gland. It consists of removal of the major and minor pectoral muscles together with parasternal lymphadenectomy by resection of the costal cartilages II-IV and marginal sternal resection at this level.

e. *Trestioreanu mastectomy* – removal of the pectoralis minor muscle and axillary lymphadenectomy through a gap in the pectoralis major muscle.

f. *Chiricuța mastectomy* – chimerization of the pectoral muscles to have wide access to the lymph nodes.

3. Dahl - Iversen supraradical mastectomy – consists of performing supraclavicular lymphadenectomy. Other supraradical methods such as: interscapulo-humeral disarticulation - Prudent, triple lymph node curettage: axillary, internal breast, supraclavicular, mediastinal lymph nodes, Wangensteen, did not confirm more favorable survival data compared to other treatment methods, instead they were accompanied by significant operative mortality and disproportionate mutilation and were soon abandoned.

4. *Subcutaneous mastectomy*– involves only the removal of glandular tissue, preserving the skin, nipple and areola. The extemporaneous morphopathological analysis of the retromammelon area is performed intraoperatively. In the case of the presence of cancer cells, only the skin of the mammary gland is preserved, with the removal of the nipple-areolar complex. This type of intervention is used in the case of subsequent reconstruction of the mammary gland.

5. *Simple mastectomy* – consists in removing the mammary gland without regional lymph nodes. It is performed in cases of severe associated somatic pathology and the impossibility of performing radical surgical treatment.

6. *Sanitary mastectomy*– is performed in the case of tumors with destruction and / or hemorrhage. The main purpose of the intervention is to remove the tumor mass, stop the bleeding and, as a rule, it is palliative and not curative. In case of bleeding, surgery is performed urgently.

Conservative Breast Surgery (BCT Brest-Conserving Procedure) - excision of the tumor with a 3-4 cm layer of normal glandular parenchyma and axillary dissection through another incision.

Organ-threatening surgeries – include performing enlarged sectoral resections with regional lymphadenectomy. In the case of these interventions, the extemporaneous histological verification of the safety margins and of the subareolar area will be mandatory. If the result is positive, a resection or radical mastectomy will be performed. The tumor lodge is marked with titanium metal clips (clips) to facilitate the field of radiotherapy administration.

Simple sectoral resection – block removal of the tumor with a margin of resection of not less than 3 cm, without lymphadenectomy. It is performed in case of severe concomitant pathologies, in early stages without affecting the lymph nodes, for diagnostic purposes or at the categorical refusal of the patient to another type of surgical treatment *(see fig. 12).*

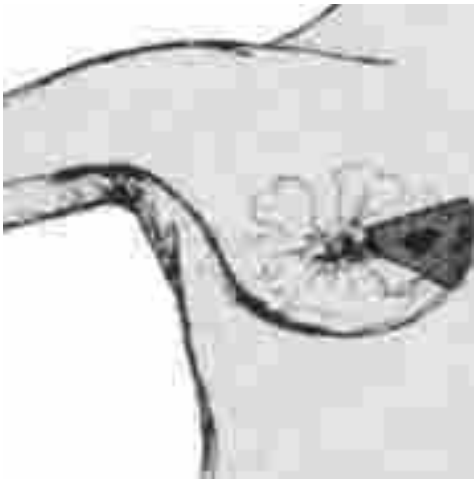

Fig.12. *Simple sectoral resection*

Excision of the lymph node sentinel is a standard staging technique in the surgical management of the mammary gland. A minimum of 6 hours and a maximum of 24 hours preoperatively, peritumoral using a radioactive tracer is injected with a radioactive substance or a pigment, or both. Technetium 99-labeled colloidal albumin, a radioactive isotope, or dyes such as methylene blue or visible substances in the FLARE-type infrared fluorescent spectrum may be used. The injected peritumoral tracer is taken by the lymphatic system and transported to the first lymph node that takes lymph from the tumor. Detection and biopsy of the sentinel lymph node is performed intraoperatively using a portable intraoperative probe, called a gamma camera, the radioactive colloid in the sentinel node is detected, which is then removed and transmitted for intraoperative histological diagnosis. The recommendation of only sentinel lymph node excision is based on the results of randomized studies, demonstrating a reduction in upper limb morbidity after sentinel lymph node excision compared to axillary lymph dissection (pain, lymphedema, sensory deficits, etc.). If the lymph node is not invaded, only the tumor without the lymph nodes is excised.

Reconstruction of the mammary gland – it can be immediate (after mastectomy) or late (after complex treatment). It depends on several factors such as: the general condition of the patient, the intraoperative technique, the probability of an adjuvant treatment - radiotherapy or chemotherapy and last but not least, the patient's desire. Immediate reconstruction is not recommended for patients requiring postoperative radiotherapy, as this may lead to inability to perform adjuvant radiotherapy and / or adverse aesthetic outcomes. In advanced locoregional processes, especially in the case of inflammatory forms, patients with severe concomitant pathologies these interventions are contraindicated.

Breast reconstruction techniques:

1. *Partial breast reconstruction:*
   - Adipose tissue transfer
   - Autologous tissue - neighboring flaps
2. *Complete reconstruction of the breast parenchyma:*
   - Expander
   - Implant
   - Autologous tissue
   - Adipose tissue

Complications and postoperative effects:

- Mutilation due to breast amputation is a pronounced psychological shock for women, being much more difficult to tolerate than a hysterectomy.
- Local complications: bleeding, postoperative hematoma, inflammatory process, delayed scarring, lymphocytes, painful keloid scars.
- Upper limb lymphedema favored by retractile and keloid scars, lymphatic ablation and / or axillary thrombosis.
- Residual pain - feeling of heaviness or chest tightness.
- Stewart-Treves Syndrome - upper limb lymphangiosarcoma after radical mastectomy.

Bilateral prophylactic mastectomy to reduce the risk of cancer in women with mutations in the BRCA 1 and BRCA 2 genes or contralateral for patients diagnosed with CGM and genetic mutation.

CHEMOTHERAPEUTIC TREATMENT OF BREAST CANCER

The therapeutic strategy is influenced by: TNM stage of the disease, estrogen and progesterone receptor levels, HER2 / neu overexpression, degree of differentiation (G) and tumor proliferation index (Ki67), vascular invasion, age, menstrual status, etc.

Indications for chemotherapy:

- As adjuvant treatment in stages I, II, III (4-6 cycles)
- In the treatment of metastatic breast cancer
- As a neoadjuvant treatment in stages II, III (3-6 cycles)
- In the treatment of recurrent breast cancer

Chemotherapy for metastatic and recurrent disease is recommended in:

- LUM subtype A or B with massive visceral impairment and clinical signs
- LUM A or B subtype resistant to hormone therapy
- ER negative breast cancer and positive PR

Possible contraindications for specific chemotherapeutic treatment:

- Lack of morphological verification of the disease
- General condition, which does not allow specific treatment
- Presence of decompensated concomitant pathologies
- Laboratory indices - outside the permissible limits sufficient to perform the specific treatment
- Lack of patient consent for specific antitumor treatment.

RADIOTHERAPY TREATMENT OF BREAST CANCER

Radiation therapy in breast cancer aims to achieve local control without recurrences and metastases and thereby increase survival and quality of life. The radiotherapy treatment is applied depending on the stage of the disease, the volume of the surgery, the morphopathological form, the risk factors and the age of the patient.

Radiotherapy is performed on the linear accelerator or on the cobalt therapy devices, and on the internal mammary lymph nodes - by alternating photons and electron beams, or only with electrons, depending on the depth of the parasternal ggl chain. Irradiation of the 60Co source parasternal area with gamma therapy devices or only with the photon beam at the linear accelerator may lead to the development of pneumonia, mediastinitis, and postradiant pericarditis.

Irradiation of the mammary gland:

The target volume of irradiation includes the breast tissue with a minimum dose distribution on adjacent tissues, which can be achieved using such compensatory methods as: wedge filters, positioning the patient on the abdomen, etc. The mammary gland should receive a dose of 44-50 Gy, with 2 Gy per session. Additional irradiation of the tumor bed (boost) is recommended in patients at high risk of local recurrence. This can be done with an electron or photon beam. The necessary condition for irradiating the tumor bed is its intraoperative marking with surgical clips.

Chest wall irradiation:

Irradiation of the chest wall and lymph nodes is performed in case of primary tumors larger than 3 cm, multicenter disease, microscopic lymphovascular and perineural invasion, degree of differentiation G3, positive resected edges, at any pN + after radical mastectomy - radiotherapy is indicated. The target volume of irradiation includes the ipsilateral chest wall, the postmastectomy scar, and the drainage hole. There are many irradiation techniques using X-rays and / or electrons. The most commonly used chest wall is 44-50 Gy with 2 Gy per session. It is recommended to plan for the treatment of radiation with the help of CT in order to identify the lung and cardiac volume in order to minimize the exposure of these organs to irradiation. Particular attention should be paid to the use of bolus material when photons (X-rays) are used to ensure adequate dose to the skin.

Irradiation of regional lymph nodes:

Irradiation of the entire ganglion regions (axillary ggl, supraclavicular) is performed in the following cases: when more than 3 ggl axillary are affected, microscopic invasion of the ganglion capsule, doubts about the quality of the axillary evidence. The assessment of the target radiation volume is performed using the planning of the radiant treatment based on CT. For axillary and subclavian ggl, the irradiation depth varies depending on the patient's weight. Considering that internal mammary glands are usually not visible on CT images, assessing the location of the internal mammary artery and vein can help identify them. Typical recommended doses are 44-50 Gy with 2 Gy per session plus additional irradiation of the tumor bed. Irradiation rate - 5 times a week. The ipsilateral internal mammary lymph nodes are irradiated in cases when they are affected,

otherwise, radiotherapy to the internal mammary lymph nodes remains at the discretion of the radiotherapist.

Preoperative radiotherapy it is applied in case of widespread local processes (T4 processes), in case of ineffectiveness of neoadjuvant chemotherapeutic treatment, to medical contraindications to surgery or refusal of the patient to surgery.

Radiation therapy for metastatic breast cancer

Brain metastases

In case of solitary metastases in the brain, the treatment tactic is established by a consultative medical council consisting of: mammal oncologist, medical oncologist, neurosurgeon and radiotherapist, to justify the refusal of surgical treatment or chemotherapy. The brain is irradiated with a dose of 30 Gy by 3 Gy per session. After irradiation, it is mandatory to consult a medical oncologist.

Bone metastatic disease

The most commonly used regimen is 3 Gy per session up to a summary dose of 30 Gy. In case of metastatic damage to the spine, the irradiated volume includes the affected vertebra and one vertebra above and below.

Other possible palliative radiotherapy regimens:

-summary dose 20-28 Gy with 4 Gy per session

-summary dose 20 Gy with 5 Gy per session

-1 single session with 8 Gy in case of violent pain syndrome and lack of spinal cord compression.

The treatment of local recurrences *is individual and depends on the previous treatment.*

Contraindications to radiotherapy:

- lack of morphological verification of the disease;
- serious general condition, which does not allow specific treatment;
- the presence of decompensated concomitant pathologies;
- deviation of laboratory indices outside the permissible limits sufficient to perform the specific treatment.

HORMONAL THERAPY IN BREAST CANCER CANCER

Indications for hormone treatment:

- As adjunctive therapy in patients with estrogen and progesterone positive tumors (tamoxifen, toremifene, aromatase inhibitors);
- Ovarian ablation as adjunctive treatment in premenopausal

women with estrogen and progesterone positive tumors (bilateral ovariectomy, ovarian irradiation, LH-RH analogues);
- Ovarian ablation (bilateral ovariectomy, ovarian irradiation, LH-RH analogues) in premenopausal women with metastatic estrogen and progesterone positive tumors or with unknown receptors with subsequent administration of antiestrogens, aromatase inhibitors, progestins;
- In postmenopausal patients with metastatic estrogen and progesterone positive tumors or with unknown receptors;
- As a neoadjuvant treatment in locally advanced breast cancers;
- In the treatment of recurrent breast cancer.

10-year survival rate depending on stage

- Stage 0 > 95%
- Stage I 75 - 95%
- Stage IIA 45 - 85%
- Stage IIB 40 - 80%
- Stage IIIA 10 - 60%
- Stage IIIB 0 - 35%
- Stage IIIC 0 - 30%
- Stage IV < 5%

BREAST CANCER DURING PREGNANCY AND POSTPARTUM

Breast cancer is the most common malignancy diagnosed during pregnancy (1 cancer per 3,000 pregnancies). Diagnosis is delayed due to physiological changes in the pregnancy of the breasts. A breast tumor that persists for more than 2 weeks should be viewed with suspicion. The medical approach of the pregnant woman with breast cancer involves close communication with the patient, her family and with the medical team of obstetricians - gynecologists. The patient is the one who, fully informed, has to make a decision about the pregnancy.

Ist Trimester

In cases where breast cancer is diagnosed in the first trimester of pregnancy, the patient will be advised to terminate the pregnancy. The decision will be individualized after counseling. If the abortion is performed, the treatment of breast cancer is the same as in a non-pregnant woman. In the absence of abortion, the therapeutic option is surgical and radiotherapy treatment. Chemotherapy should not be given until the 14th

week of pregnancy to avoid the fetal teratogenic effect.

IInd and IIIrd Trimester

Pregnancy should not be interrupted, but surgical, chemotherapeutic and radiotherapy should be indicated. Chemotherapy will not be given after the 35th week. Remote evaluation of children exposed to uterine chemotherapy did not reveal a deficiency in neuro-motor and cognitive development, nor did organic abnormalities or malignancies. Hormone therapy and anti-Her2 / neu therapy are contraindicated in pregnancy. Birth is indicated after 37 weeks (avoidance of complications of prematurity). The mode of birth will depend on the obstetric indications. The last cytostatic treatment should be scheduled 3 weeks before birth to allow the hematogenous marrow to be restored. Ablation is recommended for patients undergoing systemic treatment or who have undergone chemotherapy during pregnancy.

Pregnancy after breast cancer treatment.

Patients of reproductive age should use effective methods of contraception both during the administration of specific antitumor treatment and for a period of 3-5 years after its completion. Before initiating cytostatic treatment, patients will be informed of the possible influence of these drugs on both ovarian function and fertility. To mention about the frequent cases of generalization of oncological disease on the grounds of pregnancy or lactation. It is known that most recurrences of the disease occur in the first two years after treatment. The patient will be informed of the risks of disease progression and / or development of fetal pathology before the recommended time. In case the patient wants to get pregnant, it is recommended to consult both the mammal oncologist and the reproductive-gynecologist.

BREAST CANCER IN MEN

CGM is much less common in men than in women (1: 150). It is found mainly in men with Klinefelter's syndrome and hypogonadism. It is usually a unilateral breast tumor. Treatment includes modified radical mastectomy, radiation therapy (in signs of local advancement). Adjuvant chemotherapy and adjuvant hormone therapy will be recommended according to the same criteria as for females.

BREAST SELF-EXAMINATION

Self-control involves examining the breasts by every woman at any age and includes inspecting and palpating the breast.

Inspection is done on both breasts in a large front and profile mirror. Attention is drawn to the symmetry of the breasts (it should be noted that normally in 50 - 60% of women the physiological asymmetry of the breasts persists). Breasts are examined for possible changes in the skin (thickening, hyperemia, umbilicus, etc.) or nipples (retraction, edema, erosions, eliminations, etc.).

Palpation is done in a vertical and/or horizontal position, palpating, in turn, each sector of the mammary glands on their entire surface. The movements are made in a spiral in the direction of the "clockwise", which must include the axillary areas. It is important for the woman to be familiar with the appearance and consistency of her breasts.

Breast self-examination is done monthly, 5-7 days after menstruation, when the breasts are no longer painful and swollen, so as not to create discomfort. When the woman is no longer menstruating (menopausal), it is preferable to choose a day of the month (eg birthday) that is easy to memorize. How to perform the self-examination should be demonstrated and explained by your family doctor or gynecologist during the first consultation. Women should be trained and informed about this technique. Several studies suggest that women who examine their breasts carefully and regularly can detect tumors up to 1 cm in size. The anatomical landmarks will be identified (rib edges, glandular area, submammary fold and armpit tip). Emphasis will be placed on the correct technique and sufficient time for this examination (see Fig. 13).

Important!!! It is strongly recommended to consult a family doctor in case of any suspicion of pathology in the mammary glands.

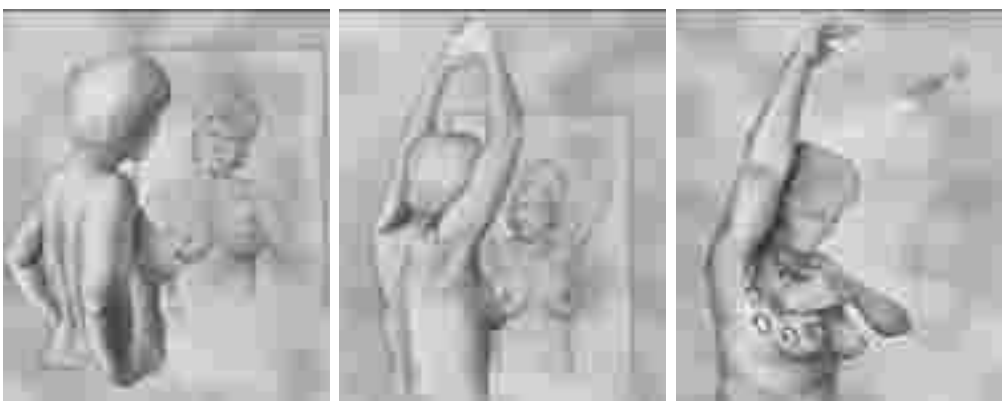

Fig.13.*Self-control of the mammary glands*

Developmental abnormalities of the mammary gland

Number anomalies:

- Amastia (congenital breast failure). The glandular tissue is completely missing. There is only the nipple, with or without the areola.
- Atelia. The mammary gland is within normal limits but the nipple is missing.
- Politelia - represents a supernumerary nipple, without an additional gland.

Polymastia - is the existence of supernumerary breasts that can be fully developed, or can be only rudiments (only the nipple) with or without areola. The supernumerary breasts are located in the anterior thoracic region, along the "milk line" (see Fig. 14). At the level of the supernumerary glands, all the diseases of the normally developed breast can develop: infections, benign, malignant tumors, etc.

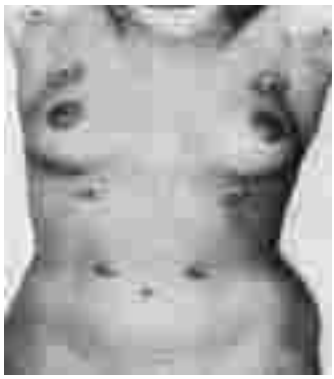

Fig.14 *Polymastia*

Volume anomalies:

- Atrophy of the mammary gland. It is most often due to the constitution, growth disorders and hormonal imbalance. It is usually bilateral.
- Hypertrophy of the mammary gland in women. It is mainly due to hormonal disorders, but can also be found in some cases of obesity. At first the hypertrophy is well tolerated, later as the breast grows it becomes painful, especially premenstrual.
- Male breast hypertrophy (gynecomastia). This condition can be uni- or bilateral. The increase in the volume of the mammary gland, which is rudimentary in men, occurs due to a hormonal imbalance between estrogen and testosterone.

Shape anomalies:

- Mastoptosis or breast prolapse. It is quite common in obese, asthenic and hypoplastic chest women. It can be of varying degrees, from mild ptosis to pronounced ptosis, in which a pronounced hypertrophy of the gland persists.
- Nipple shape abnormalities. It can be: short, umbilical or invaginated. The abnormality can be primary (congenital) or secondary (after an infection). Short history of unilateral retraction may be suggestive of breast cancer.

Benign diseases and precancerous conditions of the mammary gland

About one in two women has symptoms of a sore breast. Benign tumors of the mammary gland are characterized by a slow, expansive growth (compresses the neighboring tissue), are well encapsulated, most are the result of hormonal changes (hyperestrogenemia, hyperprolactinemia). After excision, it rarely recurs, does not invade local tissues and does not metastasize to other organs. The basic treatment is surgery - excision of the breast formations. Recurrences rarely occur, do not invade adjacent tissues and do not metastasize to other organs.

Risk factors:

- Improper diet: abuse of animal fats, smoking, alcohol abuse
- Professional and ecological factors: ionizing radiation, ultraviolet, chemicals
- Chronic mental trauma
- Traumatic gland injuries
- Pathologies of the endocrine organs (pituitary, ovaries, adrenal glands, etc.) or of the organs involved in hormone metabolism
- Hormonal disorders (hyperestrogenemia, hyperprolactinemia)
- Termination of pregnancy
- For a long time and without medical indications, hormonal preparations, including contraceptives
- Hereditary factor, etc.

Classification by tissue origin:

1. Conjunctives: lipoma, fibroid
2. Fibroepithelial: adenolipoma, fibroadenoma, phylloid tumor
3. Epithelial: adenoma, intraductal papilloma
4. Heterotopic: hamartoma, chondrome, osteoma, teratom
5. Vascular: hemangioma

Fibroadenoma– is a benign tumor consisting of glandular and fibrous breast tissue. Statistics show that 10% of women between the ages of 15 and 30 are prone to develop fibroadenomas of the mammary glands. These nodules may appear in isolation, but are often multiple. Breast fibroadenomas can be simple - and have a very low risk of developing breast cancer (about 1-2% higher than that of women who do not suffer

from these changes) and can be complex (they are slightly larger in size). and tend to occur in older women) (see Fig. 15).

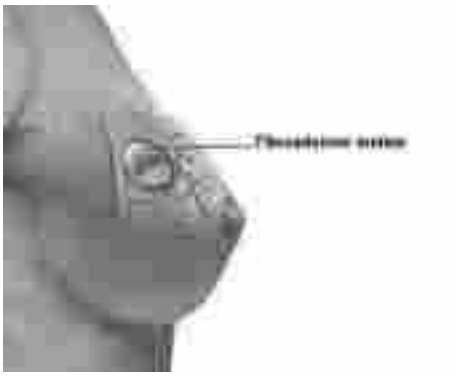

Fig.15. *Fibroadenoma*

Complex fibroadenomas have a slightly higher risk of developing malignancy than simple fibroadenomas.

The causes of breast fibroadenoma apathy are unknown. It appears to be influenced by estrogen, especially hyperestrogenemia, as it occurs most frequently in premenopausal or pregnant women, as well as in postmenopausal women undergoing hormone replacement therapy. Most fibroadenomas occur during the fertile period, with the menstrual cycle present, when the hormone level changes.

Clinical symptoms of fibroadenoma:

It is a formation with a round or oval outline, smooth and mobile. These tumors may be sensitive to palpation, even in the premenstrual period, when they may become congested due to hormonal changes. The size of the fibroadenoma varies from 1.0-5.0 cm to 15 cm.

On mammography, fibroadenomas appear as a smooth, round, oval, well-defined mass. Sometimes they are accompanied by coarse calcifications.

At breast ultrasound, fibroadenoma is a formation with a well-defined contour, homogeneous, round or oval, some slightly vascularized.

Microscopically, there are three histological forms of the disease:

- Pericanalicular type
- Intracanalicular type (fibrous stroma is abundant and compresses the ducts, creating the appearance of "deer antlers")
- Mixed type.

Treatment of fibroadenoma

It can vary depending on the histological type, size, number of tumors, etc. If the fibroadenoma is small, painless and keeps the same size, no further treatment is needed. However, regular breast ultrasound is recommended to keep the fibroadenoma under surveillance. If the fibroadenoma is more than 1.0 cm, is painful, enlarges or the result of the biopsy shows at least glandular epithelial cells with proliferation, surgical treatment is recommended - sectoral resection of the respective mammary gland.

Phyllodes tumor

Represents fibroepithelial lesions, morphologically similar to intracanalicular fibroadenoma, but characterized by a denser cellularity of the conjunctival component with generally benign evolution (see Fig. 16). Phylloid tumors are more common in women between the ages of 35 and 50, and are found in adolescents in 0.4% of cases.

Clinical features of phylloid tumors:

These tumors are hormone-dependent and have a multicenter origin. Hormonal disorders that occur at menopause can cause the tumor to develop, or it can trigger a severe proliferation in the case of a latent tumor with a sarcomatous transformation.

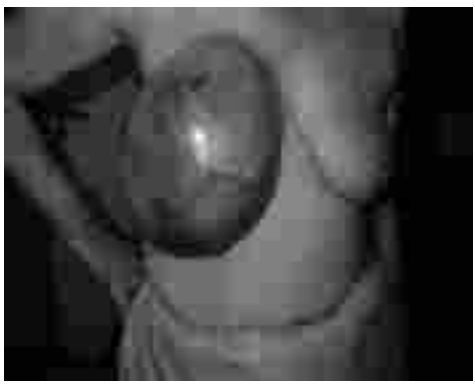

Fig.16. *Phylloid tumors*

Phylloid tumor clinically manifests itself as an inhomogeneous, dense, mobile tumor, with clear contours, polylobular character but with rapid proliferation (several weeks). The tumor can reach quite large sizes (up to 20 cm) and can cause skin changes with the prominence of the veins. The large size of the tumor leads to hyperextension of the skin with damage to the ducts, which can cause bleeding from the nipple. Nipple asymmetry is often observed. The regional lymph nodes are of normal size and consistency. Local recurrences are common (10-30%). Remote metastases are rare (<10%). Recurrences have a higher risk of malignancy than primary tumors.

Outbreaks of non-invasive cancer (in situ) or outbreaks of ductal cancer or lobular cancer can be detected in phylloid tumors.

Classification of phyloid tumors:

- Benign (75%)
- Borderline (16%)
- Malignant (9%)

Diagnosis of phylloid tumors:

- Clinical examination of the mammary glands
- Imaging explorations: ultrasound, mammography, MRI
- Fine needle puncture or biopsy - to determine the histopathological type of the tumor

Treatment of phyloid tumors:

Due to the fact that the phylloid tumor progresses rapidly and can turn into a malignant one, it can only be treated surgically.

Intraductal papilloma (cystadenoma papilloma)

Characteristics:

Intraductal papilloma (cystadenopapillum, "bleeding mammary gland") is a precancerous papillary lesion that is located in the ducts of the mammary gland. The disease can be detected at any age, both in young women and in those after 50-60 years (see Fig. 17)

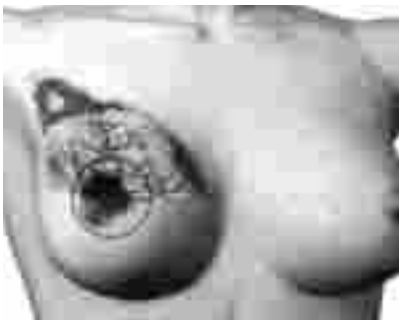

Fig. 17 *Intraductal papilloma*

In 50% of cases, intraductal papilloma can be manifested by a single symptom - the presence of clear, yellow-green or brown stools in the affected nipple.

Causes:

Intraductal papillomas can occur as a result of hormonal imbalance. Any hormonal disorder (ovarian dysfunction, uterine fibroids, abortion, obesity, stress, etc.) can cause both the appearance and growth of the tumor.

Another reason for the development of this pathology is the diffuse or nodular fibrocystic disease, a pathology in which the galactophore ducts of the mammary gland dilate and favorable premises for papillary growths appear.

Diagnosis of intraductal papilloma

Careful clinical examination may result in the presence of stools in the affected nipple, and often even the presence of a small formation in the mammary gland. To rule out the malignancy of the tumor, it is necessary to perform a smear-smear examination of the nipple. In addition, additional instrumental examinations may be used: ultrasound, ductography, mammography, and magnetic resonance imaging.

Treatment of intraductal papilloma:

Taking into account the fact that this disease belongs to the group of precancerous lesions of the breast, surgical treatment is mandatory. Usually, in order to have access to the duct affected by the papilloma, an incision

is made around the areola (paraareolar). During the operation, the affected tissue is removed and sent for emergency morphopathological analysis. In the case of malignant intraductal papilloma, a radical mastectomy is performed.

Breast lipoma

Characteristics:

Lipoma is a single or multiple tumor, made up of adipose tissue, that can appear on various areas of the body, including the mammary gland.

Cause of occurrence:

The cause of lipoma in the mammary glands has not been established. The main hypothesis was that of Wen's theory (lipoma is formed due to dysfunction of the sebaceous glands). But there is no clinical evidence for this. However, there are only a few factors that increase the likelihood of this disease: genetic predisposition (heredity), hormonal imbalance, trauma, hematomas, surgery, disorders of fat metabolism, immunosuppression, smoking, stress, etc.

Clinical symptoms:

In the mammary glands, the lipomas may be located superficially or deeply, but most are superficial. They are usually small, but can be more than 5 cm in diameter. They can grow over time. Sometimes lipomas can be painful when compressed on the nearby nerve endings or if they have many blood vessels in their structure. The appearance of the lipoma is yellowish, surrounded by a thin and transparent membrane like a protective capsule. There are also situations in which the capsule is missing and the shape is slightly irregular.

Diagnosis of lipoma:

The diagnosis is established as a result of the clinical examination of the mammary glands. The location of the tumor, its consistency and its size are determined. In cases where the tumor is large, mammography or MRI is indicated to determine possible compression or adhesion to the vessels and nerves.

Lipoma treatment:

Usually, treatment is not necessary for a small lipoma. However, if the lipoma shows signs of growth or is painful, your doctor may recommend surgical removal.

Hamartoma of the mammary gland

It represents a very rare pathology, which presents an agglomeration of fibrous tissue, even cartilaginous, of benign origin. It has a developmental flaw.

Characteristics :

- occurs in the embryonic period
- for a long time it can manifest itself without clinical changes
- more commonly diagnosed in people over the age of 30
- has a slow increase in size
- it maligns quite rarely

The treatment is surgical, sectoral resection of the mammary gland is performed with emergency morphopathological analysis of the removed material.

Lipogranuloma of the mammary gland

It is characterized by the formation of aseptic inflammatory processes, cysts and foci of lipocyte necrosis. Lipogranulomas are distinguished by the type of structure - diffuse and nodular.

Characteristics :

- The cause of the pathology can be trauma, sudden decrease in body weight, exposure to radiation and more.
- This condition is more common for women with macromastia than in women with small breast.
- Traumatic factors include bruising, medical manipulation, injuries to athletes, and more. In some cases, radiation therapy leads to the formation of lipogranuloma.

The treatment is surgical. Sectoral resection of the mammary gland is performed with emergency morphopathological analysis.

Dysplastic lesions of the mammary gland

Fibrocystic disease (Reclus disease) – represents the dysplasia of the mammary glandular tissue, manifested by the proliferation and dysplasia of all morphological components of the mammary gland: the glandular tissue, the peri- and intralobular fibrous tissue and the myoepithelium. Represents the most common precancerous breast condition (see 18th Fig). It occurs frequently around the age of 30 due to hormonal disorders (hyperfolliculinemia, hyperthyroidism, genital or thyroid hypofunction).

Clinical forms:

- *diffuse shape* - It is characterized by diffuse painful indurations in the mammary glands, often bilaterally. Patients complain of pain, discomfort, enlarged breasts, nipple eliminations.

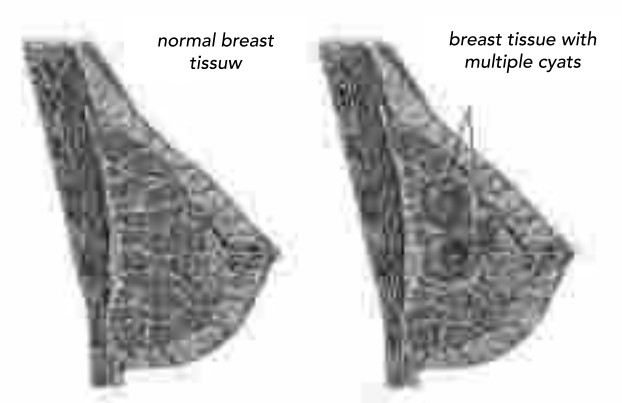

Fig.18.*Fibrocystic disease*

- Clear or pale green nipples may appear. These symptoms usually appear 7-10 days before menstruation and disappear after menstruation.

  Treatment of the diffuse form of the disease fibrocystic is etiopathogenic. A key role is played in removing the cause that caused these changes in the mammary glands.
- *nodular shape* – is characterized by the appearance of one or more hard-elastic formations of various sizes in the mammary glands. The formations have uncertain boundaries, are mobile, sometimes painful to the touch. The regional lymph nodes are not enlarged.
- *mixed form* includes manifestations of diffuse and nodular forms, which cause local discomfort or pain, especially in the premenstrual period. The formations can have different sizes (from a few mm to 2-3 cm) scattered or grouped, uni- or bilateral, mobile, slightly painful, which increases in the premenstrual period.

The treatment depends on the size of the formation. It can be conservative or surgical (sectoral resection of the mammary gland with emergency morphopathological analysis) depending on the evolution and size of the formation. In both cases, the etiopathogenetic treatment is associated with the purpose of correcting the hormonal disorders defined by the concomitant pathologies of the body.

Solitary cyst of the mammary gland

Represents a localized form of fibrocystic disease. It occurs frequently in the pre-climacteric period.

Characteristics:

Palpably - a round, mobile, well-defined tumor, sensitive to palpation.

Treatment - conservative (monitoring) or surgical (sectoral resection with emergency histopathological analysis) depending on the evolution and size of the formation.

Gynecomastia

Gynecomastia – the condition which consists in the excessive development of the breast tissue in men, as a result of a hormonal imbalance between estrogen and testosterone. Gynecomastia can affect one or both breasts *(see 19 fig.)*.

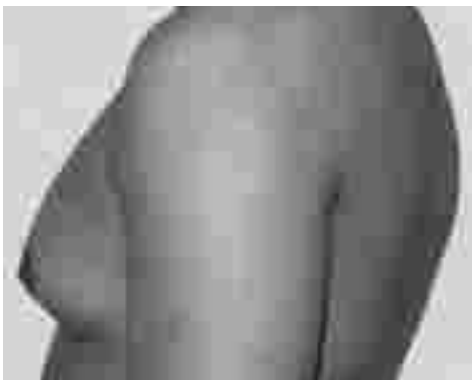

Fig.19. *Gynecomastia*

Types of gynecomastia:

Physiological gynecomastia- s transient and may occur:

- in the newborn (due to maternal estrogen)
- at puberty - in about 50% of boys
- after the age of 60, when testosterone levels drop due to testicular involution and estrogen levels (produced by increase in excess of adipose tissue)

Drug-induced gynecomastia – is caused by the administration of medicamentation that directly or indirectly alter the estrogen-testosterone balance:

- psychotropic medication used in mental illness
- steroids, herbal phytoestrogens - recreational drugs - marijuana, amphetamine, heroin, methadone
- gastric antisecretory medication - Cimetidine, Omeprazole
- cardiology and antihypertensive medication - Nifedipine, Verapamil, Digoxin, Captopril, Enalapril
- prostate adenoma medication

Gynecomastia secondary to other conditions:

- testicular or adrenal tumors that produce excess estrogen
- testicular lesions (bacterial, viral, traumatic)
- hyperthyroidism
- liver cirrhosis, chronic hepatitis
- heart failure
- familial or spontaneous genetic mutations

Idiopathic gynecomastia - gynecomastia for which no cause has been identified

Diagnostic methods:

- *Anamnesis* - aims to identify the associated conditions, the administered medication.
- *Clinical examination* - focused on the differential diagnosis with other diseases of the mammary gland, but also on the identification of diseases associated with gynecomastia (testicular tumors, cirrhosis, cardiac, renal pathology, etc.).
- *Imaging scans* - ultrasound and mammography (as directed).
- *Laboratory test* - determination of blood estrogen, testosterone, LH, beta-HCG, prolactin, TSH.
- *If necessary:*
- computed tomography
- magnetic resonance imaging
- glandular tissue biopsy

Gynecomastia treatment

Gynecomastia treatment can be conservative and surgical. Emphasis is placed on identifying the cause of the hormonal disbalance and, if possible, eliminating it. In the diffuse forms of gynecomastia, etiopathogenetic treatment and supervision of the patient until the disappearance of the symptoms is prescribed. In localized forms of gynecomastia, surgery is recommended - subareolar amputation of the affected mammary gland, with preservation of the mammary areola and nipple.

In puberty gynecomastia, supervision of the person concerned is recommended. If the glandular tissue reaches a large size, which bothers the patient and persists after puberty, surgery is recommended - subareolar amputation of the mammary gland.

In drug-induced gynecomastia, the prescribed medication is canceled or replaced with other drugs that do not cause severe hormonal disorders in

the body. The relief of drug-induced clinical symptoms occurs one month after discontinuation of the medication.

The risk of malignancy of benign tumors and precancerous conditions

- Intraductal papilloma - 7-30% of cases;
- Adenoma and fibroadenoma - casuistry;
- Phylloid tumor - up to 1/3 of cases;
- Diffuse form of Fibrocystic Mastopathy - 2.5% -5% of cases;
- Nodular form of Fibrocystic Mastopathy - 5% -7% of cases;
- Cystadenoma Papilloma - up to 15% of cases;
- Hamartoma - casuistry;
- Gynecomastia with manifestations of fibrocystic disease - 5% -7% of cases.

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BRONCHOPULMONARY CANCER

Historical data

Bronchopulmonary cancer (CBP), rarely encountered and confused in antiquity with other lung diseases, was first reported in the XVI century by Paracelsus and Agricola found in miners of Saxony (1531). In the form of cancerous phthisis was described at the beginning of the century. XIX by Bayle (1810). In the late 1840s, the British author Hasse found no more than 22 cases of lung cancer ever published. In 1912, Adler identified only 374 published cases.

Between 1852 and 1896, lung cancer accounted for 0.19%. Later, in the sec. XX the spread of this disease was found and by 1915 it reached the figure of 3.7%. The increase in morbidity from bronchopulmonary cancer followed an uneven trajectory and acquired a stable character after the end of the First World War in the industrially developed countries (Great Britain, Germany, USA).

Epidemiology

Lung cancer is currently one of the most common cancers in the world, with an estimated 6 million patients. In 2018, global statistics estimated 2 million new cases of lung cancer worldwide and 1.8 million deaths from this disease. The new estimated cases of lung cancer in the US for 2018 are 121,680 for men and 112,350 for women. , for a total of 234,030, the equivalent of 641 lung cancers diagnosed per day. Lung carcinoma is the second most commonly diagnosed behind prostate cancer for men and breast cancer for women. In 2018, lung cancer accounts for 14% of new cancers in men and 13% of new cancers in women in the US. Lung cancer mortality in 2018 was 83,550 for men and 70,500 for women, about 25% of annual cancer deaths in the US. Thanks to anti-smoking initiatives, there was a 455 decrease in male lung cancer deaths in the US between 1990 and 2015, and female lung cancer deaths decreased by 19% between 2012 and 2015.

Globally, the incidence of bronchopulmonary cancer is increasing. Rates of lung cancer in men are considerably higher in developed countries than in less developed ones, mainly related to smoking habits, but the overall incidence is decreasing in men in developed countries due to tobacco control policies. The incidence of lung cancer in women in Europe is increasing. In 2017, it surpassed breast cancer mortality rates for the first time, with deaths from lung cancer being 14.6 per 100,000, compared to 14 per 100,000 for breast cancer.

Table 1. Estimated incidence of bronchopulmonary cancer in the world in 201

Incidence of pulmonary cancer in the world per 100,000 inhabitants	**Incidence of pulmonary cancer In The World In Men**	**Incidence of pulmonary cancer In The World I n Women**
Hungary –56.7	1. Hungary - 77.4	1. Hungary - 41.4
Serbia –49.8	2. Serbia - 71.6	2. Denmark - 36.3
Caledonia - 42.3	3. Turkey - 70.6	3. The Netherlands - 32.7
Greece - 40.5	4. Greece - 67.8	4. Iceland - 32.5
5. Montenegro - 39.7	5. Montenegro - 62.9 21st place in Romania - 50.7 22nd place Moldova - 50.5	5. Serbia - 30.9

High incidence: North America - 34.5; Europe - 29.8
High mortality: Europe - 23.5; North America - 22.3; Asia - 19.6
Low incidence: Africa - 5.5; Latin America - 11.8
Low mortality : Africa - 5.3; Latin America - 10.6
(Global Cancer Observatory) 2018

Table 2. Incidence of patients with bronchopulmonary cancer in the Republic of Moldova 2014-2018

years	**Incidence**	
2014	858	24.1
2015	890	25.0
2016	939	26.4
2017	853	24.0
2018	925	26.0

Lung cancer is the most common malignant tumor of the lung that develops from the epithelium of the bronchial tree in 98% and 2% of the alveoli. Of the malignant tumors, it is the most treacherous, develops rapidly, and is difficult to treat. Lung cancer ranks first among deaths from all types of cancer. Over the past 70 years, there has been a steady increase in lung cancer and it ranks first among men in several countries around the world. Men are affected by lung cancer 7-10 times more often compared to women. There is little progress in improving the treatment of lung cancer. Of the number of patients treated surgically, only 5-35% remain alive in 5 years. The low survival of patients treated for lung cancer is not based on the effectiveness of treatment methods, but on the advanced tumor during detection or at the beginning of treatment.

Etiopathogeny

1. The role of smoking

Currently, smoking is unanimously recognized by all major medical centers in the world as the main etiological factor in the development of bronchopulmonary cancer. According to WHO data, smoking is recorded in 80-90% of lung cancer cases. The Republic of Moldova is among the countries with a high level of smoking, moreover, 90% of smokers use cigarettes with high tar content.

According to the American Association for the Fight against Cancer, it was found that the frequency of lung cancer in non-smokers was 3.4: 100,000, in people who smoke up to one pack / day- 51.3% ooo, in people who smoke 1-2 packs per day - 143.9: 100 000, and for smokers consuming more than 2 packs per day - 217.3: 100 000.

Thus, the probability of developing lung cancer in heavy smokers is at least 70 times higher than in non-smokers. The frequency of lung cancer in smokers is determined by age and smoking period. The risk of getting sick is 8.7 times higher for those who smoke for more than 20 years. Those who started smoking up to the age of 15 can get bronchopulmonary cancer 24 times more often, and those who started smoking after 25 years only 5 times.

The chemical composition of tobacco includes an impressive number of carcinogenic substances, the most impressive of which are polycyclic

hydrocarbons of benzpyrene, benzacridine. A pathogenetic feature is the penetration of cigarette smoke during inspiration deep into the bronchial tree and long-term retention of carcinogens in contact with the bronchial mucosa. Cigarette smoke also contains the radioactive isotope 210P0 with a long half-life. The resulting radiation and benzopyrene act primarily on DNA in lung tissue cells, causing mutagenic changes and cancerous rebirth. The synergism of these carcinogens amplifies the mutagenic risk and, consequently, the development of lung cancer in smokers.

The possibility of developing lung cancer in second-hand smokers has been demonstrated in US research. Studies in the US, the UK and Australia have shown that people living with active smokers have a 20-30% higher risk of lung cancer, while people working in a smoking environment have a higher risk of lung cancer.

16-19% higher risk. Passive smoking is responsible for approximately 3,400 deaths from CBP each year in the United States.

2. Air and occupational pollution

Along with smoking, the pathogenesis of lung cancer is also incriminated by air pollution specific to large urban agglomerations. Annually, 2.5 billion tons of coal are burned on the globe, hundreds of millions of car engines, planes, tractors and other engines work, the smoke of which, as a result of incomplete combustion of fuels, contains polycyclic aromatic hydrocarbons and other carcinogenic substances .At the same time, the number of toxic chemicals and mineral fertilizers used in agriculture has increased.

The International Agency for Research on Cancer in Lyon (France) has carried out special investigations into the detection of aerosol carcinogens.

The most dangerous proved to be:

- ✓ arsenic and its compounds
- ✓ asbestos
- ✓ dichloromethyl ether
- ✓ chromium and its compounds
- ✓ vinyl chloride monomer
- ✓ nickel
- ✓ fuel oil
- ✓ soot

In France, bronchopulmonary cancer is considered an occupational

disease of workers in the asbestos processing industry. In the US, workers trained in chromium processing have a 10-20 times higher risk of developing lung cancer than the rest of the population.

Higher rates of lung cancer morbidity are also cited in *miners, steelmakers, mechanics, drivers*. Even more dangerous is the fact that much higher morbidity of bronchopulmonary cancer is registered among workers with occupational toxins, smokers.

3. Ionizing radiation

External irradiation of the population has a negative impact on oncological morbidity, moreover, the carcinogenic action of radiation is manifested over decades.

Following the accident at the Chernobyl nuclear power plant (April 1986), an increased radioactive fund was registered on the territory of the Republic of Moldova. The statements of the specialists from the Institute of Radioactive Hygiene from the town are alarming. St. Petersburg claiming that the morbidity from lung cancer following the Chernobyl nuclear accident will begin to increase from the 2000s.

Occupational irradiation involves a considerable carcinogenic risk. Lung cancer in US uranium miners has been found 10 times more often than in the general population. In the Chelyabinsk region, lung cancer morbidity exceeds the average level of the Russian Federation by 30%.

4. The genetic factor

The hereditary predisposition to lung cancer was reported as early as 1913 by C. Weller, but this fact has not been given much attention for a long time.

The proof of the definite intervention of a genetic factor in the etiology of lung cancer is primarily the increased frequency of family history of cancer (20-30% of cases).

The significantly higher frequency (14 times) of lung cancer was recorded in smokers with a family history of cancer compared to those without such a history.

5. The immune factor

The increased incidence of oncological diseases was recorded in people with primary immunodeficiency and patients after organ transplantation. Malignant tumors were found in approximately 1.2% of kidney transplant recipients.

The lung is assigned a primary role in the body's immune defense. All conditions that require immunosuppression favor the activation of chronic pulmonary processes, the formation of foci of pneumosclerosis, metaplasia and atypia of the epithelium. Bronchial epithelium has a tendency to dysplasia and the formation of foci of carcinoma *in situ* .

6. Viral agents

Viral agents present a possible risk, still insufficiently studied in the development of lung cancer.

The viral agent as an etiological factor in the development of lung cancer is cited in several experimental papers. For example, NA Maximovici (1978) more frequently detected lung carcinoma in mice infected with influenza A2 virus. There is a correlation between the unfavorable action of the exogenous virus on the cells of the respiratory mucosa. As a result, outbreaks of pneumofibrosis, post-inflammatory scars, considered precancerous conditions occur.

7 . The social factor

In Western countries, lung cancer is less common in well-insured families.

Higher rates of lung cancer mortality are cited (3 times more) in unskilled workers than in the category of highly skilled workers.

Other environmental and social factors also interfere: pauperism, alcoholism, mental depression, population migrations .

8. Other factors with oncological risk

The carcinogenic iatrogenic factor in the development of bronchopulmonary cancer has been reported following radiotherapy and combined treatment of malignant lymphoma.

JF Kestner (1977) described the development of lung cancer in 3 patients over 7-11 years after mediastinal radiotherapy for a lymphoma.

A source of radiation to the lung tissue is medical radiological investigations. In most countries, 50% of radiological investigations are in the chest.

It is noted that the risk of lung cancer in patients with tuberculosis treated in the active phase or further investigated radiologically is 5-10 times higher compared to the entire population.

Precancerous conditions

A distinct place in the development of lung cancer is occupied by specific and non-specific chronic pathology. In particular, the appearance of lung cancer in the region of the post-tuberculous or post-pneumonic scar is notable.

Nonspecific chronic lung processes cause epithelial proliferation with atypia, leaving it on the path of developing a malignant process.

Chronic bronchitis, pneumosclerosis, chronic forms of pulmonary tuberculosis, bronchiectasis, silicosis, asbestosis, anthracosis, etc. can be attributed to precancerous diseases located in the lungs. Benign lung tumors (adenoma, papilloma) cannot be ignored either.

Clinical-anatomical forms of bronchopulmonary cancer

Currently, the division of lung cancer into central with initial localization in the primary, lobar, segmental and peripheral bronchi, which develop from the small bronchi, is accepted.

1. Central cancer :
   - endobronchial
   - nodular peribronchial
   - Bronchial
   - mixed
2. Peripheral cancer is found in the form of:
   - spherical tumor
   - pneumonic type
   - apical (with or without Pancoast-Tobias syndrome)
3. Atypical forms:
   - mediastinal
   - miliary carcinomatosis
   - LIVER
   - bone
   - cerebral
   - and so on

Lung cancer metastasis

The pathways of lung cancer metastasis are: lymphogenic, hematogenic and mixed.

The following groups of lymph nodes are affected by lymphatic metastasis:

- upper mediastinal: superior paratracheal, pre- and retrotracheal, inferior paratracheal (including V. azigos ganglia);
- aortic: nodules of the aortal valve, ascending aorta or diaphragmatic nerve;
- lower mediastinal: nodules at tracheal bifurcation and lower lung ligament nodules;
- prehilari;
- interlobari;
- lobari;
- segmentations.

Hematogenous metastasis of lung cancer

Brain metastases occur in 40% of cases. It is noteworthy that in every second patient the metastases are detected earlier than the primary tumor and for this reason, a large part of the patients are directed to the neurosurgery departments. Mostly, the focus is located in the frontal and occipital region, then in the cerebellum.

Liver metastases - are recorded in 40% of cases in the liver parenchyma.

Bone metastases - are reported in 30% of patients. More often it is affected the thoracic and lumbar portion of the spine, pelvic bones, ribs, tubular bones (humerus, femur). Pathological fractures are registered in 20% of cases.

Metastases in the adrenal glands - are recorded

in 30% of cases. Usually, metastases are located in the spinal cord and the function of the adrenal cortex suffers little.

Kidney metastases - are noted in 20% of patients with lung cancer. They are usually small and evolve asymptomatically.

Histological classification of bronchopulmonary cancer

The complicated anatomical structure of the lung which includes the bronchial tree, the parenchyma, the arterial, venous, lymphatic and neurotic system, the interalveolar connective tissue requires the development of the malignant tumor with a vast histological structure.

1. Carcinoma pavements (epidermoid) 30 - 35%

- with keratinization
- without keratinization

2. Macrocellular carcinoma 10%
   - with giant cells
   - with clear cells
3. Small cell anaplastic carcinoma (microcellular) 20%
   - with „oat grain" cells
   - with polymorphic cells
   - fusiform
   - with spherical cells
4. Adenocarcinoma 25 - 35%
   - acinar
   - papillary
   - bronchioloalveolar
   - solid.

TNM Classification, Geneva 2017 (refer to)

AJCC Cancer Staging Manual, Eighth Edition. Editor-in-Chief Mahul B.Amin, MD, FCAP; American Joint Committee on Cancer 2017.

Clinical evolution of bronchopulmonary cancer

Clinical manifestations of bronchopulmonary cancer consist of *primary symptoms* , directly related to tumor growth, *secondary signs* that appear as a result of complications during tumor growth, and *general signs* that develop as a result of tumor or inflammatory intoxication. The clinical manifestations are in accordance with the clinical-anatomical types of lung cancer.

It should be noted that bronchopulmonary cancer, regardless of the initial location, develops for a long time asymptomatically (especially peripheral).

Clinical manifestations of central lung cancer

- The cough appears reflective in 80 - 90% of patients. At first it is dry, and permanently bothers the patient. Subsequently, with the obstruction of the bronchus, the cough is accompanied by elimination of mucous or muco-purulent sputum.
- Hemoptysis occurs in 50% of patients in the form of streaks of red blood, later blood clots can be detected.

- Dyspnoea is present in 30-40% of patients. It is caused by obstruction of the bronchial lumen or hemodynamic component (compression of blood vessels by the tumor).
- Chest pain on the affected side occurs in 60-65% of patients.

It should be noted that obturator pneumonia is characteristic of central cancer.

Clinical evolution of peripheral lung cancer

Peripheral lung cancer is more common in the spherical shape of the tumor. This type of cancer affects the small bronchi, evolves for a longer time asymptomatically, clinically manifests itself in an advanced stage. It is usually detected by chance by the radiological method. Clinical manifestations occur when the tumor grows in adjacent structures and organs or extends to the hilum (centralization of the process).

Chest pain in the affected area develops slowly and occurs in every 10th patient with peripheral lung cancer. Initially it bothers the patient during inspiration, then they become permanent. They occur more frequently when the pleura and chest wall are affected.

Cough, dyspnea occur in case of involvement of the bronchus (centralization of the process) but they are not early signs as in central cancer.

In addition to lung symptoms, lung cancer is accompanied by general signs: *decreased work capacity, general weakness, malaise, weight loss,* etc.

Clinical evolution of peripheral lung cancer with Pancoast-Tobias syndrome

The apical shape manifested by Pancoast-Tobias syndrome (the first described in 1924, the second in 1932), is characterized by:

- radiological opacity detected in the pulmonary apex
- shoulder joint pain
- skin sensitivity disorder
- Claude-Bernard-Horner syndrome
- induration of the supraclavicular region
- muscle atrophy is determined throughout the upper limb
- more frequent costal lysis of the posterior arches I-III and adjacent vertebral bodies.

Claude-Bernard-Horner syndrome (miosis, enolphthalmia, palpable ptosis and lacrimal secretion disorders) is caused by damage to the cervical sympathetic trunk. In case of an exciting sympathetic cervical lesion, Pourfour du Petit-midrea syndrome exophthalmos (withdrawal of the eyelids) and hyperhidrosis are installed.

Paraneoplastic syndromes

Paraneoplastic syndromes are found in 10-20% of patients with bronchopulmonary cancer. Their appearance is determined by the fact that the tumor cells eliminate various biologically active substances such as hormones, antigens, capable of causing respective hormonal or autoimmune reactions in organs and tissues. These syndromes are manifested by so-called *„masks"* of the disease, some of them bearing concrete names.

Pierre-Marie-Bamberger syndrome (pulmonary hypertrophic osteoarthropathy) is expressed by thickening and sclerosis of the tubular and metatacarpal bones in the form of „drumsticks" (Fig. 1), pain and edema in the region of large joints. Figure 2

The clinical picture of dysachromelia has a very different semiological value. Simple digital Hippocratism is also noted in „rheumatic" syndromes. However, pulmonary hypertrophic osteoarthropathy is most often associated with lung cancer and accounts for 65-75% of cases.

Regarding the histological type of lung carcinoma, several authors have found a predominance of squamous cell carcinomas, which make up 75% of major dysachromelia.

Figure 1 . *Fingers in the form of « drumsticks «*

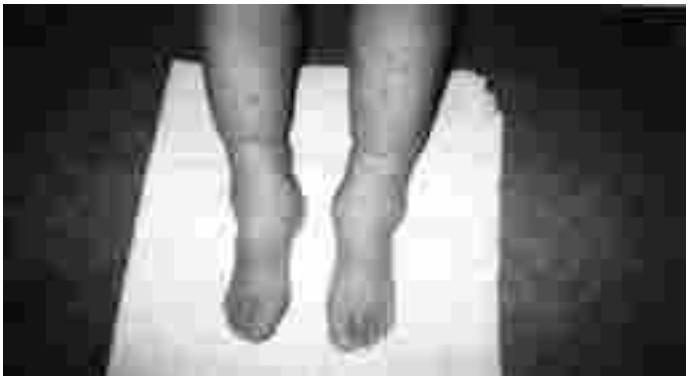

Figure 2. *Edema of the talocrural joint*

Schwartz-Barter syndrome is characterized by the association of hypertonic urine with hyponatremia, normal renal and adrenal function, and increased production of antidiuretic hormone characteristic especially for microcellular cancer.

Lambert-Iton syndrome is found in poorly differentiated forms of lung cancer and is characterized by muscle weakness similar to myasthenia, but unlike it this sign is installed in the proximal part of the lower limbs and disorders of the function of the small pelvis.

Another difference is that in myasthenia the work of the muscles causes the total exhaustion of the muscular power in comparison with the Lambert-Iton syndrome in which the continuous movements lead to the restoration of the initial muscular power. This syndrome is more common at 3-6 months until other clinical signs of lung cancer appear.

Cushing's syndrome is characterized by a disharmony of fat distribution, with a monthly erythrocyte facies, hypertension, weight gain, the development of myasthenia, often pseudo-paralytic probably by hypokalemia and the onset of diabetes.

The association of Cushing's disease with hypokalemia and alkalosis is very much in favor of neoplasia. It seems that these changes are due to hypersecretion, not so much aldosterone as glucocorticoids.

Late clinical signs of lung cancer are caused by tumor growth in adjacent organs and distant metastases.

In case of growth of the tumor in the pleura with its dissemination on the pleural sheets, serous exudative pleurisy appears, less often hemorrhagic.

Violent chest pain sets in as a result of the growth of the malignant tumor in the chest wall.

The growth of the tumor towards the mediastinum or the compression of its anatomical structures causes the compressive mediastinal syndrome: recurrent entrainment in the process - dysphonia, dyspnea and cardiac disorders.

Due to damage to the diaphragmatic nerve, hemidiaphragm paralysis occurs, dysphagia - in case of compression of the esophagus.

Headache, cyanosis and scarring of the face, edema of the cervical region, dilation of the subcutaneous venous network of the neck and the anterior pectoral part are installed as a result of compression of the superior vena cava.

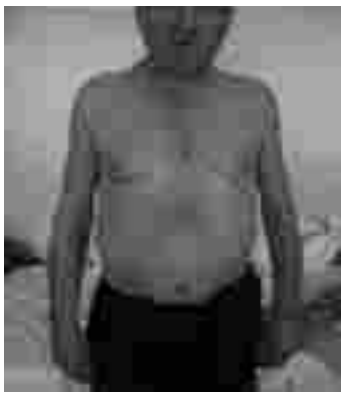

Figure 3. *Upper vena cava syndrome: edema of the face, neck, right upper limb*

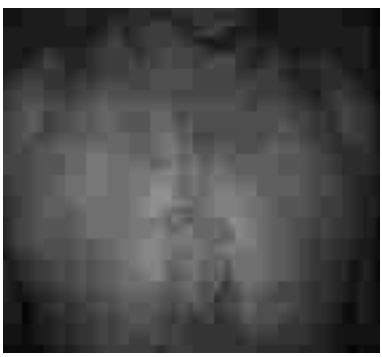

Figure 4. *Dilation of the subcutaneous veins of the thorax in the superior vena cava syndrome*

Late signs are attributed to the detection of enlarged lymph nodes, especially supraclavicular and cervical, destruction of the tumor and

atelectasis lung parenchyma (removal of purulent sputum, pulmonary hemorrhage, high fever, chills), cachexia.

The clinical manifestations of distant metastases sometimes predominate. Brain metastasis promotes intracranial hypertension and as a result there are headaches, nausea, vomiting, mental disorders.

The characteristic symptoms for liver metastases are: hepatomegaly, pain in the right hypochondrium, uneven surface of the liver and hepatic stiffness on palpation.

Bone metastases are manifested by pain, the involvement of the spinal cord is accompanied by paralysis.

Radiological diagnosis of bronchopulmonary cancer

The contribution of the radiological method in the diagnosis of lung cancer is indisputable. *The radiological examination includes:*

a) digital radiography - the simplest early method of detecting bronchopulmonary cancer
b) thoracic radiography in two projections (face and profile) is the objective and basic method in the diagnosis of lung tumors
c) Pulmonary tomography aims to dissociate overlapping, complex, or associated tumor images with other non-specific inflammatory lung images:
   - anterior section tomography of the tracheal bifurcation allows the assessment of the condition of the trachea, main bronchi, intermediate and main groups of mediastinal lymph nodes
   - anterior tomography of the pulmonary hilum allows visualization of the lobar and segmental bronchi
   - profile tomography - assessment of the lower bronchi and middle lobe .

The radiological image highlights the location, the dimensions of the pulmonary opacity, its connection with the tracheobronchial tree, the blood vessels of the pulmonary hilum and mediastinum, the pleura and other anatomical structures of the thorax.

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- abutment), enlarged lymph nodes in the hilum and mediastinum.

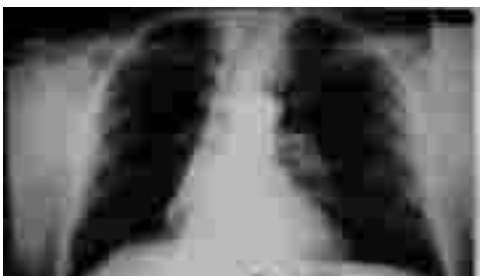

Figure 5. *Front Radiography in right central lung cancer. The right lung decreased in volume. Trachea moved to the right (from the affected side). The right diaphragm moved upwards*

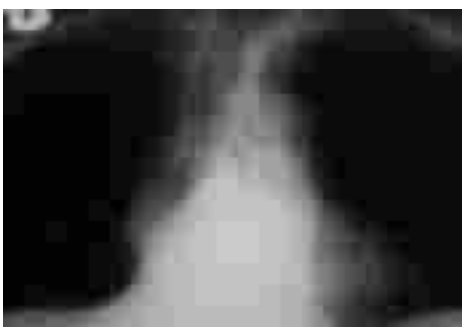

Figure 6. *Pulmonary tomography. Trachea shifted to the right. Narrowing of the lumen of the intermediate bronchus on the right*

Figure 7. *Pulmonary tomography. Amputation of the intermediate bronchus (blunt sign)*

Figure 8. *Tomography of the right lung. Upper lobe atelectasis. Amputation of the bronchus of the upper lobe of the right lung*

Peripheral lung cancer occurs as a tumor opacity of various sizes. The contour can be regular, well delimited. The opacity is usually homogeneous.

Contour irregularities, fine dendritic branches with infiltrative character may appear in evolution. The tumor can also invade the surrounding bronchi, creating the necessary conditions for the appearance of an area of pulmonary atelectasis. In these cases the opacity becomes with an irregular, inhomogeneous erased contour, difficult to differentiate with lung metastasis.

Figure 9. *Chest radiograph of the face. Peripheral cancer of the lower left lung*

Figure 10. *CT scan of peripheral cancer of the upper right lobe*

Destructive peripheral cancer occurs in the form of a cavity with thickened crenellated walls and their irregular outline.

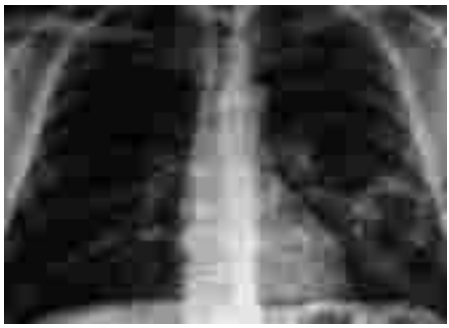

Figure 11. *Peripheral lung cancer in destruction (excavated) lower lobe left lung*

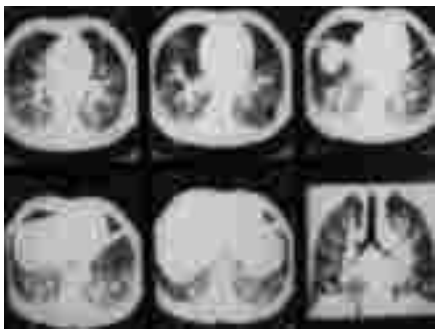

Figure 12. *Computed tomography of the chest. Pneumonic form of lung cancer*

For *apical cancer (Pancoast-Tobias)* the erosion of the first ribs (I-III) is characteristic. In earlier forms, opacity of the pulmonary apex may be confused with apical pleurisy, various forms of pulmonary tuberculosis, or benign tumors. To determine the location of the tumor (intrapulmonary

or extrapulmonary) it is necessary to apply artificial pneumothorax with radioscopic or radiographic examination.

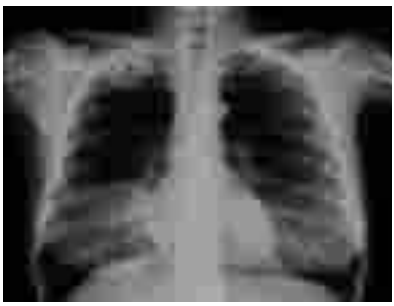

Figure 13. *Front Chest radiograph. Lung apex cancer on the right*

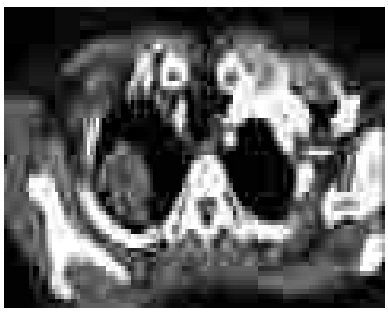

Figure 14. *Computed tomography. Lung apex cancer on the right*

Miliary carcinomatosis is a form of lymphatic or hematogenous lung metastasis and is characterized by a multitude of small nodules. It is manifested by the appearance of a primary lung node, and the rest are lymphatic metastases. There may also be hematogenous metastases starting from other organs (liver, gastric, uterine cancer, etc.). In order to establish radiologically that the process is primarily pulmonary, the location of the tumor in other organs must be excluded.

Figure 15. *Miliary lung cancer*

The radiological aspect of mediastinal bronchopulmonary neoplasm is characterized by the evolution of the tumor formation, especially in the mediastinum. The middle and partially superior mediastinum appear uni- or bilaterally enlarged, linear or polycyclic contour, the hilar regions may be masked by the enlargement of the mediastinum or may have the radiological appearance of branched opacities.

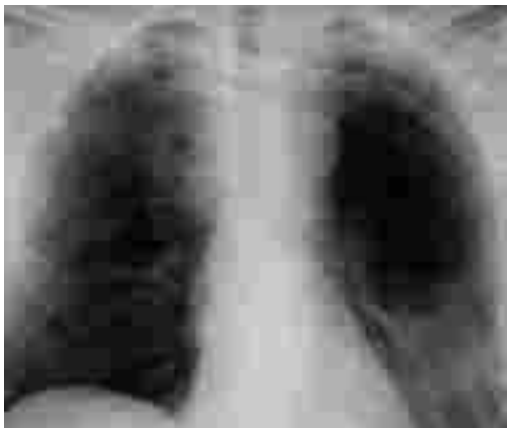

Figure 16. *Medistinal form of right lung cancer. Bilateral mediastinum enlarged*

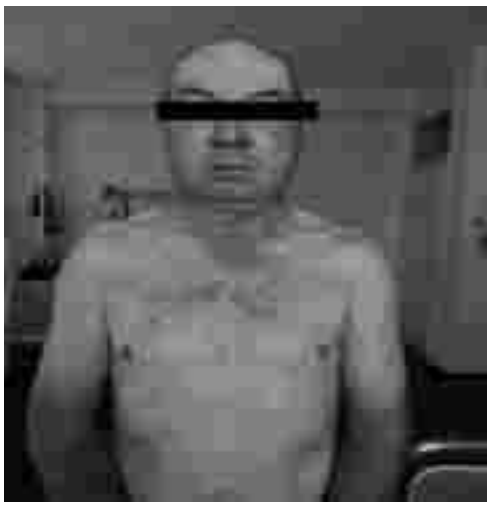

Figure 17. *Upper vena cava syndrome in patients with mediastinal cancer-pulmonary: edema of the face, neck, upper limbs, dilation of the subcutaneous veins of the thorax*

The differential diagnosis is very difficult to make with metastatic lymphadenopathy, lymph node localizations of malignant lymphomas, specific or fibrous mediastinal, etc.

Computed tomography is preceded by traditional radiological investigations. This method will provide accurate data on the relationship of the tumor with the mediastinal anatomical elements, will specify the existence of lymph node masses in the lung hilum.

Computed tomography can also be used successfully to achieve extrapulmonary changes, especially metastases in the liver, brain, bones, kidneys, etc.

In medical imaging, technical development has made progress, making PET / CT technology a revolutionary innovation in the last decade in the diagnosis of oncology, including lung cancer. The method consists in combining PET investigation (positron emission tomography) with CT investigation (computed tomography). With its help you can differentiate with great certainty whether the change is benign or malignant. PET / CT scans make it possible to detect a change of even a few millimeters in size.

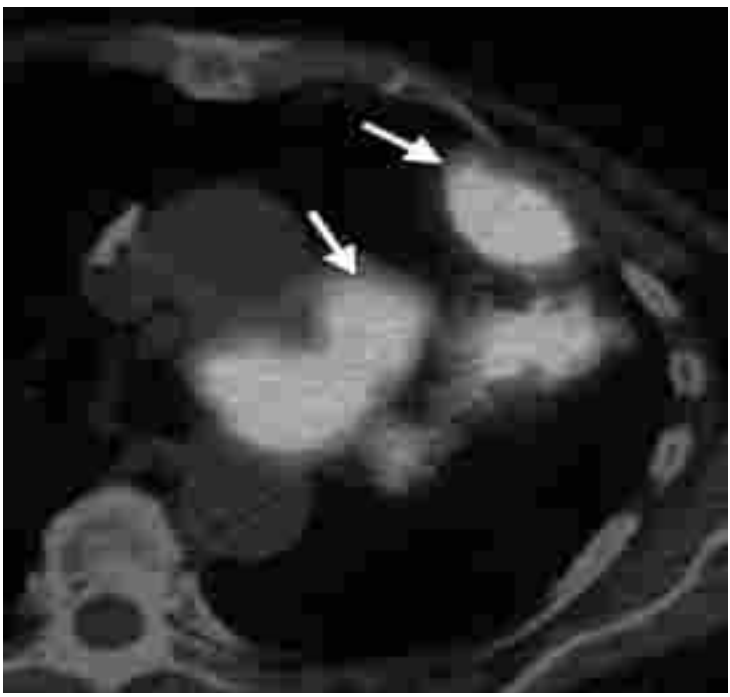

Figure 18. *PET / CT examination of the chest. Peripheral left lung cancer with metastases in mediastinal lymph nodes and chest wall*

Tumor markers in bronchopulmonary cancer

Tumor marker - a protein or any other change specific to a tumor cell, which correlates with the presence of a tumor. In general, most of the markers used so far are circulating substances (proteins, carbohydrates, lipids) determined in the blood, urine, broncho-alveolar lavage or various exudates associated more or less specifically with tumor development.

- Carcinoembryonic antigen (CEA). Its use in practice remains quite low. The sensitivity of its determination is only 30%.
- Lactate dehydrogenase (LDH). It can be used as a prognostic factor in microcellular carcinoma.
- Squamous cell carcinoma antigen (SCCA). Its sensitivity varies between 33-61% for non-microcellular carcinomas, being higher in squamous cell carcinoma.

Tumor markers used in current practice

- Neuroma-specific enolase (NSE) - An enzyme present in cells of neuroendocrine origin. It is useful in determining microcellular lung carcinoma. The diagnostic sensitivity exceeds 65% for the limited stage and 90% for the metastatic stage.
- Cyphra 21-1 - It is an analysis that measures fragments of cytokeratin in the blood. The cyfra 21-1 test uses two specific monoclonal antibodies (KS19.1 and BM 19.21) for cytokeratin 19. Sensitivity to small cell lung cancer, squamous cell carcinoma and adenocarcinoma is 20%, 62% and 39%.

Bronchoscopic examination

Bronchoscopy is the most valuable investigation that is used and which, unfortunately, is not performed everywhere. It is indicated for all patients to detect both central and peripheral lung diseases.

The purpose of the bronchoscopic examination is:

- detection of the tumor process in the tracheobronchial tree and lungs, its differentiation with other non-oncological pathologies
- appreciation of the spread of the process in the tracheobronchial tree
- morphological confirmation of the tumor
- assessment of the effectiveness of the treatment of the tumor process of the tracheobronchial tree
- curative bronchoscopy

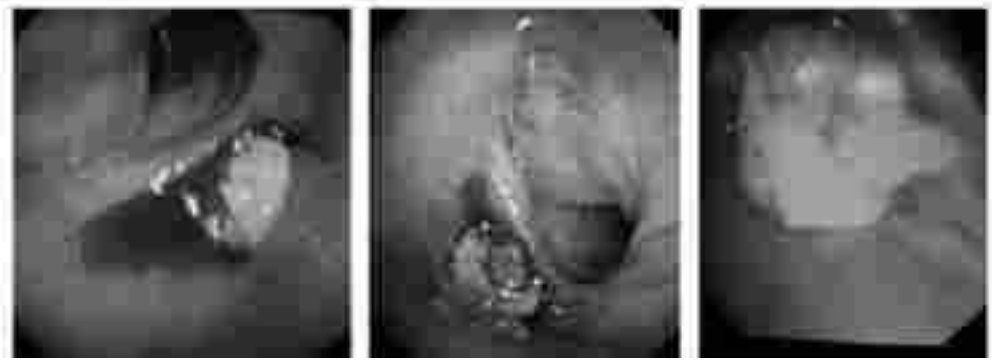

Figure 18. *Exophytic growth of the tumor in the bronchial lumen*

Figure 19. *Accentuated vascular drawing*

Transbronchial lung biopsy with forceps aspiration or on a special needle of the pathological material can optimize the diagnosis in mediastinal lymph node metastases or in case of immediate bronchial proximity of the tumor. This method is also useful in diffuse localizations of the upper lobes and in the diagnosis of carcinomatous lymphangitis. The positive diagnosis by bronchoscopy of peripheral lung cancer is established cytologically in 40-60% of cases, and in the central one up to 80%.

Transthoracic (percutaneous) biopsy puncture - is used in peripheral lung cancer undiagnosed by other investigations and allows a cytohistological diagnosis in 80-90% of cases. Due to some complications (traumatic pneumothorax, hemoptysis, local subcutaneous emphysema, gas emboli), the method is practiced less than its informative value would require. For this reason, many patients undergo surgery without performing transthoracic puncture.

Patients with a negative transthoracic puncture that cannot be operated

on due to severe contraindications need to be monitored for up to 2 years. The benign nature of tumors argues: centrally located calcifications, very slow or no growth, the age of patients up to 35 years (the probability of malignancy of the tumor in them is lower), non-smokers and non-occupational people such as contact with carcinogens.

Pleural puncture - the appearance of pleural fluid in patients with lung cancer, especially hemorrhagic cancer, often indicates that the pleura is affected by metastases. In 30-40% of cases, pleural fluid can be caused by other diseases. Pleural puncture with fluid cytological analysis is indicated in all pleurisy, especially in suspected cases of malignant pleural mesothelioma or malignant lung tumors in which the pleura is also affected. It can clarify the diagnosis in 60-80% of cases. If the malignant process is not confirmed, the pleural puncture needs to be repeated.

Thoracoscopy - this method allows a direct inspection of the pleural cavity, respectively the visceral and parietal pleura, the lung surface, the degree of damage to the intrathoracic lymph nodes and tumor invasion in the mediastinal organs and other anatomical structures. Thoracoscopy is completed by taking the biopsy material from the most suspicious place or places.

Mediastinoscopy - is a minimally invasive reference surgical method in exploring the middle and upper mediastinum. For diagnostic purposes, it is used for biopsy of the mediastinal lymph nodes and in the staging of bronchopulmonary cancer (very important for establishing optimal therapeutic behavior).

Differential diagnosis of lung cancer

The differential diagnosis of central lung cancer needs to be made with pulmonary tuberculosis, sarcoidosis, tumors of epithelial origin, Hodjkin's disease and pneumosclerosis.

Peripheral cancer needs to be differentiated from tuberculoma, benign lung tumors, and hydatid cyst.

Treatment of bronchopulmonary cancer

Radical surgery in bronchopulmonary cancer

Lobectomy is the most common operation used in lung cancer. Its advantages are related to the anatomical and functional aspect, being better tolerated by the patient compared to pneumonectomy.

Bilobectomy is rarely performed and refers only to the right lung. Medium-upper and middle-lower bilobectomy is performed in situations where the tumor in the upper lobe invades the middle lobe, respectively the middle lobe and the lower lobe (most often by overcoming the small cleft, or large cleft, by the absence of cleft or endobronchial extension and perivascular).

Pneumonectomy is mainly indicated if the bronchoscopy shows tumor infiltration in the distal part of the primary bronchus and in the transcisural extension of the tumor. It can be performed by the classic extrapericardial approach of large vessels or by their intrapericardial ligation (if the dissection of the pulmonary hilum is difficult and risky, or the vessels are invaded by the tumor in their extrapericardial portion). Pneumonectomy may be associated with mediastinal lymphadenectomy, rib resections, diaphragm, tracheal and large vessel resections and reconstructions.

Economical housekeeping operations

As a rule, economic operations are used in peripheral lung cancer in the elderly and patients with severe concomitant pathologies:

- Segmentectomy
- Cuneiform resection
- Superficial resection
- Marginal resection

Video-assisted thoracic surgery (VATS) is a different way of approaching thoracic surgery, an approach in which the maneuvers performed produce a much less aggression to the patient compared to the classic interventions that address the same conditions. The procedure is based on the fact that only a direct visualization of the thoracic cavity is necessary, this being inspected with the help of special optical instruments, of small dimensions, which can be inserted through very small holes.

robotic surgery has been applied in the surgical treatment of lung cancer . Robotic thoracic surgery means performing surgical procedures by making small incisions in the thoracic cavity, using the da Vinci robotic system.

Other methods that do not provide a rapid effect and are used for the treatment of malignant tumors.

1. *Photodynamic therapy of pulmonary Cr*
2. *Cryotherapy .*
3. *Radiofrequency ablation*

Radiation therapy may be *radical* (summary irradiation dose of not less than 60 Gy) and *palliative* (40 Gy). Radiation therapy according to the radical program is an alternative to surgical treatment in patients with stage I-III A bronchopulmonary cancer in which the operation is contraindicated for several objective reasons (age, general condition, concomitant diseases), or the patient's refusal to operate.

Endobronchial radiotherapy allows to increase the irradiation dose of the tumor with optimal protection of adjacent healthy tissues.

Stereotactic radiotherapy is a technique that accurately administers high doses of irradiation to the target volume by reducing the dose received by neighboring tissues.

Intensity modulated radiotherapy (IMRT) is the most important revolution in the field of radiation oncology. It is an advanced type of high-precision radiotherapy. The dose released depends on the 3D shape, by modulating the intensity of the beam, being increased in intensity near the center of the tumor and decreased towards the periphery.

Volumetric modulated arc therapy is a new technique in which doses with distribution are reached that cover the volume of the target and avoid the neighboring tissues. The radiation is released through 360˚ rotating fields through an arc, changing the speed and shape of the beam with a collimator.

Particle radiotherapy. In particle therapy, ionized particle beams are directed to the tumor. The dose increases as the particles enter the tissue to the maximum capacity at the peak, then decreases to 0.

The advantage: storing a small amount of energy in healthy tissues.

Radioisotope therapy (RIT) is a targeted therapy. Radioisotopes used: strontium 89, yttrium 90, iodine 131, samarium lexidronam. Radioisotopes are administered by infusion or ingestion.

Chemotherapy treatment

The appropriateness of applying chemotherapy in the treatment of non-microcellular lung cancer has long been debatable due to the chemoresistance of tumor cells.

The practical implementation *of platinum salts* (cisplatin, carboplatin), stageoside, taxanes, vincaalcoids, remcitabine have changed the view on the possibility of cytostat action on the tumor, both in widespread local treatment and in disseminated forms of lung cancer without small cells.

The contribution of chemotherapy in the treatment of microcellular lung cancer is indisputable.

Immunotherapy in lung cancer

Immunotherapy does not fight directly with the tumor cell like chemotherapy or targeted molecular therapy, but creates the body's ability to self-defend by reactivating T lymphocytes.

Treatment of lung cancer with a high mutation load with nivolumab / ipilimumab, pembrolizumab leads to more frequent and lasting remissions.

Prognosis of bronchopulmonary cancer

Lung cancer has a poor prognosis in general. Despite diagnostic and therapeutic improvements in recent years, no significant improvement in survival over time has been achieved. The prognosis of bronchopulmonary cancer is primarily determined by the stage of the tumor process. The 5-year survival data are as follows: stage I - 65%, stage II - 40%, stage III - 25% and stage IV - 1-2%

The late results and the prognosis of the treatment of these patients also depend on the age, the general condition of the patient, concomitant pathologies, the hereditary factor. In the assessment of the patient with lung cancer has an important role: the size and degree of spread of the primary tumor, age, general condition and hereditary-collateral history of the patient.

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ESOPHAGEAL CANCER

Historical data

Esophageal cancer was first described by Avenzoar in the 15th century. XII. A simpler description of this disease was made by the Dutch scientist Hermann Boerhaave. The first gastrectomy was performed in 1849 in a patient with total dysphagia who survived 24 hours after surgery.

In 1887 Czerny performed the first resection of the esophageal tumor in the cervical region. Removal of the esophagus due to cancer was first performed by Franz Torec in 1913 on a 67-year-old patient who survived 13 years after surgery.

Subsequently, operations for esophageal cancer were performed by great surgeons such as Amza Jianu and Dan Gavriliu who proposed and performed esophagoplasty using large curvature of the stomach for plastic surgery.

Ivor Lewis proposed resection of the esophagus by his plastic surgery with the stomach above the aortic buttock at one time by right laparotomy and thoracotomy in 1946. Later Garloc performed gastroesophagoplasty below the aortic buttock by laparotomy and left thoracotomy in one moment.

A special place in esophageal surgery was held by the great surgeons in Russia, among them: SS Iudin, EL Beriozov, BV Petrovschi, EB Peterson and others.

Epidemiology

Esophageal cancer is the most common and most serious pathology of the esophagus. It accounts for 70-90% of all esophageal diseases. According to the latest report of the International Agency for Research on Cancer within the World Health Organization through the Global Cancer Observatory platform (GLOBOCAN 2018) esophageal cancer ranks seventh in the world in terms of incidence (572,034 new cases in 2018),

which is in increase in the last three decades (17.39% compared to 2012 (456,000 new cases / year), 39.68% compared to 1990 (345,000 new cases / year)). Esophageal neoplasm ranks sixth globally in terms of cancer mortality with 508,585 deaths in 2018. Esophageal neoplasm in digestive tract cancer is ranked 3rd after gastric and large intestine cancer.

The high incidence of esophageal cancer has been found in France, several countries in South Africa, the northern region of Iran, the republics of Central Asia, Mongolia and China. High mortality rates from the disease have been reported in northern Iran: 109 per 100,000 men and 174 per 100,000 women. In Europe, the highest mortality from esophageal cancer was 17.7 per 100,000 men and 5.8 per 100,000 women in France. In the US, the incidence is higher in people of color.

It is much less common in the Baltic countries and Moldova, where the incidence is 2.6 and 1.5% 000, respectively. Men get esophageal cancer more often than women. The majority of patients with this disease (up to 80%) are people aged 50-60 years. The population in villages is more often affected compared to that in cities.

Etiopathogeny

An important role in the etiology of esophageal cancer belongs to smoking and alcoholism. The risk is higher when alcohol is associated with smoking.

Tobacco use is the strongest risk factor for esophageal cancer. The risk of esophageal cancer was 5 times higher among smokers compared to non-smokers.

From food factors it is estimated the use of products containing nitrates and nitrosamines . *A high-fat, low-protein, low-calorie* diet increases the risk of esophageal cancer. Another etiological factor is chronic microtrauma - eating bony fish, using hard-to-eat products, hot food and tea.

Extension and metastasis of esophageal cancer

The spread of esophageal cancer takes place directly within the boundaries of the adjacent organ, structures and organs. It metastasizes by lymphogenesis and hematogenesis. The spread of the tumor on the wall of the esophagus can take place both proximal and distal. Infiltrative cancer affects the esophageal wall and circularly stenoses the lumen. Outside the esophagus, the tumor may involve adjacent structures and organs (aorta, pericardium, lung, trachea, bronchi, etc.). In case of tumor destruction,

fistulas with trachea, bronchi, pericardium and aorta are formed. These complications are more common in the middle third of the thoracic portion of the esophagus. Fistulas form in 8-50% of cases of esophageal cancer.

Esophageal cancer metastasizes to 40-70% of patients. The lymphogenetic pathway is preferred.

Cancer of the cervical portion and upper thoracic third of the esophagus metastasizes to the paratracheal, superficial and deep cervical, upper, lower and paravertebral tracheobronchial ggl. The tumor located in the middle third of the esophagus metastasizes proximal to the cervical ggl, as well as in the posterior and prevertebral mediastinal ggl.

In lower third cancer, lymph drains into the celiac, lateral pericardial, upper diaphragmatic, bronchopulmonary, paraesophageal, and gastric glands on the left. Lymphogenic metastasis in esophageal cancer is found in 59%.

Hematogenous metastases are much less common (5-7%), in advanced stages in the liver, lungs, kidneys, bones, brain. Metastasis in esophageal cancer is consistent with growth and histological form. More aggressive is the infiltrative form of growth and the squamous one without keratinization, as well as undifferentiated cancer.

Precancerous conditions

- Chronic esophagitis.
- Diverticulias, achalasia lasting more than 20-25 years.
- Strict scars, especially post-combustion.
- Peptic ulcers.
- Benign tumors: adenomas, papillomas, esophageal diverticula.
- Hyperplastic processes: leicoplakia, dysplasia.
- Genetic factor: Plumer-Winson syndrome manifested by achlorhydria, anemia, hypertrophy of the oral mucosa, pharynx and esophagus. It is found only in women.
- Barett's esophagus (metaplastic adenomatosis of the distal esophagus).

Growth and histological forms of esophageal cancer

Esophageal cancer more frequently affects the thoracic part (up to 60%) followed by the abdominal part (20-25%) and the cervical part (10-15%).

Esophageal cancer has 3 forms of growth: exophyte (polypoid,

cauliflower or papillomatous), endophytic (infiltrative or ulcerative) and sclerosing.

The exophyte or nodular form is found in 30-35% of patients. The tumor grows in the lumen of the esophagus, then there is destruction, hemorrhage.

The ulcerative form is detected in 60-65% of cases. The tumor appears as a nodule, then ulcerates and infiltrates the esophagus both in length and thickness, affecting the entire wall.

Sclerosing esophageal cancer or squirrel is less common in 5-10% of patients. The tumor usually spreads in a circle and completely stenoses the esophageal lumen.

1. Squamous cell carcinoma is the most common (95-97% of cases).
   - with keratinization or high differentiation.
   - without keratinization (poorly differentiated).
2. Adenocarcinoma affects the distal portion of the esophagus and usually develops from the stomach epithelium and spreads proximal to the esophagus. It occurs in 3-5% of cases.
3. Undifferentiated cancer is detected much less often (1-2%).

TNM classification of esophageal cancer (Geneva, 2017)

CLINICAL EVOLUTION

The clinical signs of esophageal cancer fall into 3 main groups:

- Local signs
- General symptoms
- Signs of damage to adjacent organs.

The main symptom of esophageal cancer is dysphagia, which occurs in 70-95% of patients. Initially, it appears unexpectedly during a hurried supply of solid products. After a sip of water the dysphagia usually disappears and the patients do not pay attention for a long time. Subsequently, it acquires a permanent character or can be manifested by frequent attacks of acute dysphagia. The mechanism of dysphagia is determined by the spastic component and the narrowing of the esophageal lumen following tumor growth.

There are 4 degrees of dysphagia:

- grade I - it is difficult to pass the food bowl of solid consistency
- grade II - there are difficulties with the transit of the semi-liquid food bowl

- grade III - there are difficulties in liquid transit
- grade IV - complete esophageal transit stop (fluid does not pass).

The second sign is pain. It is found in 5.5-50% of cases of esophageal cancer. The pain can be systemic, independent and periodic, appearing only during the meal. Later in the advanced stage it is permanent. The sensation of pain is marked retrosternally, at the level of the tumor or above. It occurs as a result of tumor ulceration, inflammation of the inflammatory mucosa, esophageal spasm and peristalsis. In advanced stages, pain may occur in the event of tumor invasion into adjacent tissues and compression of vessels and nerve endings.

Another sign found in patients with esophageal cancer is hypersalivation. It is noted in 8-45% of cases. Hypersalivation occurs as a result of the reaction of the salivary glands to the pathological process , the accumulation of saliva due to the slowing down of the esophageal transit and the involvement of the vagus nerves. Hypersalivation is considered a late symptom of esophageal cancer.

Regurgitation is characteristic in 3-16% of patients with esophageal cancer. It occurs immediately after eating (if the tumor is located in the upper and middle third of the esophagus) or after a long time (if located in the lower third). For esophageal cancer in the lower third, vomiting is also characteristic, which occurs 1-2 hours after eating.

General signs include fatigue, decreased work capacity, arousal, weight loss, anorexia, insomnia, etc.

Involvement in the process of adjacent structures and organs is manifested by dysphonia in case of damage to the recurrent nerve most often the left.

Involvement in the tumor process of the trachea or bronchi causes a dry and excruciating cough. Horner syndrome develops due to damage or compression of the cervical or thoracic sympathetic chain . If the tumor grows in the lung, pneumonia, abscess, pleural empyema may develop. The invasion of the tumor in the bronchus with its destruction can lead to the formation of esophagobronchial fistula and is manifested by excruciating cough, sometimes hemoptysis and fever. Other complications such as mediastinitis and aspiration pneumonia may also occur. Signs of pericarditis and hemorrhages caused by blood vessel erosions are not excluded in the outgrown spread of the tumor.

In metastatic esophageal cancer (metastases in bones, liver, lungs, brain,

etc.) the most characteristic signs are pain in the described regions and the manifestation of the pathology of those organs involved in the process.

Diagnostic methods

The clinical diagnosis of esophageal cancer is established based on accusations, anamnesis, objective data, radiological, endoscopic and morphological investigations.

At the general inspection, the skin and the turgor of the diminished skin or the almost complete disappearance of the subcutaneous adipose layer (cachexia) draw attention. Enlarged ggl can be detected in the supraclavicular region.

One of the main methods of diagnosing esophageal cancer is the radioimaging method. Radiological investigations begin with radioscopy and chest radiography.

Radiological semiotics of esophageal cancer depends on the size of the tumor, the shape of the growth and the level of involvement of the esophageal wall. In esophageal cancer with exophytic growth the main radiological sign is the filling defect.

The infiltrative endophytic form is manifested radiologically by a segmental rigidity in the tumor or by lumen stenosis accompanied by a suprastenotic dilation in the form of a „funnel" (Trimadeau sign).

Ulcerative cancer manifests itself radiologically through barium deposits or „niche".

To study tumor invasion in neighboring tissues and organs, parieto- and angiography, pneumomediastinography, fibrobronchoscopy and chest CT are performed.

Esophagoscopy enhances the diagnosis by allowing the tumor to be visualized and the material to be taken for cytological and histological analysis.

Figure 1. *Endoscopic and macroscopic appearance of esophageal cancer*

The radiological and endoscopic method allows the diagnosis of esophageal cancer to be established in 99-100% of cases. Remote metastases are detected by USG, CT, laparoscopy.

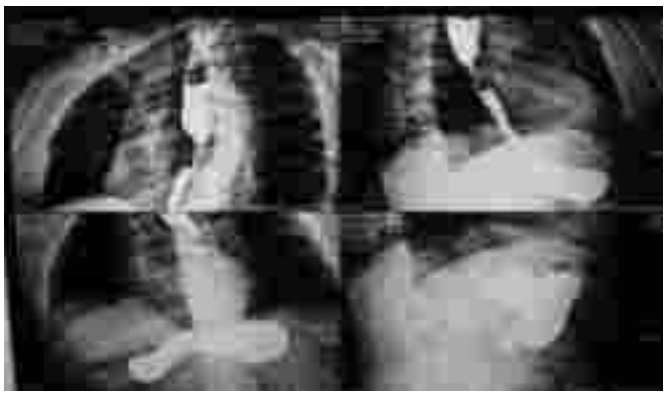

Figure 2. *Barite radiography of the esophagus. Infiltrative form of esophageal cancer*

Differential diagnosis in esophageal cancer

It is done with esophageal or extraesophageal pathologies that have as clinical manifestation the presence of dysphagia. Hiatal hernias, esophageal diverticula, benign esophageal strictures, reflux esophagitis, cardiospasm, are diseases that may have as a manifestation the presence of dysphagia. Some difficulties in the differential diagnosis of esophageal cancer also have benign tumors (adenomas, papillomas, fibroids, leiomyomas), mediastinal diseases (plunging or aberrant goiter) aortic aneurysms, pericarditis, by extrinsic compression. The differential diagnosis is made clinically by the progressive and short historical character of the esophageal neoplasm, of the clinical picture and is confirmed by endoscopy, barium radiography of the esophagus, tomography and morphology.

Treatment of esophageal cancer

It is well known that there can be no radical treatment of esophageal cancer located in the chest and abdomen without the surgical component.

Surgery is considered the standard treatment in localized disease (T1-2 N0-1 M0), although long-term survival does not exceed 25% in the presence of regional lymph node involvement.

Esophageal cancer surgery

Operation Lewis

The principle of the operation is esophagectomy with concomitant gastric plasty in one moment, the access being transthoracal on the right and laparotomy, which aims at two purposes: staging the tumor process, preparing and mobilizing the stomach for its transfer into the thoracic cavity. Esophageal plasty with the stomach is performed above the aorta.

Operation Garlock

This operation is indicated in tumors located below the aortic arch.

Left thoracotomy with resection of the left costal rim and extension of the incision to the umbilicus. Stomach mobilization, cardiac resection with cardiac orifice suturing. The esophagus is removed and then gastroplasty is applied one moment below the aorta.

surgery *- 2 stages*

Stage I - Thoracotomy on the left. The esophagus mobilized all the way. Resection of the esophagus in the upper part. Left cervical esophagostomy.

Laparotomy. Mobilization of the stomach (cardia). Esophagus extracted with the tumor in the abdominal cavity and resected together with the stomach cardia. Subsequently gastrostomy procedure Vitzel is applied.

Stage II - In a few months, if there are no signs of recurrence or metastases, plastic surgery is performed with the loops of the small or large intestine.

Operation Khirschner - Nakayama

The operation is indicated in esophageal cancer located above the aorta.

Thoracotomy on the right. Mobilization of the esophagus to the cardia, resected and sutured. Subsequently, cervical mediastinotomy is performed. The esophagus is extracted from the surface with the tumor. Laparotomy, mobilization of the stomach. Under the presternal skin, a tunnel is made through which the stomach is mobilized on the neck and in the cervical region, esophagus-gastro-anastomosis is applied.

Operation Gavriliu

It is performed in the middle and upper third of the thoracic portion. At the base of this operation is the intrathoracic gastroesophagoplasty with a

tunnel flap, formed by the large curvature of the anisoperistaltic sutured stomach.

Radiotherapy

The enlarged tumor volume includes the primary tumor and the regional lymph nodes. The planned target volume includes the tumor plus 5 cm above and below the tumor and 1.5 - 2 cm in addition to the radial edges. IMRT (intensity modulation radiotherapy) can be used in some cases to reduce the doses given to the heart and lungs.

Doses: Preoperative or postoperative 41.4 - 50.4 Gy (1.8-2Gy / day)

Definitive therapy: 50-50.4 Gy (1.8-2Gy).

Radiation therapy has been used as an alternative to surgery in the primary treatment of esophageal cancer. It is used in patients with widespread local disease and patients who cannot be operated on. Provides temporary palliation. Survival at 1 year is 18% and at 5 years - 6%.

Chemotherapy for esophageal cancer

Esophageal cancer responds poorly to applied chemotherapy. Response rate _ _ varies from 10% to 40% and usually the answer is incomplete (minor regression of the tumor) and temporary. No agent is much more efficient than another . Cisplatin and 5-fluorouracil are most commonly used in combination chemotherapy . There are other drugs, such as mitomycin, doxorubicin, vindesin, bleomycin and methotrexate, that are active against squamous cell carcinoma.

Prognosis

Survival in patients with esophageal cancer depends on the stage of the disease. Squamous cell carcinoma and adenocarcinoma, in a similar stage, have practically the same survival rates.

The overall 5-year survival rate for esophageal cancer is 19%. Patients without lymph node involvement have a significantly better 5-year prognosis and survival rate than patients with lymph nodes involved. Patients with stage IV disease have a 5-year survival rate of less than 5%.

5-year survival by stage:

St. I> 50%

St. II 10-30%

St. III> 10%

St. IV rare

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GASTRIC CANCER

Gastric cancer (GC) is one of the major problems in medicine. In one year, about 2 million people worldwide die from CG.

In the last 5 years there has been a decrease in the number of people with gastric cancer. However, there are countries where CG not only does not tend to decrease, but on the contrary the number of patients increases.

The highest incidence for both men and women is in Japan, with 90 per 100,000 in some regions. The incidence of GC in Chile, the countries of Central and Western Europe is quite high.

In Moldova in the last 5 years CG has a declining trend and ranks 4th in the oncology structure, amounting to 13.2 in 1997 while in 2018 were recorded 445ca which is an incidence of 12.5% 00.

The countries with the lowest incidence of CG are Mexico, Senegal, Indonesia.

Ethiopatogenesis

Like other sides, localizations in the appearance of GC can be listed a number of factors and precancerous conditions that can promote the onset of the tumor process.

Factors that may promote GC (some are carcinogenic) make up the following list:

1. Hydrocarbon-rich foods.
2. The presence of benzipiren (a carcinogen unanimously recognized by scientists and clinicians) which is the result of the preparation of dishes rich in animal fats at high temperatures (fried products on the pan, skewers, etc).
3. Foods and drinking water rich in nitrites and nitrates against which another carcinogen is formed - nitrosamine.
4. The role of alcohol abuse is not excluded - CG in chronic alcoholics is 3 times more common than in the rest of the population.
5. The hereditary factor is very rarely found ≈1-3% of cases (Gardner's syndrome, family polyposis, etc).

6. CG is more common in some syndromes of immunobiological disorders: Bruton's disease (agamaglobulinemia X, thymoma immune deficiency, NHL, etc).
7. Chromosomal disorders: pigmented xeroderma, anemia Fanconi.
8. Chromosomal fragility syndromes (xeroderma pigmentozum, Fanconi anemia, telangiectatic ataxia - Louis-Barr syndrome, etc).
9. Helicobacter pylori infection.

Precancerous conditions

A series of pathological processes of the gastric mucosa refer to precancerous diseases of the stomach, among them the most important role belongs to chronic gastritis with reduced secretion, ulcer disease, gastric polyps, pernicious anemia, etc.

1. Chronic hypoanaacid atrophic gastritis. Of all gastric pathologies, 50-60% are chronic gastritis. Gastric cancer occurs on the background of gastritis in 5-10% of patients. Patients with chronic gastritis (especially those with hypo- and anacid secretion) should be monitored systematically, with clinical, radiological, endoscopic examinations to determine the secretion and biopsy no less than twice a year, and this category of rehabilitation is performed. sick. At the slightest suspicion of malignancy, patients should be urgently investigated and, in case of confirmation of the diagnosis, undergo surgery.

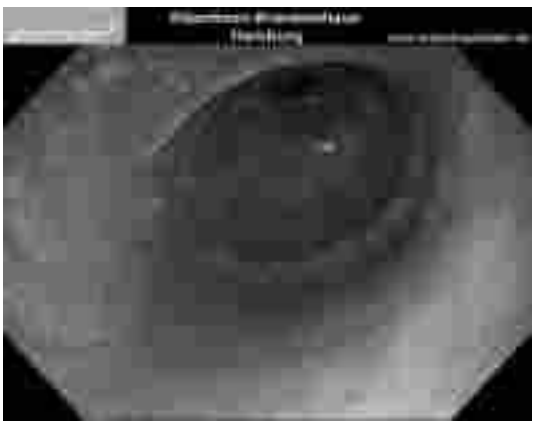

Fig. 1. *Endoscopic appearance of chronic atrophic gastritis*

2. Ulcerative disease, gastric ulcer. The frequency of ulceration is 2-25% (L.M. Ratner). It more often maligns „high" ulcers (ulcer of the heart

and subcardium, ulcer of the great curvature). The malignancy of the gastric ulcer is manifested by the following clinical signs: the disappearance of the periodicity and the evolution of the ulcer cycle, the varied modification of the pains, which become permanent and less intense, independent of the feeding period. In the case of ulcer malignancy, characteristic radiological and gastroscopic signs appear: transformation of the ulcer size, lack of peristalsis, indistinct ulcer edges, disappearance of convergence of the folds of the gastric mucosa at a distance of a few centimeters (2-3 cm) from the edge of the ulcer crater. ulcerative defect.

In cases of gastric ulcer more than two years with scaly edges, more than 2 cm in diameter, located in the proximal part or on the large curvature, without effect after drug treatment, frequent exacerbations - all this dictates a surgical treatment.

At the same time, the Japanese do not include gastric ulcer in precancerous pathology. As early as 1912, Aschoff said, „It does not malign the ulcer, but ‚ulcerates' the cancer." Hisamichi and Kobiyama oncologists agree that in 2180 ulcer patients found cancer in 2.6% of cases.

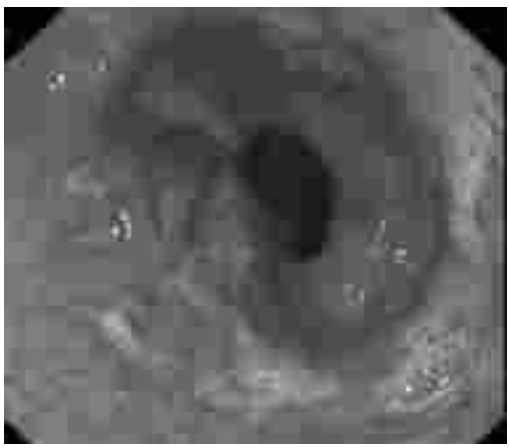

Fig 2. *Prepyloric gastric ulcer - endoscopic appearance*

3. Polyps: constitute 5-10% of all stomach tumors and are more common at the age of 40-50 years and are located primarily in the antral region. Malignant 1.5-60% (Melnicov). Family polyps often malign. Inflammatory polyps rarely malign.

a. solitary– 5%

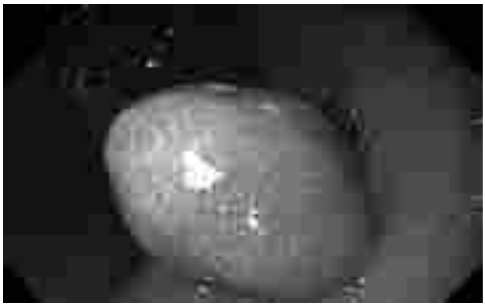

Fig 3. *Endoscopic appearance of solitary gastric polyp*

b. diffuse polyposis – 15%

Fig 4. *Endoscopic appearance of diffuse gastric polyposise*

c. familial polyposis– 100%

Surgery (endoscopic polypectomy, segmental resection, subtotal resection, or diffuse polyposis gastrectomy) is included in the prophylaxis of polyp malignancy.

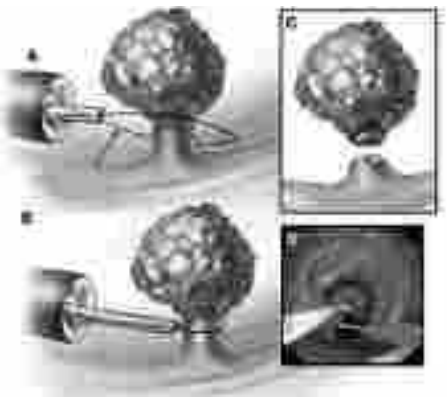

Fig 5. *Schematic image of the endoscopic excision of a solitary polyp*

4. Stomach cancer resect due to ulcer does not matter the location of the ulcer. According to several authors, resected stomach cancer occurs 15-20 years after gastric resections due to ulcers, both gastric and duodenal, and is found in 0.1-4.9%.

Dispensing, radiology and gastroscopic examination are the main methods of differential diagnosis.

5. Menetrier disease - diffuse hyperplastic gastritis with elements of pseudopolyposis. It presents with a segmental hyperplastic gastritis with elements of pseudopolyposis sometimes with metaplasia of the gastric mucosa. It requires the same thorough dispensing and regular investigations to rule out malignancy.

Fig 6. *Endoscopic appearance of diffuse hyperplastic gastritis (Menetrier Disease)*

6. B12-deficient anemia, Adisson-Birmer disease. The frequency of gastric cancer in pernicious anemia is 2.5 - 8.1%. The treatment of patients with pernicious anemia dictates the application of hepatic, gastric, vitamin B12 and other preparations. Dispensing, radiology and gastroscopic examination are the main methods of differential diagnosis.

Fig 7. *Endoscopic appearance of Addison-Biermer disease*

7. Hereditary cancer. In Lauren's classification, gastric cancer is divided into intestinal cancer that appears on a mucosa with pathologies that would serve as factors that cause malignancy. The hereditary factor is registered only in the diffuse forms.

Tumoral stage:

50 - 60% - pyloroanthral
15 - 20% - the proximal region of the stomach (cardia and large tuberosity)
10 -15% - small curvature
2% - large curvature
3% - total affection.

Macroscopic forms or forms of tumor growth

1. Exophyte - grows in the lumen, gastric cavity, is slightly more delimited in growth (polypoid, cauliflower, growth „in the plate") very rarely causes stenosis, but bleeds more frequently, metastasizes later.

Fig 8. *The endoscopic appearance of gastric cancer with exophyte growth, „plate cancer"*

2. Endophyte:
   a) infiltrative-diffuse

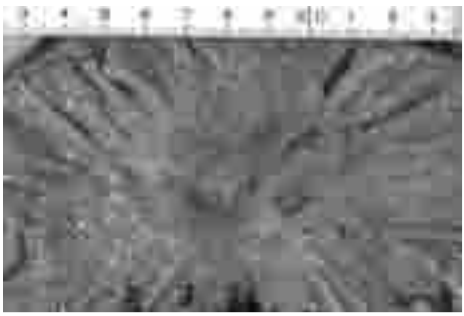

Fig 9. *Macroscopic appearance of gastric cancer, infiltrative-diffuse form*

   b) infiltrative-ulcerative

Fig 10. *Macroscopic appearance of gastric cancer, infiltrative-ulcerative form*

Infiltrative forms cause pylorostenosis and cardioesophageal stenosis with dysphagia, much earlier metastasis.

3. Mixed form - there are both exotic and endophytic elements.

Histological forms

It is usually the adenomatous form (adenocarcinoma) with different degrees of differentiation (G1 - well-differentiated, G2 - moderately differentiated, G3 - poorly differentiated or undifferentiated, anaplastic), pavement. There are also non-epithelial malignancies - leiomyosarcoma, lymphosa and others.

The clinical picture

Gastric cancer has no pathognomonic signs, the clinical picture is manifested by a polymorphism of symptoms and the diagnosis may be suspected as a result of thorough inspection.

On inspection, the skin is pale and sometimes pronounced with low turgor, with cachexia elements. In 5% of cases, the left supraclavicular ganglia are palpated, the major ones being hard, often immobile (Wirchow-Troisier metastasis).

In 2/3 of cases the tumor is detectable in the epigastrium in pyloroanthral cancer, the importance mobility of the tumor is huge (if it is immobile most of the time it is an outdated locoregional stage). Cancer of the gastric body or that of the proximal region is usually not accessible to palpation except

when the tumor has spread distally. In the presence of liver metastases, hepatomegaly with multiple neoplasms or solitary nodules of a hard, painless consistency may be found. It can also be splenomegaly, in which case ascites is also determined.

In the vaginal touch is determined mt Kruckenberg, and in the rectal - mt Schnitzler-Blummer (pararectal).

The clinical picture of GC is very varied and manifests itself according to the location of the tumor, the form of growth, the character of the evolution and the metastasis. It is often almost asymptomatic in the early stages, but a thorough history and inspection provide grounds for suspicion of stomach pathology, which is confirmed by further and intentional investigations.

The Japanese school warns that people over the age of 50 only have a single charge in the appearance of the gastrointestinal tract, first of all investigations must be carried out to confirm or deny gastric cancer.

In the advanced stages, symptoms characteristic of gastric pathology appear and the clinical picture is in accordance with the location and form of tumor growth.

In patients with antral cancer (the most common localization) there are symptoms characteristic of pyloric stenosis and are characterized by fullness and sensation of postprandial epigastric embarrassment. Later regurgitation occurs, often with a foul odor, nausea, vomiting. As a result of food stasis in the stomach, anorexia occurs and progresses.

Sometimes in the infiltrative form of pyloric cancer growth, at first there may even be an increase in appetite to bulimia. This phenomenon is explained

by the fact that the tumor, infiltrating all the layers of the antral sector, causes the rigidity of the pylorus, which remains open permanently with the rapid evacuation of the food bowl from the stomach into the duodenum, dictating the ingestion of a new food portion.

As the tumor expands, its size increases and the signs of pyloric stenosis progress and the stomach passage becomes impossible. Vomiting with food content becomes constant, with a rotten, unbearable odor, which dehydrates and exhausts the patient. The stomach expands, increases in volume, which is observed on inspection and palpation (sign of splashing).

As the exophyte forms of antral cancer decompose, they cause bleeding, which is manifested by hemorrhagic vomiting and melena, accompanied by secondary anemia.

Proximal GC, especially the heart and subcardium, develop asymptomatically for a long time or with a small gastric discomfort. Later, with the evolution of the tumor, dysphagia appears. At first it has a functional character, becoming organic quite quickly. Functional dysphagia is an earlier sign of the disease and occurs as a result of esophageal or cardiac spasm, when the tumor is not yet the cause of the mechanical barrier, and the patient has a feeling of access, caused by the food passage and requires concomitant fluid reception. Such a spasm may recur after a few days or weeks. Over time, the tumor grows, involving the abdominal part of the esophagus or the heart, and the dysphagia changes its character, changing from functional to organic, and the patient has accusations regarding the passage of food every time, even receiving liquid food. In this case, epigastric pain such as angina pectoris, ihorous regurgitation occur. The patient loses weight even if the appetite is maintained; concomitantly with dysphagia, patients also show hypersalivation.

In stomach cancer, the disease is manifested by pain in the region of the heart, being very similar to ischemic pain. If objective data are missing, EGC does not indicate pathology and ischemic heart disease is ruled out, radiological and endoscopic investigations are indicated.

Cancer of the gastric body, especially of the anterior and posterior walls and of the large curvature, does not manifest itself for a long time. The first signs are the syndrome of „small symptoms" with the appearance of anemia and pain in the epigastrium, which appear only after feeding, and after the release of the stomach disappears or vice versa, patients feel pain on the stomach „empty" on fasting who disappear postprandial.

Permanent and persistent pain with back irradiation, which does not diminish or disappear with drug therapy, demonstrates the involvement of the pancreas or solar plexus.

If the walls of the stomach are involved in a circular motion, the stomach is stenosed in the shape of a clock with sand (hourglass). Because gastric cancer is detected late, the first signs may be bleeding, especially in exophytic forms of growth.

Complications of GC are: hemorrhages, pyloric and esophageal-cardiac stenosis, perforation of the tumor in the abdominal cavity with the evolution of peritonitis or the formation of gastro-colic fistulas, clinically manifested by fetid vomiting, tumor expansion involving adjacent structures and organs (liver, pancreas, mezou, parietal peritoneum, etc.).

The presence of GC complications does not always prove that the malignant process is outdated in terms of stage.

Paraclinical methods

The blood count shows anemia, sometimes very pronounced with leukopenia, accelerating ESR. Biochemical analyzes cause disorders of all types of metabolism, especially hypovolemia, disorders of hydrosaline balance, hypodisproteinemia.

The determination of ACE (carcinoembryonic antigen) - N-5-10ng / ml, is of relative importance and is recommended in the surveillance of radically treated patients.

Instrumental diagnostic methods

Radio-imaging methods begin investigations with contrast-enhanced radioscopy-spelling (barium sulphate or contrast with iodine cardiotrastetc).

Radiosemiotics is in line with tumor growth forms. In exophyte cancer we have to determine the gap, filling defect, in infiltrative-diffuse form there are different degrees of pylorosthenosis or stenosis in the cardioesophageal region, if the tumor is located on the anterior or posterior wall there is a segmental stiffness (in radioscopy): infiltrative cancer- ulcerative - is manifested by „deposition" of barium - niche.

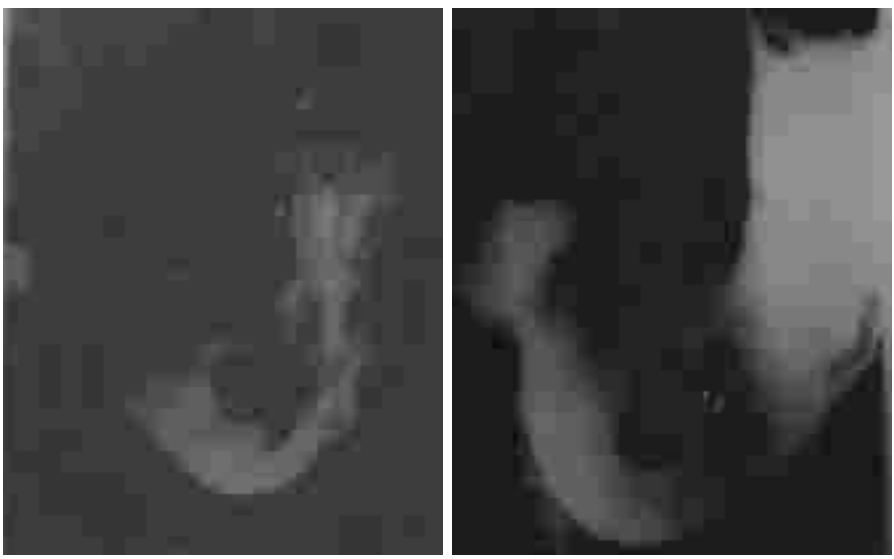

Fig 11. *Radiological mark gap or filling defect*

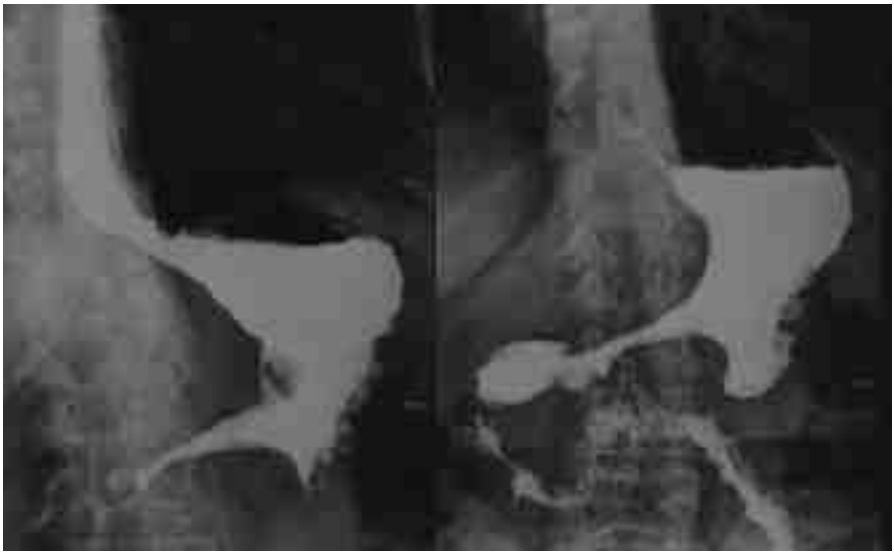

Fig 12. *Radiological aspect of gastric cancer - infiltrative-diffuse form*

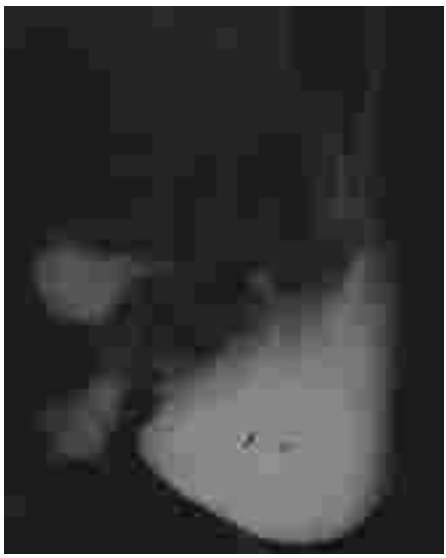

Fig 13. *Radiological aspect of gastric cancer - infiltrative-ulcerative form*

With the construction of the fibrogastroscopy (Hirschovitz, 1958), a great perspective was opened in the diagnosis of gastric cancer, and targeted gastrobiopsy allows the histological character of the tumor to be verified, the malignancy of polyps to be detected and the character of the mucosa surrounding the tumor to be studied. The application of gastroscopy with the sampling of bioptate and the material for histocytological examination

allows the diagnosis of GC in 90-98%, even in early cases („in situ" cancer, superficial cancer with involvement of the mucosa and submucosa). It should be noted that negative biopsy data do not always refer to the absence of gastric cancer, as the biopsy could be taken from tumor sides in destruction, but not at the borders of macroscopically unchanged tissues, as well as in cases of infiltrative growth with submucosal enlargement cancer. In exophyte and infiltrative ulcerative forms of cancer, the endoscopic diagnosis is not difficult and characterizes the growth, the location of the tumor, its size and the condition of the mucosa around the tumor. During gastroscopy, for histological examination, 5-6 slices should be taken from different places of the suspicious mucosa, including from the unaltered sectors. (See slides in the Tumor Growth Forms section).

The Japanese Endoscopic School classifies superficial (early) gastric cancer into the following types:

Type I	protruding form (prominent)
Type II	superficial shape
Type IIa	elevated
Type IIb	flat
Type IIc	sublevel, depressed
Type III	excavated shape

Fibroesophageal-gastro-duodenoscopy has the advantage that the tumor can be visualized and the biopsy can be performed with histological examination.

In infiltrative-diffuse forms the advantage is on the part of radioscopy-spelling. In terms of staging the tumor process, USG, CT (computed tomography) and laparoscopy with tumor biopsy are indicated.

Finally, in case the diagnosis remains uncertain, diagnostic laparotomy is recommended.

Additional methods are used to stage GC and detect metastases: a) ultrasonography (USG or ultrasound) especially of the liver, which increases the detection of liver metastases; b) scintigraphy of the liver and pancreas, also for the detection of metastases in the respective organs; these two methods have a disadvantage - no metastases smaller than 1.5-2 cm are detected; c) selective angiography (celiacography) also detects liver and pancreatic metastases; d) laparoscopy is one of the basic methods in detecting liver metastases, parietal peritoneum and ascites, its advantage being very good visualization of metastases and sampling of bioptate

for histological examination or ascites for cytological examination; e) computed tomography (CT) of the liver and pancreas.

Among the biological markers sought with interest and hope for possible screenings, CEA (plasma carcinoembryonic antigen) occurs in only 40-60% of cases and especially in advanced forms. Lately, its dosage is used in gastric juice, which is a promising test, because it becomes positive early and seems to have a sensitivity of 80-90%.

This marker is valuable in monitoring radically treated patients.

Differential diagnosis

The differential diagnosis should be made primarily with precancerous diseases: chronic gastritis, polyps and polyposis, stomach ulcers, pernicious anemia, menstrual disease and resected stomach disease due to ulcers (duodenal or gastric).

It is also necessary to differentiate between TB, syphilis and benign tumors: leiomyoma, lipoma, angioma, etc. A special place is occupied by sarcomas and other mesenchymal tumors.

Anamnesis, radiological data of the lungs, sputum analysis, positive tuberculin tests, gastroscopy with histological and cytological examination allow the confirmation or refutation of tuberculosis.

Syphilis occurs at a younger age, gastric disorders are slow and less pronounced, being always accompanied by achlorhydria and do not correspond to radiological data (extensive pathologies with a fairly satisfactory condition of the patient). Positive serological tests confirm the diagnosis.

Leiomyoma and myoma develop in the thickness of the gastric muscle without damaging the mucosa and thus lead to thickening of the wall, which requires a differential diagnosis with diffuse endophytic tumor growing in the initial phase; In this case, the diagnostic advantage belongs to the radiological method, especially to tomoparietography.

Cardiospasm (achalasia) is very difficult to differentiate from heart cancer. Cardiospasm is more common in young, middle-aged, psycho-emotionally unstable women. Cachexia occurs very late, dysphagia and hypersalivation in cardiospasm have a functional character over decades; radiology supra stenotic dilation of the esophagus is funnel-shaped (Tremadaux sign) and is more pronounced in cardiospasm. Due to the very long process, the mucosa and peristalsis of the esophagus are preserved and elements of chronic esophagitis are detected.

Clinically Menetrier disease is very difficult to differentiate from GC, also lacks hydrochloric acid, sometimes cytologically determines the atypia of cellular elements. The most important method is gastroscopy, which detects edema and hyperemia of the mucosa, which moves in the stomach cavity over its entire surface or in certain sectors of the gastric body or antrum. Sometimes the folds are covered with pseudopolyps and the mucosa is not smooth, reminiscent of a pavement. Local or diffuse radiology shows a thickening of the folds, stiffness resistant to palpation. The uneven, twisted deformation of the folds indicates a malignant relief. Tomoparietography and sometimes triple contrast are necessary, because in this case the relief of the mucosa, the thickness and the contours of the stomach are observed; biopsy plays a key role in diagnosis. See slides above.

Sarcoma, lymphosarcoma, GIST tumor and others are difficult to detect both radiologically and gastroscopically. The main role in diagnosis is laparoscopy and especially laparotomy. In endogastric and mixed forms these tumors can be detected by gastroscopy with biopsy. Often the diagnosis is confirmed only intraoperatively with extemporaneous histological examination.

TNM Classification, Geneva 2017

The classification applies only to carcinomas.

The changes in this edition (compared to the seventh edition) were based on recommendations from the International Gastric Cancer Assodation Staging Project.

The procedures for assessing categories T, N and M are as follows:

T Categories Physical examination, imaging, endoscopy and / or surgical examination

N Categories Physical examination, imaging and / or surgical examination

M Categories Physical examination, imaging and / or surgical examination

Regional lymph nodes

In addition to the regional lymph nodes described above, the involvement of other intra-abdominal lymph nodes will be characterized, such as the retropancreatic, mesenteric and paraaortic nodes, which are included as distant metastases.

Clinical classification of TNM

T -Primary tumor

T_X The primary tumor cannot be evaluated

T_0 No evidence of primary tumor

T_{is} Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia

T_1 The tumor invades the lamina propria, the muscular mucosa or the submucosa

T_{1a} The tumor invades the lamina propria or muscle of the mucosa

T_{1b} The tumor invades the submucosa

T_2 The tumor invades its own muscle

T_3 The tumor invades the serosa

T_4 The tumor perforates the serosa (visceral peritoneum) or invades adjacent structures [a,b,c]

T_{4a} The tumor perforates the serosa

T_{4b} The tumor invades the adjacent structures[a,b]

Note

[a] Adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneal space.

[b] The intramural extension at the level of the esophagus or duodenum will be classified according to the depth of the largest invasion in any of these locations, including the stomach.

[c] Tumor that extends to the gastrocolic or gastrohepatic ligaments or to the large or small omentum without perforating the visceral peritoneum will be classified as T_3.

N - Regional lymph nodes

N_X Regional lymph nodes cannot be evaluated

N_0 There are no metastases in the regional lymph nodes

N_1 Metastases in 1 or 2 regional lymph nodes

N_2 Metastases in 3 to 6 regional lymph nodes

N_3 Metastases in 7 or more regional lymph nodes

N_{3a} Metastases in 7 to 15 regional lymph nodes

N_{3b} Metastases in 16 or more regional lymph nodes

M - Remote metastases

M_0 There are no distant metastases

M_1 The presence of distant metastases

Note

Remote metastases include peritoneal seeding, positive peritoneal cytology, and omental tumor that is not part of a continuous extension.

pTNM pathological classification

Categories pT and pN correspond to categories T and N. for pM.

pN_0 Histological examination of a piece of regional lymphadenectomy will typically include 16 or more lymph nodes. if the lymph nodes are negative but the number normally examined is not met, it will be classified as pN_0.

Clinical staging			
Stage I	T1, T2	N0	M0
Stage IIA	T1,T2	NI, N2, N3	M0
Stage IIB	T3,T_{4a}	N0	M0
Stage III	T3, T_{4a}	NI, N2, N3	M0
Stage IVA	T_{4b}	Either one N	M0
Stage IVB	Either one T	Either one N	Ml

Pathological staging*			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	NI	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	NI	M0
	T3	N0	M0
Stage IIB	TI	N3a	M0
	T2	N2	M0
	T3	NI	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0

	T3	N2	M0
	T4a	NI, N2	M0
	T4b	N0	M0
Stage IIIB	T1,T2	N3b	M0
	T3,T4a	N3a	M0
	T4b	N1, N2	M0
Stage IIIC	T3,T4a	N3b	M0
	T4b	N3a, N3b	M0
Stage IV	Either one T	Either one N	Ml

Metastatic pathways

Topographic Lambert divides the regional gastric lymphatic system into 3 stations collectors:

Station N1:

- paracardial on the right
- paracardial on the left
- ganglia of small curvature
- ganglia of large curvature
- suprapyloric
- infrapyloric (subpyloric)

Station N2:

- lymph nodes in the left gastric arteries
- lymph nodes in the common hepatic artery
- celiac trunk ganglia
- lymph nodes in the spinal artery
- ganglia of the splenic hilum

Station N3:

- hepatoduodenal ligament ganglia
- lymph nodes in the small intestine
- lymph nodes along the mesocolic artery
- paraaortal ganglia
- retropancreatic ganglia

Also in the lymphatic pathway are distant metastases as follows: Virhov-Troisier (supraclavicular cervical metastases, usually on the left);

Kruckenberg (ovarian metastases); Schnitzler - Blummer (pararectal) and the regional apparatus of the gastric lymph nodes.

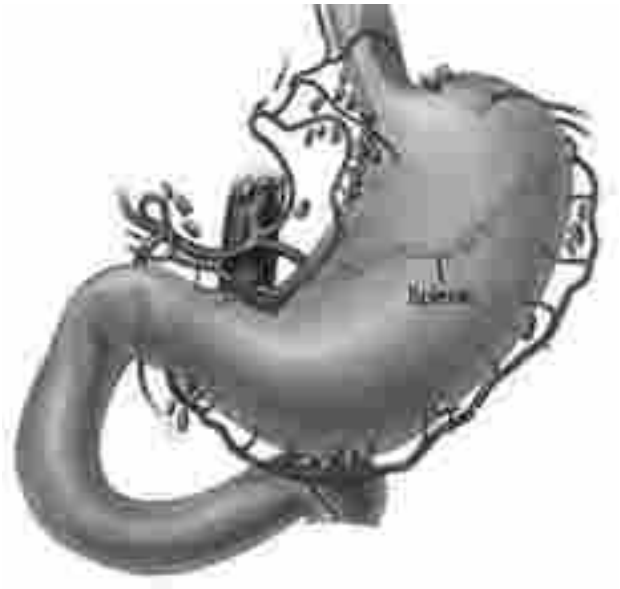

Fig 14. *Groups of peri- and paragastral lymph nodes, schematic aspect*

Hematogenous (distant metastases, 2/3 are those of the liver, lungs, brain, etc.).

Mixed pathway: directly from the visceral peritoneum to the parietal and again visceral, also through the lymphatic vessels.

Methods of treatment

1. Surgical:
a) radically
b) palliation
2. Combined:
a) surgical + chemotherapy
b) surgical + radiotherapy
3. Complex: surgical + chemotherapy + radiotherapy.

Prognosis

5-year survival after radical treatment does not exceed 25-35%, and in the early stages $T_{1-2}N_0M_0$ high and moderate degree of differentiation survival is - 70-90%.

The main radical operations due to GC are performed depending on the form of growth and the location of the tumor. According to the volume and character, the surgical interventions are divided into three main types.

Gastrectomy or distal radical resection (distal subtotal resection). The level of resection on the small curvature is 2 cm below the cardia and on the large curvature - at the level of the lower pole of the spleen. It is removed 4/5 from the stomach, simultaneously with the large omentum by coloepiploic detachment, gastrocolic ligament, small omentum to the origin of the monobloc gastric coronary artery with supra- and retropyloric ganglia of the right gastroepiploic artery and the suprapancreatic ones. Digestive continuity is restored by gastro-jejunal anastomosis (CJA) type Bilroth II (on short jejunal loop, or Roux, or Balfour in omega anastomosis).

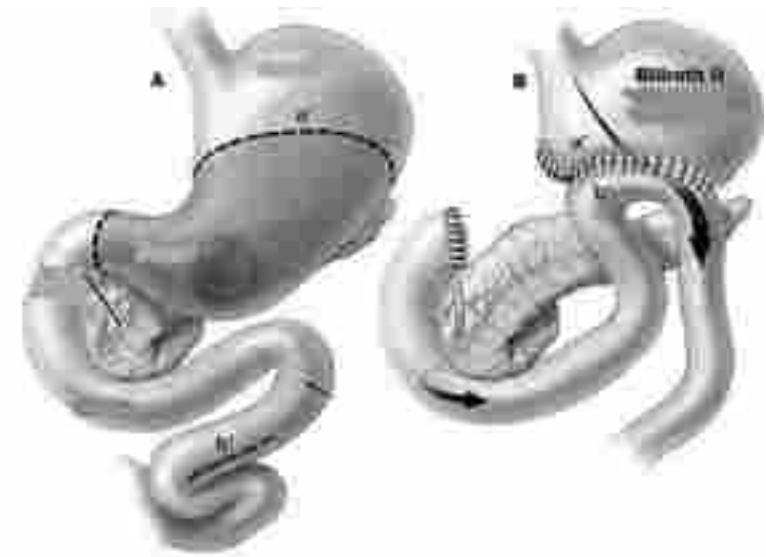

Fig 15. *Schematic aspect of gastric resection Billroth II, Hofmeister-Finsterer*

Gastrectomy, proximal subtotal resection. Theoretically, 4/5 should be removed from the stomach (80%), but in practice, for technical reasons, only 50% is removed, maximum 60%. Simultaneously with the proximal gastric pole, a large part of the great omentum, gastrocolic ligament, gastrosplenic ligament and small omentum are removed to the origin of the gastric coronary artery. The digestive tract is restored by gastroesophageal anastomosis.

In case of heart cancer, ablation of the abdominal esophagus is mandatory and subtotal proximal esophagogastrectomy is performed. In this case, a thoracotomy should be used.

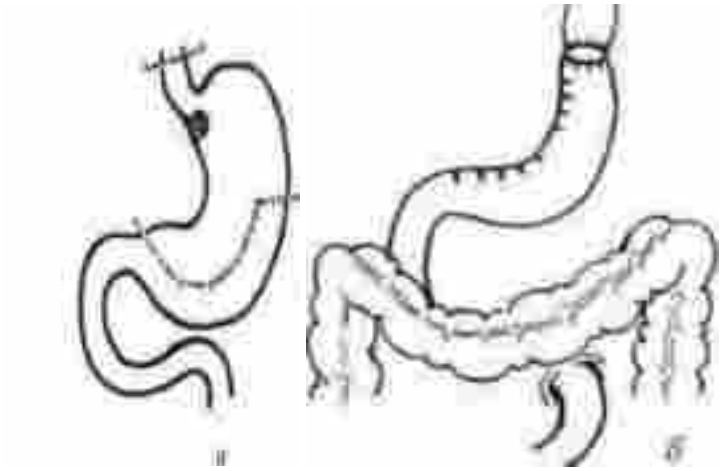

Fig 16. *Schematic appearance of proximal subtotal partial gastrectomy*

Total gastrectomy. The excision piece includes the cardia and the pylons, all the formations that contain the afferent lymphatic territory. According to the Japanese authors, all 16 lymph nodes must be removed, which is practically impossible, because the intrahepatic, paraaortal and mediastinal lymph nodes are inaccessible for excision.

This operation is indicated in gastric cancer, in pyloroanthral and proximal cancer, in infiltrative forms of growth, as well as in diffuse polyposis with multiple malignancies.

Restoration of the digestive transit can be achieved by end-to-end or end-to-side esophageal-jejunal anastomosis, or esophagus-duodenal anastomosis (Nakayama type).

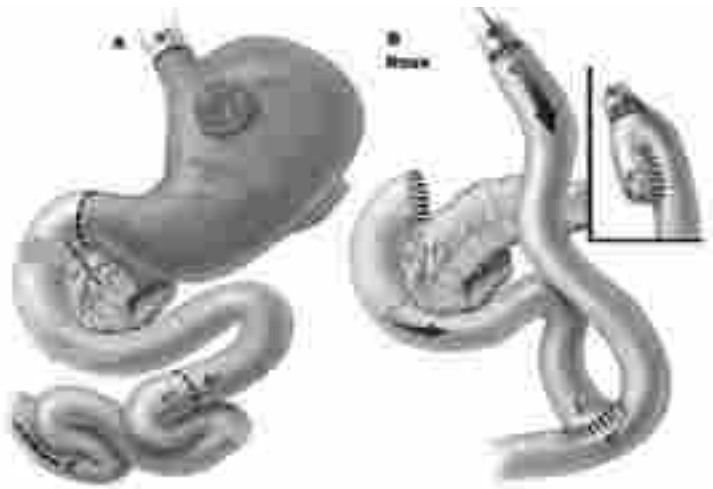

Fig 17. *Schematic aspect of total gastrectomy, Roux-en-Y*

Complex radical operations. These operations are aimed at removing the tumor-bearing stomach or most of it, and are enlarged in the adjacent anatomical areas, imposed by the extension of the tumor by contiguity (partial resection of the liver, pancreas, donor, diaphragm and spleen). , lymphatic territorial invasion or vascular extension.

Palliative surgery. The range of palliative surgery is wider and includes: palliative resections, „bypass" of the tumor through various collateral anastomoses, gastro- or jejunostomies or intubation with the use of different prostheses. There is still a palliative operation „unwanted" by patients today - gastrostomy in case of total dysphagia, when the „by-pass" is impossible to apply for technical reasons. Decompensated pyloric and cardiac stenoses with complete dysphagia, uncontrollable gastric hemorrhages, either with an acute allure, or more frequently chronic and persistent, leading to severe and uncorrected anemia, may serve as indications for palliative surgery.

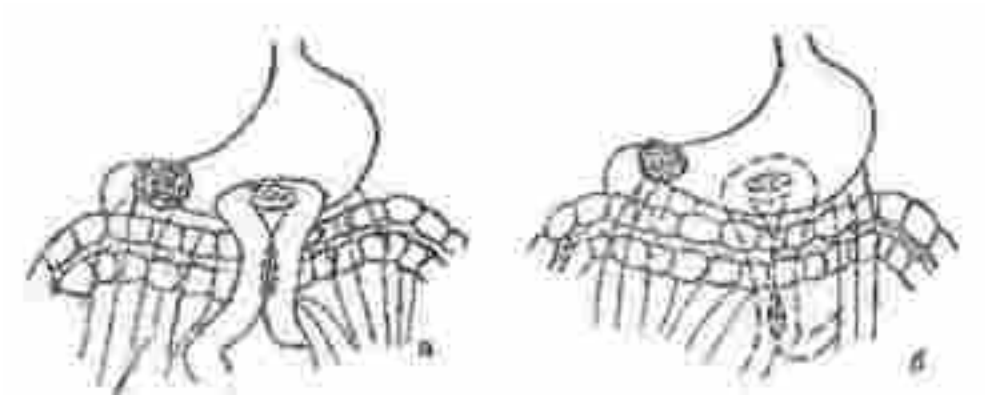

Fig 18. *Schematic aspect of digestive bypass: (a) anticholic gastro-jejunostomy; (b) retrocholic gastro-jejunostomy*

Exploratory operations are performed for diagnostic purposes in occult tumors, when the diagnostic methods have been inconclusive and the volume and nature of the operation are decided intraoperatively. These operations can also be used for staging in obsolete forms (distant lymph node metastases or blood metastases).

Adjuvant therapy. Classical radiotherapy was not required in the treatment of GC, and studies on external irradiation have almost

disappeared from the current literature. One method that may benefit as an adjunct to surgery is intraoperative irradiation with a single, important dose. This method was initiated by Kimura, Matuda and Abl (1964), being the last therapeutic possibility in the advanced stages. Co60 was used as the radiation source. A single dose is currently used in a single session to irradiate the primary tumor, metastatic lymph nodes, and residual lymph nodes after resection. The dose applied for the primary tumor is 40 Gy, for metastatic lymph nodes - 30-50 Gy and for residual cancer after resections - 28-30 Gy.

Another method of interest is chemotherapy. Monotherapy is applied with 5% 5-fluoruracil 10, 15, 20 ml intravenously over a day, a total of 4-5 grams.

Polychemotherapy FAP (5-fluoruracil, adriamycin, cisplatin) especially in poorly differentiated and undifferentiated cancer.

Immunotherapy with BCG, levamisole is prescribed 150 mg 3 days preoperatively and also 3 days postoperatively.

Preparing patients to undergo surgery, postoperative treatment, postoperative complications and their treatment, prognosis

It is known that functionally the stomach is connected with many organs: it participates in the regulation of hydrolytic, carbohydrate and protein metabolism. It is known that the pylorus protects the blood and tissues from the „flood" of the water (Soloviev, 1969). After resection, the body is unable to regulate the penetration of water into the tissues, which results in hydremia. In renal failure and acidosis in the gastric juice increases the amount of K and Ca ions and suddenly worsens the motor-evacuation function.

Disruption of protein and electrolyte elimination by the stomach affects liver function, which plays a major role in the metabolism of albumin and hydrocarbons. For these reasons, when the patient is hospitalized, he is infused with 500-1000 ml of NaCl, 500 ml of 5% glucose daily or over a day. In anemia, 250 ml of blood transfusions are performed, 10% solutions $CaCl_2$. If necessary, administer cardiac, protein, plasma, etc.

Patients with chronic bronchitis are indicated suction cups, inhalations, breathing gymnastics. In case of constipation and other evacuation disorders, 33% magnesium sulfide is administered a tablespoon 3-5 times

a day, and in the evening - cleansing enemas. In case of pyloric stenosis, stomach washes in the evening more than 3-4 hours after dinner.

The diet consists of vegetable soups, minced meat, cheese, butter, eggs and other easily digestible products. On the eve of the operation in the evening and in the morning, even on the day of the operation, cleansing enemas are performed, the last one no later than 2-3 hours before the operation.

In the postoperative period it is necessary to ensure full analgesia in order to prevent pain shock and parenteral nutrition in the ratio 2200-2400 calories in 24 hours, which dictates infusions of concentrated solutions of glucose with vitamins, amino acids (10% aminone, alvezin, moriamine, etc. .), lipid emulsions (20% intralipid, lipofundin, etc.).

The main postoperative complications are dehiscence of anastomosis or duodenal abutment with connection of infection and peritonitis or pleural empyema. There are other serious complications such as bleeding from the anastomosis (intragastric) or exogastric and wound vessels due to imperfect hemostasis, mesenteric vessel thrombosis, pulmonary artery thromboembolism, postoperative pancreatitis.

Less dangerous are the following complications: anastomosis, reflux-esophagitis, afferent loop syndrome, early postprandial syndrome or dumping-syndrome. The appearance of this syndrome can have several explanations: a) mechanical, as a result of the collapse of food masses from the stomach into the intestine in the wide anastomosis larger than 4 cm, which causes overloading the loops of the small intestine; b) humoral (chemical), the basis is the enzymatic insufficiency of glucose decomposition and resorption disorder, which leads to food repulsion; c) electrolytic, reflexive hypokalemia with a vegetative dystonia related to the lability of the individual. We distinguish 3 degrees of dumping syndrome. In grade I and II a therapeutic treatment is performed, and in grade III, sometimes in grade II - surgery. In surgical treatment the types of operations are recommended depending on the type of anastomosis, in gastro-jejunal anastomosis it is recommended to reconstruct the operation from Billroth II to Billroth I, operations with interposition, iso- or anisoperistaltic intestinal transposition (Henley-Soupault-Bucaille Zaharov type).

There may also be late postprandial syndrome, nutritional disorders, multi-deficiency syndrome, postoperative anemia, etc.

Prognosis of GC remains reserved with all the technical progress made in the last 20 years. The situation is explained by the still low percentage of early detection and treatment. About 1/3 of the operations are exploratory, and a large part are palliative interventions. Radical operability with resection is possible in 40-66%. In the case of proximal cancer, the situation is even more unsatisfactory, with a resectability between 35 and 65%.

Postoperative mortality: marks an important trend of reduction below 10% for subtotal radical operations and around 10-15% for total ones.

Improving late results in CG can be done with early detection, which Japanese surgeons have shown by detecting superficial cancer 2-3 times higher than in Europe and the United States.

In conclusion, it can be said that the long-term results in the treatment of gastric cancer are in full accordance with the stage of the tumor process (5-year survival is much higher in the case of lymph node deficiency), with histological form (less differentiated cancer and especially undifferentiated has a much lower survival rate than the differentiated one), with the form of tumor growth (exophyte forms have a much higher survival than infiltrative ones).

Prognosis: according to Japanese authors who present numerous statistics on early cancer, 5-year survival is 80-90%; at the same time, the survival rate is much lower after radical operations, including T3-4N0-2M0, which draws the attention of clinicians to make every effort to detect GC in the preclinical and early stages, which is currently possible due to specialized and thorough investigations. both radiological and endoscopic.

Prevention of GC:

1. Primary with the exclusion of factors with a directed diet;
2. Secondary - treatment of precancerous pathologies (polypectomy, gastric resections in gastric ulcer, etc.).

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PRIMARY HEPATIC CANCER

History - first descriptions

C. A. Rokitansky (1849) was probably the first author to define primary liver carcinoma as a separate nosological entity. Until then, both forms of liver cancer were accepted, both primary and secondary, and the differentiation was based on the tumor histological pattern.

Epidemiological-geographical features of liver cancer

Primary liver cancer (PLC) is much less common than metastatic (secondary) 1: 8-10 cancer. Men and women alike suffer from liver cancer. Like gastric cancer, it has epidemiological-geographical features. PLC is more common in China and on the African continent (Senegal, RSA, etc.). In China and Senegal, the incidence of PLC is 70-80% 00. It is also rarely found in America, Australia and Western Europe.

In the Republic of Moldova, the incidence of PLC is 7.8-8 per 100,000 population - it has doubled in 5 years. Benign liver tumors are much less common than malignant tumors 1: 10-15 (hemangiomas, various cystic nonformations, echinococcosis, teratoma, hemartoma, etc. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. It mainly affects males, being associated with aging and chronic liver pathologies.

Intrahepatic cholangiocarcinoma (CHF) represent for 10% - 20% of primary liver malignancies [2-4].

Malignant liver tumors can be grouped as follows:

1. primary liver tumors, originating in the liver
2. secondary, metastatic liver tumors
3. extrahepatic tumors involving the liver from the outside (for example: gallbladder carcinoma).

Primary liver tumors, are tumors that develop from liver cells: hepatocytes, intrahepatic bile duct epithelium, neuroendocrine cells or mesodermal structures. In rare cases, tumors of ectopic tissues can develop in the liver.

Clinically-anatomically, primary liver tumors have the following forms:

1. The massive form is manifested by a large nodule, which can affect an entire lobe, sometimes with smaller nodules peritumor - metastases.
2. The nodular shape is manifested by the presence of several nodules of different sizes, which never reach the size of the nodule of the massive shape. The nodules are multiple right from the start of the disease and can be located in both lobes.
3. Infiltrative form - the entire liver parenchyma is affected by

Ethiopatogenesis

The factors that favor the appearance of CPH are: aflatoxins that are derived from the infestation with Aspergillus flavus (African Continent - Senegal, etc.), hepatitis B virus infection.

Both factors cause chronic hepatitis, cirrhosis and cancer on the background of cirrhosis.

The Chinese believe that in the background of cirrhosis, cancer occurs in 90% of cases, French clinicians and scientists report the hepatitis-cirrhosis-cancer relationship in 78-80% of cases.

Chronic alcoholism eventually exacerbates cirrhosis and cancer. In the two regions of France (Normandy and Brittany) CPH is 3 times more common than in the rest of the regions. It correlates, according to the French people, with the consumption of strong drinks (Calvados - an apple brandy).

We can not exclude the role of nitrosamines, various preservatives and colorants that are on the list of carcinogens.

Pathogenesis.The development of HCC begins in small diploid hepatocytes, which have a high growth rate. Pathogenesis is a multifactorial event. Sequentially this mechanism comprises 3 main phases:

- *initiation*: various toxins cause genetic defects, which can be repaired by various endogenous mechanisms. Thus this mechanism at this stage is reversible;
- *promotion*: if the genetic defect cannot be repaired, the initiated hepatocytes are stimulated and mitosis begins. As a result, daughter cells receive the „genetic defect";
- *progression*: clonal expansion of genetically modified cells („malignant" cells).

The tumor suppressor gene, the p53 gene, is located on chromosome 17. Some toxins can cause the mutation of this gene, resulting in the loss of the ability to regulate suppression [20,21]. Mutations in the autosomal dominant p53 gene cause the development of these tumors during adolescence and are part of Li-Fraumeni Syndrome.

Interaction between liver viruses (HBV, HCV), alcohol, chemicals, hormones, etc. is the crucial moment in the development of HCC manifest.

Topographic anatomy, physiology and vascularization of the liver.

C It consists of 2 lobes, each lobe has 4 segments - a total of 8 segments. The segments are composed of lobes ≈1.5 mm. There are over 500,000 (thousand) lobules in the human liver. The connective tissue forms the stroma of the organ. In it (stroma) are the blood vessels and the bile ducts, structurally and functionally are connected to the lobules. In humans, the interlobular connective tissue is poorly developed and because of this the lobules are poorly delimited from each other. Excessive development of connective tissue would cause cirrhosis.

The liver is the largest parenchymal organ, fulfilling a wide range of important functions in the general economy of the body. It is considered an ancillary gland of the digestive tract due to its origin in the epithelium of the duodenal loop of the primary intestine and due to the fact that the external secretion produced by it, participates in the digestion process. It is an asymmetrical glandular organ, located in the supramesocolic floor, it molds in the concavity of the diaphragm up to the 5th intercostal space, which constitutes the upper limit of the hepatic lodge. In the lower part, the hepatic lodge is delimited by the colon and the transverse mesocolon, and the horizontal plane corresponding to this limit passes through the Th12 vertebra. Anterior, lateral and posterior, the hepatic lodge is delimited by the abdominal walls, and the medial communicates widely with the gastric lodge, projecting up to 5-6 cm to the left of the midline. Thus, the liver, by its disposition, corresponds to the right hypochondrium, the epigastrium and partially to the left hypochondrium.

Ligament apparatus (view **Fig. 1**) of the liver consists of:

1. sickle ligament,
2. round ligament,

3. coronary ligament,
4. triangular ligaments,
5. small oment.

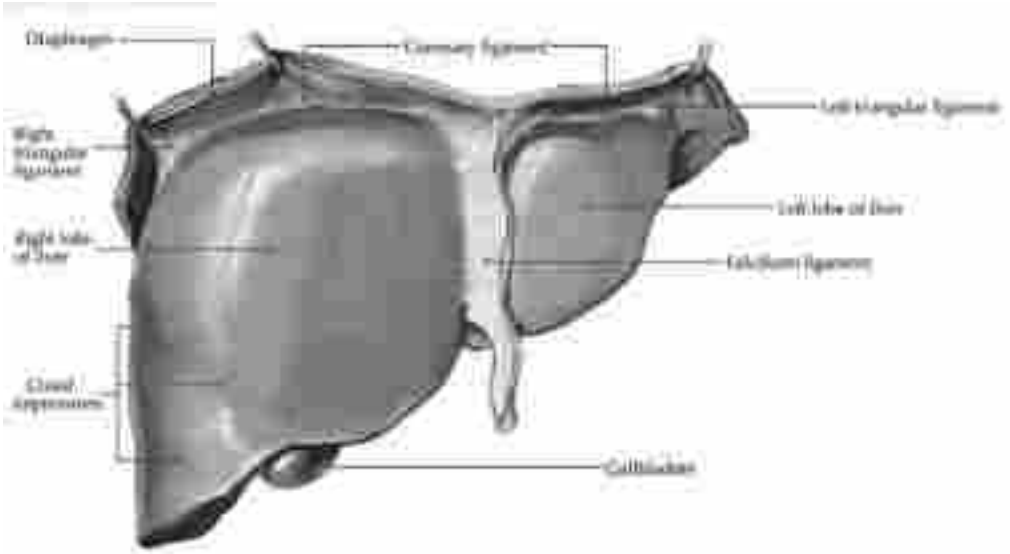

Fig.1. *Liver ligaments*

However, the liver is given an act of mobility, highlighted in the act of breathing, which descends in inspiration and ascends in expiration.

The weight of the liver is about 1.4 - 1.5 kg (for the corpse), and in humans it can reach approx. 900 g heavier, depending on the amount of blood it contains. The shape of the liver is irregular, similar to an ovoid with a large axis oriented transversely and the extremity more voluminous to the right. It has two faces, diaphragmatic and visceral, which anteriorly form the lower edge - sharp, and posteriorly the posterior margin which is rounded.

Vascularization and innervation of the liver. The liver, due to its functions, has 2 types of circulation: nutritious circulation, which provides nourishing blood supply, rich in oxygen provided by the hepatic artery and functional circulation, through which the blood loaded with nutrients absorbed from the abdominal digestive organs , is brought through the portal vein. From the liver, in both types of circulation, the blood flows through the hepatic veins into the inferior vena cava.

Hepatic artery (AH),50% ensures oxygenation of the liver. Frequent common hepatic artery is a branch of the celiac trunk, initially having

a horizontal trajectory, at which level it emits the gastroduodenal artery. Then it goes cranially to the hepatic hilum, giving rise to the right gastric artery (pyloric), after which it becomes its own hepatic artery which divides into two branches:

– *left hepatic artery (AHS)* continues the ascending trajectory in the left lateral extremity of the hepato-duodenal ligament, emits a few smaller branches for the caudate lobe, after which it enters the hepatic parenchyma at the left extremity of the hilar plate, where it usually divides into a medial branch (for segment 4) and a lateral branch which in turn is later divided into two branches (for segment 2 and segment 3) [8]. Rarely can this division be made at the level of the hilum;
– *right hepatic artery (AHD)* it has a longer trajectory, ascending to the right, passing posteriorly to the choledochal duct and the right hepatic duct. Sometimes the branch for segment 4 can be detached from the AHD

The portal vein (VP) arises posteriorly from the neck of the pancreas, through the confluence of the superior mesenteric, splenic and inferior mesenteric veins. Its length varies between 5.5 -8 cm, and its caliber is estimated between 12-15 mm. After describing an ascending path, it is divided into the depth of the transverse groove in the right and left branches.

Right portal branch - it is more voluminous, continues the direction of the trunk of the portal vein, receives the cystic vein and sends a few small branches to the caudate lobe, after which it ends in the anterior and posterior branches that are distributed to the homonymous segments of the liver.

Left portal branch it is longer, thinner and has from the beginning a segment, called the transverse portion, of 3-5 cm, which crosses from right to left the hepatic hilum, emitting a few branches for the caudate lobe. In the fissure of the round ligament and curved at a right angle, describing its umbilical portion, which is oriented forward, and almost 2 cm from the lower edge of the liver, its lumen ends at the bottom of the sac, continuing with the round ligament of the liver. In its way, the left branch sends several lateral and medial branches, which reach the respective segments of the liver. The segmental branches on both sides are divided into upper and lower branches, which go like the parallel branches of the hepatic artery to the corresponding subsegments. The last branches of the portal vein are

represented by the interlobular veins, from which the perilobular network is formed. The accessory veins come from various territories and penetrate the liver where they capillary.

The port system communicates at certain points with the cavity system, forming the so-called portocave anastomoses. The most important are the rectum and the heart. At the level of the rectum, the superior rectal veins, tributary to the port system, anastomose with the middle and inferior rectal veins, which belong to the inferior cavity system. At the level of the cardiac orifice, the roots of the left gastric vein and of the short gastric veins, representing the port territory, anastomose with the esophageal veins, which drain the arrows in the superior cavity system.

The accessory portal veins and the portocave anastomoses ensure the hepatopetal and hepatofugal collateral circulation in various pathological situations, especially in the portal hypertension syndrome. An obstruction of the portal vein leads to ascites, splenomegaly and the development of collateral circulation to divert portal blood. If the obstruction is intrahepatic, in cirrhosis or a tumor involving the hepatic hilum, or posthepatic, in hepatic vein thrombosis, the portal blood will not be able to pass through the liver, thus being diverted to the portocave anastomoses described above.

The hepatic veins constitute as a whole the efferent pedicle, which does not accompany the branches of the portal pedicle, having a direction perpendicular to them. The blood drained from the hepatic lobules through the centrolobular vein passes into larger and larger veins, from which three hepatic veins are subsequently formed:

- *left hepatic vein,* ensures the drainage of segments 2, 3 and partially 4.
- *the middle hepatic vein* is considered the main vascular axis of the liver and is located in the plane of the main cleft (median intersectional plane) that separates the right hemisphere from the left hemisphere (see below). Drain the blood from the right segment 4 and the anterior (paramedian) section.
- *the right hepatic vein* is the largest caliber and about 11–12 cm long, draining most of the blood from the right hemisphere.

The blood from these veins is taken up by the inferior vena cava, into which it flows into the upper part of its hepatic portion. Almost constantly, the left vein joins the middle one, and the right vein remains independent. In addition to the 3 hepatic veins mentioned, the hepatic blood is also drained by:

– *caudate lobe veins,* which drains both the free portion of the caudate lobe (upper and middle veins) and the caudate process (inferior veins) and flows into the anterior face of the inferior vena cava.
– *the accessory veins of the right hemisphere* are short and ensure in particular the drainage of the posterior segments of the right hemisphere.

Lymphatic vessels are differentiated into superficial and deep. Superficial lymphatics arise from the interlobular spaces on the surface of the liver, infiltrating under the peritoneum. These are divided into a group that passes through the sickle ligament and diaphragm to the parasternal lymph nodes, a group that passes through the coronary ligament and diaphragm to the phrenic nodules and a group that takes lymph from the visceral face of the liver, directing it towards hepatic nodules. Some of the deep lymphatics are oriented upwards and accompany the hepatic veins, the inferior vena cava, after which they enter the thorax reaching the phrenic nodules, and the rest describe a descending direction and accompany the elements of the portal triad in the perivascular fibrous sheaths, ending in the hepatic nodules. celiac disease.

The nerves contain sympathetic and parasympathetic fibers from the vagus nerves and the celiac plexus. At the level of the liver, the nerve branches form the anterior hepatic plexus, which includes fibers coming mainly from the left celiac ganglion, but also from the right vagus nerve, and the posterior hepatic plexus formed from fibers from the right celiac ganglion and the left vagus.

Morphological structure of the liver. The structural anatomical unit of the liver is the liver lobe. It has an ovoid shape, and its dimensions are estimated at an average of 1.5 - 2 mm long and 1 mm wide. Between the lobes there is the layer of interlobular connective tissue, best represented at the confluence of 3-4 lobes, in places that are also called Kiernan portal spaces. Each interlobular space contains a branch of the portal vein, an interlobular vein, a branch of the hepatic artery, an interlobular artery, an interlobular bile duct, lymphatic vessels, and nerve threads. From the first three elements, which form Glisson's triad, the perilobular vessels that besiege the periphery of the lobe detach.

The bile ducts are a complex set of channels through which the product of external secretion of the liver, the bile is transported from the hepatocytes

to the duodenum. The segments inside the liver are called the intrahepatic bile ducts, and those outside the liver are called the extrahepatic bile ducts.

Intrahepatic bile ducts arise from the bile ducts or bile capillaries, which form between the contacting facets of adjacent hepatocytes. The bile ducts of a hepatic lobe do not have their own wall, anastomosing each other in the form of a three-dimensional network, and towards the peripheral area they form the Hering intralobular canal, which converges to the perilobular canal, open in turn into the interlobular canal, located in the portal spaces. The latter lead the bile through the bile ducts to the right and left hepatic duct, respectively.

In general, the path of the intrahepatic bile ducts respects the branching of the portal vein and the hepatic artery, especially in the case of the larger tributaries that will form the right and left hepatic ducts. The right and left hepatic ducts leave the liver through the hilum, after which, by joining them, the common hepatic duct is formed, through which the bile continues its path to the gallbladder and further to the duodenum.

Liver physiology. In the liver there is a 24-hour rhythm of secretory processes: during the day bile secretion predominates, at night - glycogen synthesis. Probably this rhythm is regulated by the hypothalamus and pituitary gland. Hepatocytes eliminate glucose, urea, protein and fat from the blood, and bile capillaries - bile.

Liver functions are:

1. *Metabolic function*
2. *Glucose hemostasis*
3. *Synthesis function* - most serum proteins, except immunoglobulins, are synthesized in the liver.
4. *Storage function* - Glycogen, triglycerides, iron, copper and fat-soluble vitamins are stored.
5. *Catabolic function.* Certain endogenous substances (hormones, serum proteins) are catabolized in the liver, maintaining a balance between their production and elimination.
6. *Excretory function.* Bile, conjugated bilirubin, bile salts, phospholipids, cholesterol and electrolytes.
7. *Immune function,* due to the reticuloendothelial system and macrophages (Kupffer cells).

Diagnosis of liver cancer

Paraneoplastic syndromes encountered in HCC

hypoglycemia
hypercalcemia
hypercholesterolaemia
fever
carcinoid syndrome
erythrocytosis
water diarrhea syndrome
late cutaneous porphyria / pseudoporphyria
hyperthyroidism
osteoporosis
gynecomastia
testicular atrophy
early pubert

Clinical anamnesis

The characteristic clinical manifestations of HCC are:

- „Deaf" pain (in the initial stages of the disease), later with increasing intensity, located in the right hypochondrium and epigastrium;
- dyspeptic syndrome: loss of appetite, nausea, flatulence;
- physical asthenia, weight loss, anorexia;
- bone pain (in case of cancer metastasis to the bone);
- fever (caused by tumor necrosis, possibly with superinfection) or subfebrile condition;
- manifestations of paraneoplastic syndrome.

Objective clinical examination:

- hepatomegaly;
- jaundice (occurs in 1-12% in the case of tumors located in the liver gate or due to the large tumor volume that compresses or invades the bile ducts);
- ascites with increase in volume of the abdomen;
- in a patient with cirrhosis of the liver: ascites refractory to treatment, hemorrhagic syndrome, the appearance and accentuation of jaundice, the development of hemorrhages of the digestive tract, hepatic encephalopathy;
- altered general condition;
- cachexia in advanced stages of liver cancer.

Paraclinical and laboratory investigations

Bloodcount- anemia, leukopenia, ESR acceleration, hypodisproteinemia, serological reactions - hepatitis B antigen, tumor marker α-fetoprotein - norm up to 10ng / ml. Discovered by G. Abelev et al. In animal experiments in 1963, this type of oncofetal protein was later identified in human HCC by Y. S. Tatarinov in 1964. AFP is a glycoprotein initially formed in the fetal sac, later in the liver and gastrointestinal tract of the fetus. Serum values of approximately 70,000 μg / l are determined in newborns, decreasing to the normal value of <10 μg / l at 9-12 months. Higher values can be detected in regenerating liver cells (acute hepatitis and chronic,

cirrhosis) and especially in HCC (> 20 μg / l). Thus, the continuous increase of AFP values arouses suspicion; a value of> 100 μg / l is highly suspicious for HCC. The correlation between serum AFP levels and tumor size is non-essential. The false-negative result of AFP determination in patients with HCC is approximately 20%. The response to chemotherapy usually corresponds to a decrease in AFP values. The specificity of this diagnostic method is between 76-91%, the sensitivity being 39-64% (in approximately 85% when ferritin is increased simultaneously). In the case of liver metastases, the AFP level usually shows values of <150 μg / l, with no tendency to increase. AFP values in the normal range exclude HCC in 90-95% of cases.

An important role in the diagnosis of HCC is also attributed to des-γ-carboxy prothrombin (60-80% positivity in HCC) (H.A. Liebman et al., 1984). This marker is synthesized in normal hepatocytes and therefore in HCC. The accuracy of diagnosis in small hepatocellular carcinomas (<3 cm) could be greatly improved by determining its precursor (PIVKA II) in combination with AFP.

Diagnostic imaging investigations

Diagnostic imaging methods in HCC contribute to the screening of liver carcinoma, the confirmation or differentiation of other tumors, the staging and the evaluation of its therapeutic response.

- ***Liver ultrasound:*** is the standard method of screening for liver cancer, with a sensitivity and specificity of about 90%. Ultrasound, hepatocellular carcinoma appears as a circumscribed formation of various sizes, usually hypoechoic. It can be unicentric, multicentric or diffuse. The finding of a portal thrombosis adjacent to an ultrasound-diagnosed liver node is highly suggestive of liver cancer.
- ***Ultrasound and AFP*** performed in cirrhotic patients at an interval of 6 months have a role in the early detection of a hepatocellular carcinoma developed on a cirrhotic liver. In the case of small tumors, ≤ 2 cm, ultrasound is less specific for diagnosis. To increase specificity it can be associated with selective angiography (invasive method).
- ***Doppler ultrasound:*** identifies neoformation vascularization of liver tumors.
- ***CT* (computer - tomography)** abdominal: represented the standard method of highlighting hepatocellular carcinoma, with a sensitivity of 95% (see Fig. 2). CT in combination with arteriography is useful in detecting very small tumors, and has a sensitivity of over 90% for lesions less than 2 cm, with the possibility of differentiating liver cancer from hemangiomas.

- ***Nuclear magnetic resonance (NMR):*** eIt is useful in the detection of small neoplastic lesions (2-3 cm) especially on the cirrhotic liver, it evaluates the permeability of the portal vein and the existence of portal thrombosis.
- ***Hepatic scintigraphy with Technetium:*** is a method of mapping liver radioactivity obtained after administration of a radioactive substance (Tc^{99}).
- ***Hepatic angiography:*** visualizes the hepatic arterial circulation and helps in the selection of patients for chemotherapy, chemoembolization, ligation of the hepatic artery.
- ***Exploratory laparoscopy:*** is the safest method of diagnosing hepatocellular carcinoma because it directly visualizes the liver, appreciates its cirrhotic character and contributes to the performance of targeted liver biopsy puncture.
- ***Histopathological examination*** performed by percutaneous liver puncture has many limitations: it requires increased experience, in the case of small tumors the rate of false negative results can reach 40%, in 1-3% of cases malignant cells can be inseminated along the needle that can compromise subsequent surgical treatment.

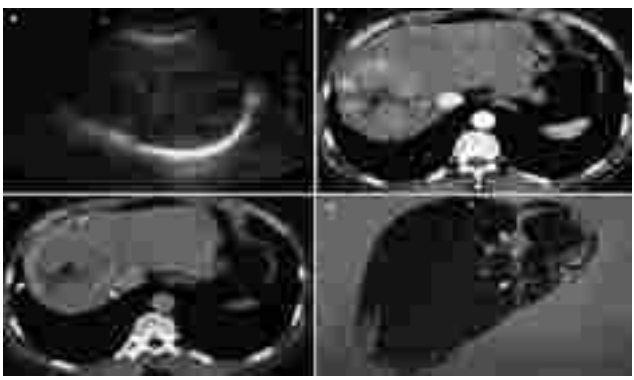

Fig. 2. *HCC. (a) nodular formation with heterogeneous hypoechoicity of the right hepatic lobe. (b) CT scan of the arterial phase shows an increase in the heterogeneous density of the tumor (arrow) with a hypoattenuated center (asterisk). (c) Venous phase CT scan shows the tumor with a thickened peripheral pseudocapsule and intratumoral necrotic area (asterisk). (d) the macroscopic appearance of the operating part. (JM Lee et al., Imaging Findings of Cirrhotic Liver, in Multislice-CT of the abdomen, 2012)*

Puncture - biopsy

- it is useful for the histopathological examination of the liver, and cannot be replaced by another examination for the correct and certain assessment of liver diseases.

- it can be direct (by laparoscopy) or indirect (under ultrasound control).

Confirmation of the diagnosis of HCC is made based on ultrasound results, CT, MRI and Doppler ultrasound that characterize liver lesions, and the definite diagnosis is established based on histopathological examination (liver or laparoscopic puncture);

Clinical-morphological classification of HCC

Macroscopic shapes:
Expansive form (approx. 18%)
uninodular
multinodular
Infiltrative form (approx. 33%)
Combined (approx. 42%)

Microscopic forms (of growth):
Trabecular type
Pseudoglandular type
Schiros type
Solid type
Fibrolamellar type
Spino-cellular type

Degree of differentiation:
High degree of differentiation
Average degree of differentiation
Low degree of differentiation
Undifferentiated or Anaplastic

Cell differentiation:
With polygonal cells
With pleomorphic cells
With clear cells
With small cells

TNM classification of liver cancer:
(AJCC 8th edition).

Primary tumor characteristic (pT):
TX: The primary tumor cannot be assessed.
T0: There is no primary tumor.
T1: Solitary tumor ≤ 2 cm or> 2 cm without vascular invasion.
T1a Solitary tumor ≤ 2 cm (with or without vascular invasion).
T1b: Solitary tumor> 2 cm without vascular invasion.
T2: Solitary tumor> 2 cm with vascular invasion or multiple formations, none> 5 cm.
T3: Multiple tumors, at least one of them> 5 cm.
T4: The tumor involves the major branches of the portal vein or hepatic veins, or the tumor directly invades adjacent organs other than the bile duct, or the tumor pierces the visceral peritoneum.

Regional lymph nodes (pN):
NX: Regional lymph nodes cannot be appreciated.
N0: There are no regional lymph nodes with metastases.
N1: Lymph nodes with metastases.

Note!: *Regional lymph nodes include hilar lymph nodes, hepatoduodenal ligament, lower phrenic and paracaval lymph nodes.*

Remote metastases (pM):
M0: There are no distant metastases
M1:There are distant metastases

Note!: *Prefix "y" - neoadjuvant chemotherapy or radiotherapy, "r" - recurrent tumor.*

Stage grouping according to TNM staging				
Stages	T		N	M
Stage I	T1		N0	
Stage II	T2		N0	
Stage III	T1-2		N1	
	T3		N0	
	T4		N1	
Stage IV	any T		any N	M1

WHO classification of primary malignant liver tumors

Tumors of epithelial origin	Tumors of mesenchymal origin	Hepatic lymphoma	Neuroendocrine liver tumors	Mixed tumors
• Hepatocellular carcinoma (HCC) • fibrolamellar carcinoma (special form) • Cholangiocarcinoma (CHF) • Combined shape • HCC / ICC • Biliary Cystadenocarcinoma • Hepatoblastoma	• Embryonic hepatic sarcoma • Hemangioendothelioma malignant epithelioid • Angiosarcoma • Leiomyosarcoma • Rhabdomyosarcoma • Fibrosarcoma • Malignant Schwanom • Hepatic liposarcoma • Hepatic osteosarcoma	• B-cell hepatic lymphoma • Hepatosplenic T-cell lymphoma	• Hepatic gastrinoma • Liver carcinoid	Carcinosarcoma

Differential diagnosis

The differential diagnosis for hepatocellular carcinoma is made with the following pathologies:

- liver metastases of other neoplasms (especially organs whose blood drains to the portal vein: stomach, colon, pancreas);
- non-Hodgkin's malignant lymphoma;

- medullary malignant histiocytosis;
- benign tumors: hemangioma, benign adenoma (after contraceptive treatment);
- focal nodular hyperplasia;
- hydatid cyst.

HCC complications

Evolutionary complications of hepatocellular carcinoma:

- tumor rupture with intraperitoneal hemorrhage;
- invasion of the portal vein with exacerbation of portal hypertension syndrome;
- suprahepatic vein thrombosis (Budd-Chiari syndrome);
- invasion of the intrahepatic bile ducts or the main bile duct with the appearance of jaundice;
- in the case of the development of HCC on a cirrhotic liver: accentuation of hepato-portal encephalopathy, hepatic insufficiency, development of upper digestive hemorrhages through cardio-esophageal varices.

Metastatic ways

Remote metastases are identified in 1/3 of patients with HCC. The preferred organs for HCC metastasis are: lungs, lymph nodes, bones, adrenal glands. The presence of intrahepatic or extrahepatic metastases radically changes the therapeutic approach.

Treatment of hepatocellular carcinoma

The treatment of hepatocellular carcinoma with curative or palliative intent depends mainly on the local extent of the tumor and the pre-existing liver disease. Curative treatment for hepatocellular carcinoma:

Surgical treatment.

Surgical resection is the treatment of election in localized, asymptomatic hepatocellular carcinoma with preserved liver function or mild liver cirrhosis.

Partial or extended hepatectomy: Segmentectomy (excision of a liver segment) or lobectomy (excision of a liver lobe) remains the most effective therapeutic method, but only 13-35% of patients with hepatocellular carcinoma are candidates for surgery. The best results (5 - 40% survival at 5 years) are obtained in stages I and II of the disease, at which margins of surgical resection of at least 2 cm in the normal liver parenchyma can

be obtained. Survival is lower (12 - 37%) in patients with large tumors, vascular invasion and advanced cirrhosis. Perioperative mortality is <5% (higher in the presence of liver cirrhosis). Recurrence is commonly seen in the remaining tissue. Extension of hepatectomy is possible in 10-29% of patients. Large tumors can be removed by extensive hemihepatectomy; the risk is small metastases in the liver tissue. Reinterventions can also be helpful. The prognosis is bleak: 5-year survival is only 25% even after surgery with curative intent (intrahepatic recurrences or lung and bone metastases).

- ***Liver transplant:*** In the case of hepatocellular carcinoma, it is currently considered the most effective treatment for hepatocellular carcinoma (it addresses at the same time the primary tumor, secondary liver lesions and liver cirrhosis). It is indicated in patients with severe cirrhosis or extensive resection but with minimal liver reserve; it is actually performed in only 5-15% of patients (numerous contraindications, absence of donors). Liver transplant criteria:
  1. *General criteria:*
     - Child-Pugh > 7 score;
     - Complications of portal hypertension: upper gastrointestinal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, regardless of Child-Pugh score;
     - Probability of survival estimated at 1 year <10%.
  2. *Specific criteria:*
     - Primary cholestatic disorders (primary biliary cirrhosis and primary sclerosing cholangitis) - Mayo criteria;
     - Sudden hepatic impairment - King's College criteria;
     - Liver cancer - Milan criteria (single tumor node ≤ 5 cm or ≤ 3 tumor nodules, largest diameter ≤ 3 cm); it was proposed to extend the Milan criteria with a set of criteria developed by UCSF (University of California San Francisco) (single tumor formation ≤ 6.5 cm, two or three tumor formations: none> 4.5 cm or total diameter ≤ 8 cm, without vascular invasion) or even less rigid criteria (without invasion of the portal vein, without extrahepatic disease) as an indication for liver transplantation.
  3. *Absolute contraindications to liver transplantation are:*
     - extrahepatic malignancies;
     - malignant liver tumors with macrovascular invasion or diffuse tumor invasion;

- active or uncontrolled infections, except in the hepatobiliary system;
- abuse of active substances or alcohol;
- severe cardiopulmonary conditions or other comorbidities;
- psychosocial conditions that endanger post-TH recovery;
- technical and / or anatomical difficulties;
- severe pulmonary hypertension.

4. *Relative contraindications:*
   - age;
   - cholangiocarcinoma;
   - chronic or refractory infections;
   - HIV infection;
   - active psychiatric illness;
   - inadequate social support.

Long-term survival (4 years) is 60 to 75% (mortality due to transplant complications reaches 12-14%), results improved with more thorough selection of patients. Recurrences occur in less than 15% of cases.

- ***Ablative techniques*** local destruction of hepatocellular carcinoma.

Local destruction is the latest method of healing; uses simple methods (short hospitalization), well tolerated and that can be administered percutaneously:

1. chemicals (alcohol, acetic acid);
2. physical (hyperthermia, laser, cryotherapy, radiofrequency, microwave coagulation, intraoperative radiotherapy, interstitial radiotherapy).

Local destruction is not feasible in cases of ascites, hypocoagulation, subcapsular localization with an increased risk of bleeding and tumor spread.

Percutaneous injection of 95% ethanol causes a combination of destructive effects through cell dehydration and coagulation necrosis. However, it fails to destroy malignant cells at the periphery of the tumor, nor it can be used to treat tumors that are too small and undetectable on ultrasound. The advantages of this method are:

- simplicity of procedure,
- low price and minimal side effects.

Response rates are variable, ranging from 90 - 100% (liver cancer <2 cm, single tumor, Child Pugh A) to 70% (liver cancer 3 - 5 cm, multiple

tumors, Child-Pugh B) and 50% (liver cancer> 5 cm, advanced liver failure). Survival at 5 years is 40-70%.

- *Radiofrequency thermal ablation* is an alternative to percutaneous treatment in patients with unresectable hepatocellular carcinomas developed on cirrhosis with a Child-Pugh A or B score. It is contraindicated in hilarious localized hepatocellular carcinoma, extrahepatic organs, diaphragm or vessels. It results in greater and more homogeneous necrosis, other potential benefits over ethanol injection, including fewer treatment sessions and better local control. Survival at 2 years seems more advantageous for radiofrequency thermal ablation compared to percutaneous ethanol injection.
- *Cryotherapy* can be used in tumors> 3cm, but requires a laparotomy. Radiation therapy has a limited role in treatment due to intolerance to hepatocyte irradiation (up to 20-25 Gy in a single session).

Adjuvant and neoadjuvant treatment in HCC:

- *Hepatic transarterial chemoembolization* is used in the case of large tumors, in the treatment of pain or bleeding caused by liver cancer and can positively influence a possible subsequent surgical procedure (decreases the risk of bleeding) and survival rates. Intra-arterial hepatic chemotherapy would allow a response rate of 41-60%, with a median survival of 19-20 months.
- *Systemic chemotherapy* has limited value and is more toxic.
- *Hepatic chemotherapy minimizes systemic toxicity but does not improve survival.* It is indicated for inoperable tumors, but has many limitations.

Palliative treatment

Systemic chemotherapy did not show the expected results in inoperable liver cancer, possibly due to the genetically determined multidrug resistance of this neoplasm. Chemotherapy is usually used to alleviate unresectable disease, and in the case of disseminated tumors is the main treatment option in patients with good performance status. Doxorubicin, 5-Fluorouracil, Cisplatin, Etoposide, Irinotecan are used in systemic chemotherapy. Systemic chemotherapy is not routinely recommended for non-resectable or metastatic hepatocellular carcinomas.

Hepatic transarterial chemoembolization for hepatocellular carcinoma. Due to the peculiarities of vascularization, liver tumors (primary and secondary) are candidates for embolization procedures ± regional (transarterial) chemotherapy.

- *Hepatic artery embolization* has developed as an alternative to intraoperative arterial ligation. The embolizing substance (starch, polyvinyl alcohol, iodized oil, Guelph, Spherex, collagen) will be administered, possibly repeatedly, by fluoroscopic catheterization of the femoral artery to the hepatic artery and selectively the branches irrigating the tumor), as close as possible from the periphery of the irrigated territory.
- *Hepatic transarterial chemoembolization* is an active treatment for patients who cannot benefit from curative surgical treatment, but who still have good liver function (Child - Pugh A), are asymptomatic, have ECOG / WHO performance status 0-2), portal hypertension or portal thrombosis, without renal failure or extrahepatic metastases.

Immunotherapy. Interferon has been shown to be somewhat effective in preventing hepatocellular carcinoma in patients infected with hepatitis B or C virus, even in the cirrhosis stage. Interferon-α reduces liver damage and progression to cirrhosis in 10-30% of patients with chronic hepatitis B. In combination with chemotherapy, interferon-α appears to increase the tumor response, but does not improve survival.

Molecular therapies for hepatocellular carcinoma.

- Epidermal growth factor receptor (EGFR) inhibitors. Hepatocytes (both normal and malignant) have the ability to regenerate through a number of growth factors, including epidermal growth factor (EGF) and alpha transformation factor (TGF-α).
- Cetuximab alone has shown a good safety profile, but with a poor tumor response and minimal effect on survival. Genistein, a specific tyrosine kinase inhibitor, is active in human hepatocellular carcinoma cells, suggesting a role in the treatment of this disease.

Antiangiogenetic agents. Hepatocellular carcinoma is a highly vascularized malignant tumor associated with elevated levels of endothelial growth factor (VEGF) and fibroblast.

- Thalidomide alone or in combination with chemotherapy (Doxorubicin, Gemcitabine) causes a 5% response rate in liver cancer. Because the toxicity of Thalidomide is minimal, except for peripheral neuropathy, it seems an attractive option in advanced forms of liver cancer.
- Sorafenib, a VEGF receptor inhibitor, thus appears to be the first

rigorously tested molecular agent to provide a survival benefit in patients with advanced liver carcinoma. The combination of Sorafenib plus Doxorubicin also has encouraging results.

- Bevacizumab, VEGF inhibitor. Pravastatin (HMG-CoA reductase inhibitor) has cytostatic activity in cancer cells, demonstrating (in association with transarterial embolization) a survival benefit.

Screening and prophylaxis of hepatocellular carcinoma.

Prophylaxis of hepatocellular carcinoma includes:

- vaccination against hepatitis B virus. Primary - 3 injections every month - 3 months a month, repeated over a year and every 5 years.
- antiviral treatment of viral hepatitis C;
- Interferon treatment once cirrhosis has developed - significantly reduces the risk of developing liver cancer in post-viral liver cirrhosis C (not viral etiology B);
- banning alcohol consumption, especially for people infected with B and C viruses.

Screening for hepatocellular carcinoma is undoubtedly a basic step in the management of this disease.

Clinical diagnosis in late stages, therapeutic difficulties related to the association with chronic liver diseases, relatively ineffective therapies in advanced stages require the development of early detection measures, screening in high-risk populations. Over 90% of liver cancers occur in the context of a known risk factor. In this context, it is obvious that screening is recommended in risk groups.

Target groups for HCC screening
• liver cirrhosis (Child-Pugh stage A / B, Child-Pugh stage C waiting for liver transplantation);
• viral hepatitis B and C virus infections (non-cirrhotic patients with active hepatitis B virus infection or family history of liver cancer, non-cirrhotic patients with hepatitis C virus infection and advanced hepatic fibrosis F3 - F4);
• chronic alcohol consumption;
• rare causes of liver cirrhosis (hereditary haemochromatosis, Wilson's disease, α1-antritrypsin deficiency, autoimmune hepatitis.
• causes of insulin - resistance (diabetes, obesity).

Prognostic factors for hepatocellular carcinoma:

- the number, size and location of liver tumors;
- tumor growth rate;
- the presence of vascular invasion;
- hepatic function reserve (bilirubin <2.0 mg / dl, serum albumin> 3.5 g / dl, absence of ascites and neurological dysfunction, excellent nutritional status);
- α-fetoprotein level;
- general condition of the patient, associated diseases;
- the presence and severity of cirrhosis in relation to the Child-Pugh classification.

Classification Child-Pugh			
Criteria	**1 point**	**2 points**	**3 points**
Serum albumin (g / l)	> 35	28 – 35	< 28
Total Serum Bilirubin (mg / dl)	< 2	2 – 3	> 3
INR	< 1,7	1,7 – 2,2	> 2,2
ascites	Absence	medically controlled	medically uncontrolled
Encephalopathy	Absence	medically controlled	medically uncontrolled

Correlation between CHILD-PUGH score and life expectancy:

Child Class A - score 5 - 6 points; life expectancy is 15-20 years

Child B class - score 7 - 9 points; life expectancy is 4-14 years

Child C class - score 10 - 15 points; life expectancy is 1 - 3 years

The prognosis of untreated patients remains unfavorable: median survival is 3-6 months and depends on the degree of liver damage. Hepatic impairment is the most common cause of death in patients with hepatocellular carcinoma.

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PANCREATICODUODENAL CANCER

Epidemiological features of pancreaticoduodenal cancer

Pancreaticoduodenal cancer (PDZ) clusters the following organs and structures: pancreas, duodenum, extrahepatic bile ducts, and Vater papilla.

Of all malignancies, 90% of PDZ maligns belong to the exocrine pancreas and originate in the acinus or acini of the pancreatic ducts. This cancer does not have epidemiological-geographical features and only in the USA the population of color has a cancer of PDZ 2-3 times more frequent than the rest of the population. The incidence of PDZ cancer in Moldova does not exceed 4-5 per 100,000 population.

Pancreatic cancer is one of the most aggressive malignancies, considered a fatal disease, with the lowest long-term survival rate (less than 5% at 5 years), in which the incidence rate is almost equal to the death rate. Surgery is the only option for long-term survival. Despite advances in imaging diagnosis, staging, adjuvant therapy, aggressive surgery, and neoadjuvant therapy, the prognosis for this type of cancer has not improved in the last 20 years, as more than 80% of patients have advanced disease and only 20%. among them are candidates for pancreatectomies. Moreover, the prognosis of pancreatic cancer is unfavorable even in those with potentially resectable disease.

Ethiopatogenesis

Probably this cancer type has much more unknown and unclear causes in terms of etiopathogenesis than in other locations. Also listed in the world literature are a number of factors, some of them carcinogenic: benzopyrene in smoking, N-nitrosomethyl (urea), various dyes and preservatives (betanaphthalamine, benzidine), chronic alcoholism, diet rich in aromatic hydrocarbons, chronic pancreatitis and even diabetes.

Hereditary risk factors

About 5-10% of patients with pancreatic cancer have a genetic

predisposition to developing the disease. Pancreatic adenocarcinoma has mutations in the KRAS2 gene in 80-95%; mutations, deletions or hypermethylation in the CDKN2 gene in 85-98%; mutations in the p53 gene in 50% and homozygous deletions or mutations in the SMAD4 gene in 55%. Some of these mutations can be found in precursors at high risk for pancreatic cancer.

Familial pancreatic cancer (CPF) represents only 5% -10% of all cases of pancreatic cancer and is due to hereditary mutations (germinative, inherited). Familial pancreatic cancer (CVT) is defined as an inherited predisposition to pancreatic cancer, based on the presence of at least one pair of first-degree relatives with pancreatic ductal adenocarcinoma (parent-child or 2 siblings), if not included in one of the syndromes, genetics associated with pancreatic cancer. No specific genetic defect responsible for CPF has been identified. It is suggested that a rare but dominant sensitivity gene is carried by about 7 out of 1,000 individuals.

People with or without pancreatic cancer are considered at high risk for hereditary pancreatic cancer if they have one of the following criteria:

- is included in pancreatic cancer-associated genetic syndrome (hereditary breast / ovarian cancer syndrome; atypical familial multiple melanoma syndrome; dysplastic nevus syndrome; Peutz-Jeghers syndrome; Lynch syndrome and Li-Fraumeni syndrome or other mutations in genes associated with increased risk of pancreatic adenocarcinoma (mutated ataxia-telangiectasia gene [ATM]
- has two relatives with pancreatic adenocarcinoma, one of whom is a first-degree relative
- have three or more relatives with pancreatic adenocarcinoma on the same side of the family
- supports hereditary pancreatitis

Blood type after ABO is a hereditary trait, with a risk for several gastrointestinal malignancies, including pancreatic cancer.

Topographic anatomy of PDZ, physiology and vascularization

The pancreas is a parenchymal organ, located deep retroperitoneally in the upper floor of the abdomen, elongated transversely with a slightly ascending direction, adhering to the posterior abdominal wall with the help

of the Treitz retroduodenopancreatic fascia. The projection of the pancreas within the organocomplex is shown in Figure 1.

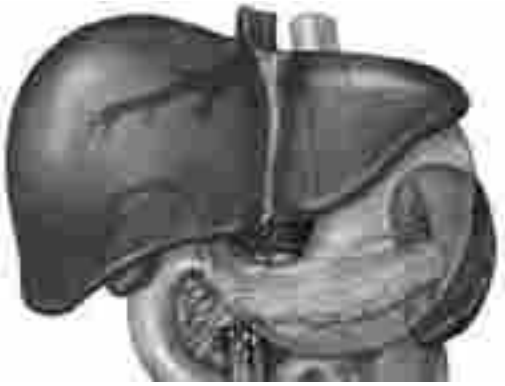

Fig. 1. *The pancreas - organocomplex projection*

Topographically it is placed anteriorly by the vertebrae L1 and L2; posterior stomach, between the horseshoe of the duodenum, arranged circumferentially around its right extremity (head of the pancreas), and the spleen, in the vicinity of which reaches the left extremity (tail). Its size varies according to sex, being more voluminous in men, or age, after 50 years they gradually decrease. The length varies between 15 and 20 cm, and the maximum width is at the level of its right extremity, where it measures 4-5 cm. During the activity, the color of the pancreas turns red, it is normally pink-gray. The consistency is relatively firm, but the elasticity determines the fingerprints of the neighboring organs. Frontal and sagittal pancreatic synopsis is shown in Figure 2.

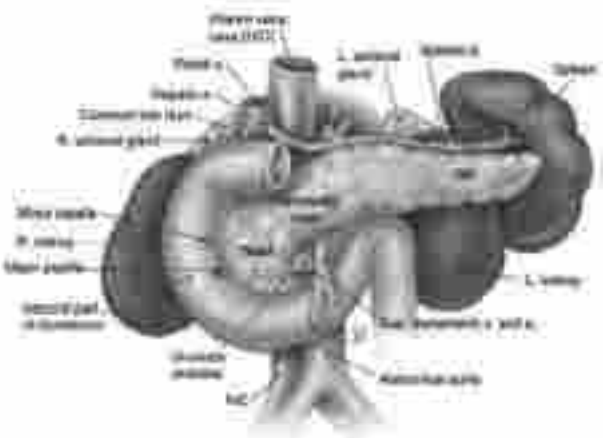

Fig. 2. *Relationships of the pancreas with adjacent organs and tissues*

The right extremity corresponds to the epigastrium and is represented by the cephalic region, more voluminous, or the head of the pancreas, which continues with the body, oriented obliquely upwards and to the left, through the neck. The body extends with the tail of the pancreas to the vicinity of the splenic pedicle, at which level it projects into the left hypochondrium (see Fig. 3).

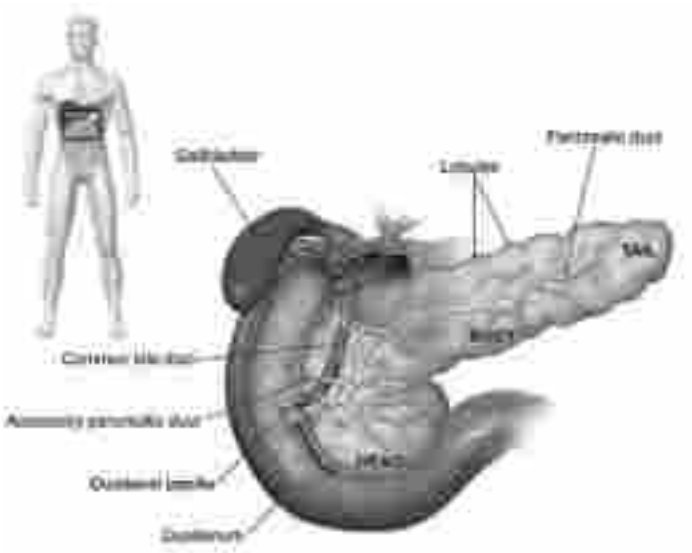

Fig. 3. Regions of the pancreas

Wirsung Canal it crosses the gland from tail to head, keeping equal distances between the upper and lower edges along its entire path, but closer to the posterior face. At the head, it curves downward, posteriorly, and to the right to join the choledochus duct, along with which it pierces the tunics of the descending duodenal wall, opening into Vater's hepatopancreatic ampulla, which protrudes on the inner surface as a large duodenal papilla.

The structure of the pancreas

The periphery of the gland consists of a thin, less developed conjunctival capsule, which extends inside the organ through a network of conjunctiva-vascular septa, also poorly developed, organized in the form of a stroma, which incompletely delimits the *pancreatic lobes and lobules*.

Exocrine pancreas constitutes 97-99% of the volume of the gland and is represented by the pancreatic acini. Acini have a spherical or ovoid shape, and in their structure are found sero-zymogenic cells. They are arranged on a basement membrane, and at their apical pole have zymogen

granules. Inside the acini there are centro-acino cells, which constitute the incipient segment of the intercalary channels, which join to form the collecting channels, of interlobular and then interlobar level. The latter converge resulting in the main pancreatic ducts Wirsung and the Santorini accessor.

Vascularization and innervation of the pancreas

Arterial vascularity is provided by the celiac trunk, from which the pancreas receives branches through the common hepatic artery and splenic artery, and from the superior mesenteric artery. The pancreaticoduodenal arteries provide vascularity to the head of the pancreas, and the body and tail of the pancreas are vascularized from the splenic artery.

Upper pancreaticoduodenal arteries are branches of the gastroduodenal artery, which detaches from the common hepatic artery and descends on the anterior face of the pancreatic head, and at the level of the inferior flexion of the duodenum passes below the lower edge of the pancreatic head, anastomosing with the anterior branch of the inferior pancreaticoduodenal artery. to constitute the anterior pancreaticoduodenal arch. From its concavity leave pancreatic branches towards the head of the pancreas, and from convexity, duodenal branches towards the duodenum. The posterior pancreaticoduodenal arteries detach from the posterior gastroduodenal artery from the superior duodenum, anastomosing with the posterior branch from the inferior pancreaticoduodenal artery, forming the posterior arch of the head of the pancreas, from which pancreatic and duodenal branches leave.

Inferior pancreaticoduodenal arteries (anterior and posterior) derives from the superior mesenteric artery, from its retropancreatic portion or from the lower edge of the pancreatic body and participates in the formation of vascular arches of the pancreatic head, by anastomosis with the superior pancreaticoduodenal arteries of the same name.

Dorsal pancreatic artery it detaches from the splenic artery, close to the emergence of the celiac trunk. It descends to the posterior face of the pancreatic body, giving small collateral branches to the posterior face of the gland. Later it ends with three branches: two straight ones: one ascends anteriorly from the head of the pancreas, anastomosing with the anterior arch or directly with the gastroduodenal artery, and another, enters the hooked process, where it anastomoses with the posterior arch; and a left branch called **the lower pancreatic artery.**

Inferior pancreatic artery it is oriented towards the lower edge of the pancreatic body, positioned posteriorly to the level of the tail of the pancreas, where it anastomoses with the caudal artery. Along its path, it emits numerous branches to the body and tail of the pancreas and anastomoses through them with other pancreatic branches, especially from the splenic artery. It can descend from the common hepatic artery, directly from the celiac trunk or from the superior mesenteric artery.

Large pancreatic artery it is distributed to the left portion of the body of the pancreas and has a larger caliber compared to the splenic artery, from which it arises at the level where the two right thirds of the pancreas join with the left third. The large pancreatic artery has a descending trajectory on the posterior face of the body, where at half the distance between the upper and lower edge of the pancreas it trifurcates into the right, middle and left branches, which will anastomose with the lower pancreatic artery.

The artery of the tail of the pancreas it comes from a terminal branch of the splenic artery, at the level of the spleen hilum. Having a recurrent trajectory, it enters the tail of the pancreas and goes to the lower edge where it anastomoses with the inferior pancreatic artery (see fig. 4).

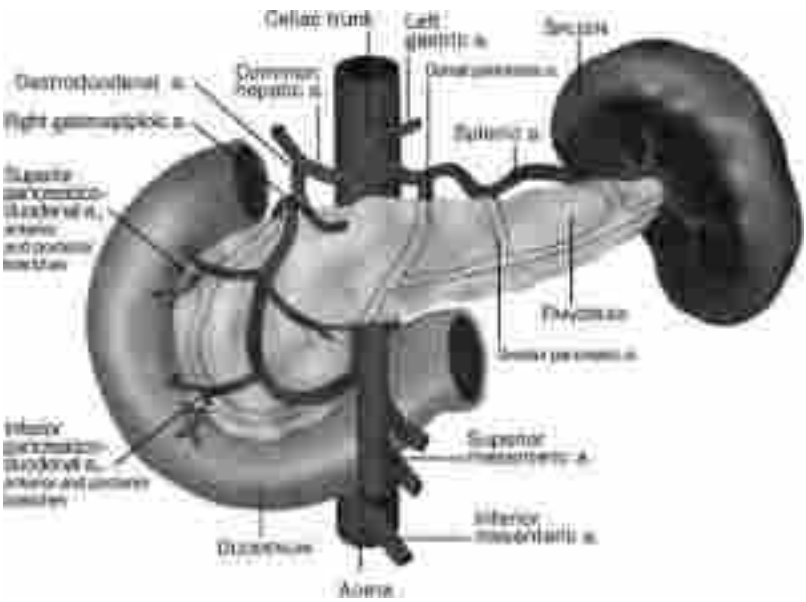

Fig. 4. *Pancreatic arteries*

The arteries that penetrate inside the gland will branch at the level of the conjunctivo-vascular septa into interlobar branches, from which later

will leave intralobular branches, which will cross the connective tissue between the acini, giving rise to the arterioles and the periacinar capillary network. Also, from the intrapancreatic arterial system, arteriolar branches are detached destined for the capillary network of the wall of the excretory ducts. One or two arterioles enter the Langerhans Islands, from which larger-sized capillaries will form than in the rest of the gland, which promote the passage of pancreatic hormones into the bloodstream.

The veins of the pancreas gather in parallel networks and are comparable to those formed by arteries, generally having the same disposition as those that accompany them.

From the anterior venous arch of the pancreatic head, the blood is drained into the inferior pancreaticoduodenal vein, tributary to the superior mesenteric vein, and from the posterior venous arch of the pancreatic head, the blood will be collected by the portal vein and the inferior pancreaticoduodenal artery. portal veins and superior mesentery. From the venous arches of the body of the pancreas, the blood reaches the left gastroepiploic vein, which flows into the superior mesenteric vein, after receiving as a tributary the right colic vein.

The pancreatic veins drain the blood from the body and the tail of the pancreas into the splenic vein, and can sometimes form the superior marginal venous arch (see Fig. 5).

Fig. 5. *Venous drainage of the pancreas*

The lymphatic circulation arises at the level of the interlobular septa, where the vessels are organized in the form of the perilobular lymphatic network, from which emerge collectors of increasing caliber that will constitute the afferent vessels of the pancreaticolienal ganglia, superior mesenteric, sometimes pyloric and finally celiac. Links are established between the lymph nodes of the pancreas and the hepatic, left gastric or other neighboring ganglion groups, which determine that the pancreatic region is an area of convergence of large lymphatic currents, the pancreas being relatively common for metastases in some cancers (see Fig. 6).

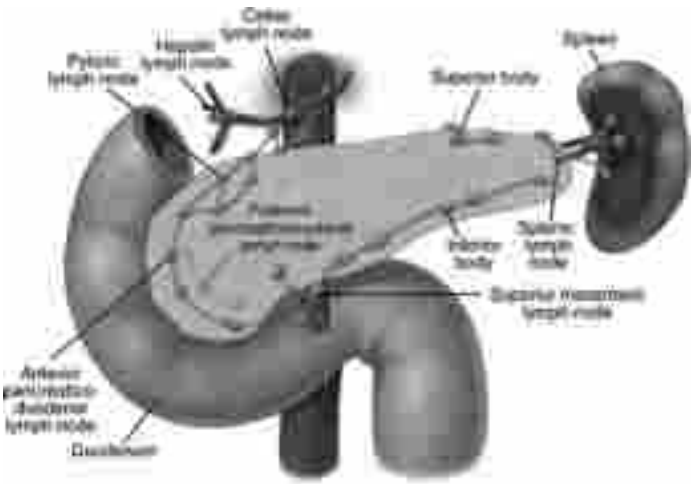

Fig. 6. *Lymphatic circulation of the pancreas*

The anterior surface of the pancreatic head drains lymph in 3 ways: the superior pathway drains into the lymph nodes of the common hepatic artery; the middle and lower path drain the lymph into the lymph nodes of the upper mesenteric artery. All these 3 ways and the drainage of the lymph from the hooked process ends in the celiac-mesenteric lymph node as superficial. The posterior surface of the pancreatic head drains into the deep right celiac-mesenteric lymph node. Both right celiac-mesenteric ganglia (superficial and deep) adhere to each other and contact the nerve plexus of the pancreatic head, and from this level the lymph drains into the interaortico-venous lymph nodes, located at the venous angle between the inferior vena cava and the left renal vein, and from here the lymph drains into the retroaortic space.

The body and tail of the pancreas drains the lymph in 2 ways: in the

lymph nodes of the spinal artery and the inferior pancreatic artery, both ways ending in the left celiac-mesenteric lymph node, from where the lymph drains later in the left latero-aortic lymph nodes, placed at the level of the left renal vein, after retroaortic space.

Perverex innervation it is provided by the celiac plexus, from which sympathetic and parasympathetic fibers reach through the periarterial splenic, hepatic, superior mesenteric plexuses. Also, parasympathetic fibers reach all segments of the pancreas through the vagal trunk. Parasympathetic fibers act on glandular acini and pancreatic islets with an excitosecretory effect, and sympathetic fibers are responsible for vasomotor innervation. The free nerve endings and the Vater-Pacini corpuscles are found in the connective tissue of the pancreas, which includes its capsule, thus giving it reflexogenic zone attributions. In general, pancreatic disorders are accompanied by severe pain due to the abundance of receptors at this level. The splanchnic nerves conduct the painful sensitivity to the laterovertebral sympathetic-thoracic ganglia 6-11, from where through the communicating branches the painful stimuli reach the thoracic spinal nerves, which will synapse with the second neuron in the spinal cord. The existence of sensory fibers, which follow the path of the phrenic nerves, explains why the pain can radiate to the scapular regions.

Diagnosis of pancreaticoduodenal cancer

Clinical anamnesis

The pancreas is divided into 3 regions: head, body and tail. The cephalic region is affected by cancer in 63.8%, the body - in 23%, the tail - in 7.2% and the total condition - 5.9% of cases (Shalimov). Macroscopically, the following forms of pancreatic cancer are found: nodular (may be multinodular) and diffuse or infiltrative.

There are no pathognomonic symptoms for pancreatic cancer. At the same time, it is possible to suspect a pancreatic cancer with a history and a thorough examination. Symptomatic (symptomatic complex) manifests itself according to the location of the tumor and the degree of involvement of the extrahepatic bile ducts, duodenum and liver.

The main signs are epigastric pain, general weakness, anorexia, anemia (pallor of the skin).

Other symptoms include intestinal disorders, hyperglycemia (diabetes, jaundice, Courvoisier-Terrier sign), liver failure, chills fever, etc.

In the evolution of pancreatic cancer we distinguish 2 phases: preicteric and jaundiced. In the preicteric phase the diagnosis is occasionally found by USG, CT or other methods. In this case there are different diagnoses (gastritis, duodenal or gastric ulcer, cholecystitis and others) which is why a very long treatment is sometimes administered.

Most patients have various complaints, such as loss of appetite, flatulence, repulsion towards food, especially meat. The first signs appear 2-3 weeks before the onset of jaundice, the shorter the preicteric period, the earlier the patient is hospitalized and the probability of operability is higher.

The most common symptom of pancreatic cancer is mechanical jaundice, the intensity of which depends on the location and size of the tumor. As jaundice progresses and its intensity increases, there are qualitative disorders in the body with the manifestation of colemia, colia, dark urine, functional disorders of the liver and nervous system.

The frequency of jaundice differs depending on the location of the tumor in the pancreas. In cephalic cancer, in the early period jaundice occurs in 7-42% of cases and 87% in full manifestation of the disease.

If the site of the tumor is the body and especially the tail of the pancreas, the jaundice manifests itself much later and when it appears in 16-38%, it is in fact the result of liver metastases.

In Vaterian cancer, jaundice is found in 90-100% and is often the only and earliest symptom. Duodenal papilla cancer manifests itself with jaundice and fever, chills, often intermittent, the latter being explained by the disappearance of spastic factor, decreased papilla edema or destruction of the tumor, which presents difficulties in differential diagnosis of lithiasis pathologies biliary.

Itching and cholangitis are characteristic of mechanical jaundice. Cholangitis is the result of an ascending secondary infection in the tumor site, but the time of endogenous cholestasis infection is not ruled out. Characteristic for cholangitis is thirst, chills, splenomegaly, etc.

Often the patient's condition is aggravated by the septicemic component and hepatic insufficiency, which intraoperatively detects purulent bile or even intrahepatic abscesses.

Pain not only accompanies jaundice but often precedes it. At first the pain is uncomfortable in the epigastrium with relaxation and embarrassment in the right hypochondrium. As the tumor grows in size, the intensity of the pain increases, becoming very excruciating when the tumor expands in the

retropancreatic space and has a radiating character in the belt. In duodenal papilla cancer, the pain may be colic, preceding jaundice.

Weight loss is very common, especially in pancreatic cancer. Progression of weight loss is caused by mechanical jaundice with digestive and absorption disorders due to isolation, exclusion of exocrine function of the liver and pancreas (lack of pancreatic ferments and bile in the duodenum), but also in duodenal stenosis.

The dyspeptic elements are caused in pancreaticoduodenal cancer due to functional disorders of the liver and pancreas.

Physical examination

Objective examination is correlated with the location and size of the tumor, as well as the presence of metastases. The most obvious signs are hepatomegaly and enlargement of the gallbladder, palpation of the tumor and determination of ascites. The palpable determination of the tumor most often testifies to an inoperable process. Enlarged gallbladder is detected as a result of tumor compression of the choledochus. The positive Courvoisier-Terrier sign (palpation of a large gallbladder, painless elastic) is significant for pancreatic cephalic cancer or distal choledochal or duodenal papilla.

The presence of thrombosis of the lower limbs (Trousseau's symptom), sometimes, and upper limbs is explained by the penetration of trypsin into the blood, affected by the tumor, which causes the exacerbation of blood clotting activity.

Diabetes in pancreatic cancer is 2 times more common than in patients who have died of other diseases and is caused by the absence of insulin from the insular apparatus or by inhibition of insulin secretion due to intracanalicular pressure.

Table 1. *Signs and symptoms of pancreatic cancer*

Clinical manifestations	Frequency	Objective signs	Frequency
Physical asthenia	86%	Jaundice	55%
Weight loss	85%	Hepatomegaly	39%
Anorexia	83%	Palpable tumor in the right rim	15%
Abdominal pain	79%	Cachexy	13%
Epigastric pain	71%	Courvoisier-Terrier sign (distinguished gallbladder, palpable in right costal rim)	13%

Hyperchrome urine	59%	Epigastric palpable tumor	9%
Jaundice of the sclera and skin	56%	Ascites	5%
Nausea	51%		
Low back pain	49%		
Diarrhea	44%		
Vomiting	33%		
Steatorrhea	25%		
Migratory thrombophlebitis (Trousseau's sign) and Venous thrombosis	3%		

Paraclinical and laboratory investigations

Paraclinical examinations of patients with PDZ tumors confirm the biological and organic changes characteristic of tumor jaundice (with a predominance of direct bilirubinemia, conjugated bilirubin), increased serum alkaline phosphatase, hypercholesterolemia, and altered serum dysproteinemia and transaminases. Determination of the CA-19.9 marker.

Radioscopy, spelling - hypotonic duodenography– enlargement of the duodenal "horseshoe" (see fig. 7), CT - (see fig. 8), endoscopic retrograde cholangiopancreatography (CPGRE) - (see fig. 9 norm); (see fig. 10 - with amputation of choledochus and Wirsung with suprastenotic dilatation of the ducts, angiography, splenoportography, transcutaneous-hepatic cholangiography, in mechanical jaundice, isotope scintigraphy with Te99), USG - (see fig. 11), endoscopic USG (see fig.), laparoscopy to stage the tumor process, MRI (see Fig. 13) [1,4,11].

Fig. 7. *Enlargement of the duodenal horseshoe in cephalopancreatic cancer*

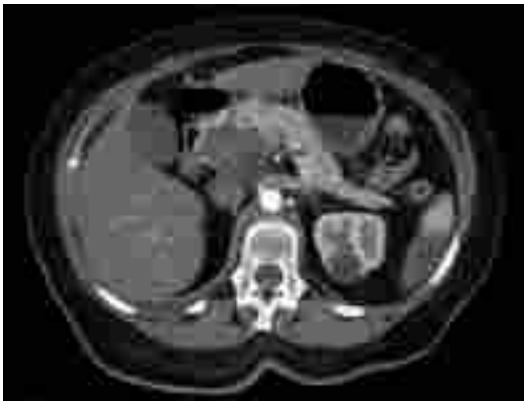

Fig. 8. *TC – Cephalopancreatic volume formation with gallbladder distension*

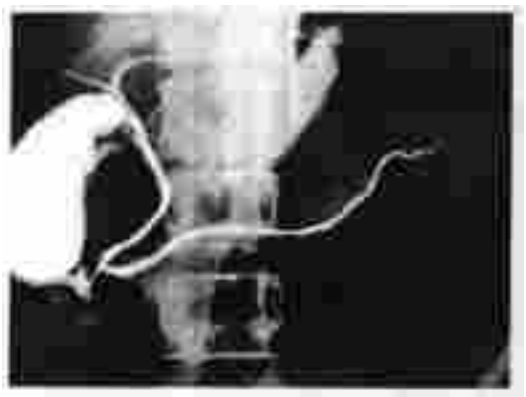

Fig. 9. *CPGRE standard*

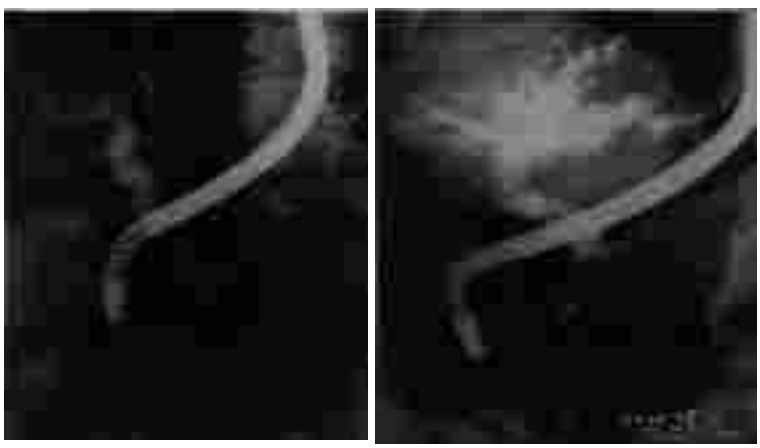

Fig. 10. *CPGRE - Pancreatic cancer with prestenotic dilation of the bile duct and complete obstruction of the Wirsung duct.*

Fig. 11. *USG - Pancreatic head tumor with dilated gallbladder*

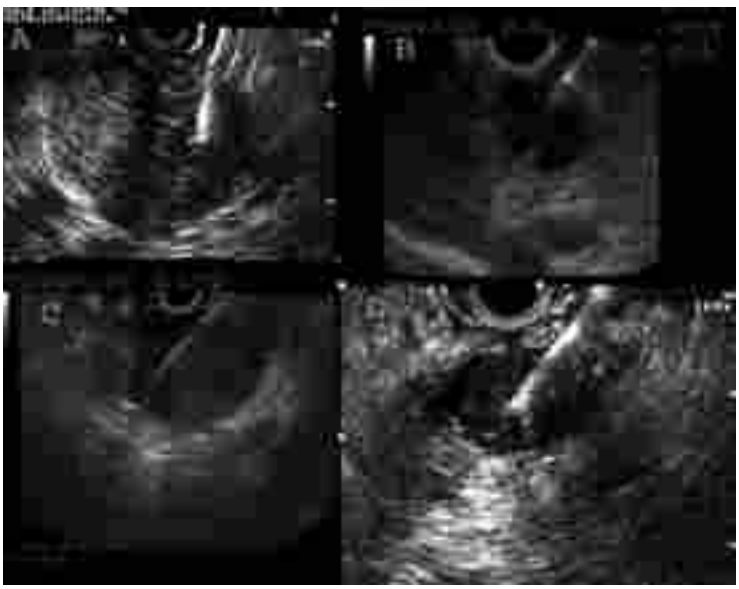

Fig. 12. *ABC-guided fine needle biopsy - EUS: from the pancreas; D: from the peripancreatic lymph nodes*

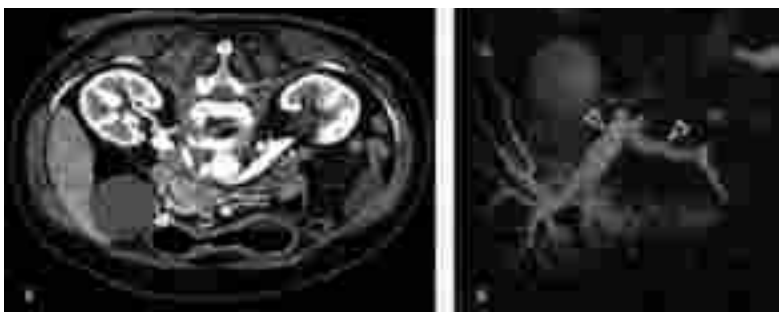

Fig. 13. *MRI of the pancreas*

Positron emission tomography (PET-CT) examination has a role in staging for assessing the spread of the process, evaluating the effectiveness of treatment and monitoring in dynamics (see Fig. 14).

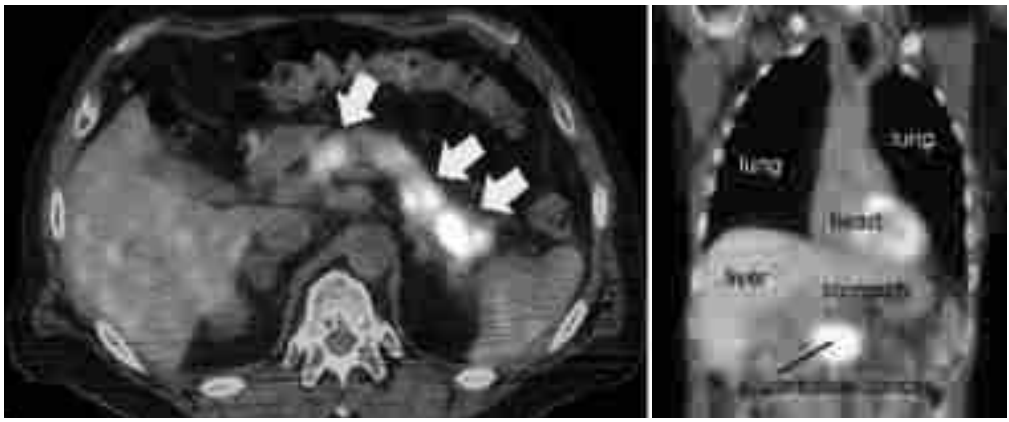

Fig. 14. *PET-CT of the pancreas*

Laparoscopy can detect small peritoneal and liver metastases, which modifies the therapeutic strategy in <15% of patients. This investigation may be performed before resection in large tumors, located on the left side and / or in the presence of elevated levels of CA19.9 or when neoadjuvant treatment is considered. However, in many cases, the extent of cancer spread can be accurately determined in pancreatic cancer only during surgery.

TNM Staging for Pancreatic Cancer, AJCC / UICC, 8th Edition, 2017

T - Primary tumor

Tx -The primary tumor cannot be evaluated

T0 – There is no evidence of a primary tumor

Tis -Carcinoma in situ also includes the PanIN-III classification

T1 - Tumor 2 cm or less in maximum size

T1a - Tumor 0.5 cm or less in maximum size

T1b - Tumor larger than 0.5 cm, but not larger than 1 cm in maximum size

T1c - Tumor larger than 1 cm, but not larger than 2 cm in maximum size

T2 – tumor larger than 2 cm, but not larger than 4 cm in maximum size

T3 –tumor larger than 4 cm in maximum size

T4 – the tumor invades the celiac trunk, the superior mesenteric artery and / or the common hepatic artery.

N - Regional lymph nodes

- Nx - regional lymph nodes cannot be evaluated
- N0 - no metastases in the regional lymph nodes
- N1 - metastases in 1 to 3 regional lymph nodes
- N2 - metastases in 4 or more regional lymph nodes

M – Remote metastases

- M0 - no distant metastases
- M1 - distant metastases

The regional lymph nodes are the following groups:

- Upper: of the head and body
- Inferior: head and body
- Anterior: pancreaticoduodenal, pyloric (for cephalic cancer), proximal mesenteric
- Posterior: pancreaticoduodenal, choledochal, proximal mesenteric
- Splenic: of the spinal and caudal hilum (for corporeocaudal tumors)
- Celiacs: for cephalopancreatic tumors

Note! Examination of a piece of regional lymphadenectomy will typically include 12 or more lymph nodes [11].

Table 2. TNM staging

Tumor stage	T	N	M
0	Tis	N0	M0
IA	T	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N0	M0
III	T1-3	N2	M0
	T4	any N	M0
IV	any T	any N	M1

Clinical (radiological) staging of pancreatic cancer

Stage I and II: Resectable disease (T1-3, selected cases of T4a, Nx, Mo)

- there are no signs of tumor extension to the celiac trunk or upper mesenteric artery
- port vein confluence - obvious superior mesenteric vein
- there is no extrapancreatic disease

Stadiul III: Boala local avansată (T1-4, Nx-1, Mo)

- present arterial invasion (celiac trunk or superior mesenteric artery)
- present venous occlusion (portal vein, superior mesenteric vein)
- there is no extrapancreatic disease

Stage IV: Metastatic disease (T1-4, Nx-1, M1) in the liver, peritoneum and rarely in the lung

Stage 0: Refers to in situ cancer, in which the cancer has not yet grown outside the duct in which it started (Tis, N0, M0).

Stage IA: The tumor is 2 cm or smaller in the pancreas. It did not spread to the lymph nodes or other parts of the body (T1, N0, M0).

Stage IB: The tumor is larger than 2 cm, located in the pancreas. It did not spread to the lymph nodes or other parts of the body (T2, N0, M0).

Stage IIA: The tumor is larger than 4 cm and extends beyond the pancreas. It did not spread to arteries, veins, lymph nodes or other parts of the body (T3, N0, M0).

Stage IIB:

- The tumor is of any size and has not spread to nearby arteries or veins.
- It has spread to 1 to 3 regional ganglia, but not to other parts of the body (T1, T2 or T3; N1; M0).

Stage III: Each of the following conditions:

- Tumor of any size that has spread to 4 or more regional lymph nodes, but not to arteries, veins, or other parts of the body (T1, T2, or T3, N2, M0).
- Tumor, which has spread to nearby arteries and veins and may have spread to regional lymph nodes. It did not spread to other parts of the body (T4, any N, M0).

Stage IV: Any tumor that has spread to other parts of the body (any T, any N, M1).

MD-CT or MRI plus MRCP should be used for staging. EUS can complete staging with information about blood vessel invasion and possible lymph node damage; In addition, this is the preferred method for obtaining a biopsy of the pancreatic lesion. Chest MD-CT is recommended for the evaluation of potential lung metastases. In the absence of typical symptoms, bone scintigraphy is not useful, as only a small proportion of patients with pancreatic cancer have bone damage at the time of diagnosis. Currently, PET screening is not routinely recommended for staging of ductal pancreatic cancer.

Histological classification of primary epithelial pancreatic tumors (WHO, 2010):

Benign

- Acinar cell cystadenoma
- Chistadenom seros

Premalignant lesions

- Pancreatic intraepithelial neoplasia, grade 3 (PanIN-3)
- Papillary mucinous intraductal neoplasia (IPMN) with low or intermediate degree of dysplasia
- Papillary mucinous intraductal neoplasia (IPMN) with a high degree of dysplasia
- Tubulo-papillary intraductal neoplasm (ITPN)
- Cystic mucinous neoplasm (MCN) with low or intermediate degree of dysplasia
- Mucinous cystic neoplasm (MCN) with a high degree of dysplasia

Malignant lesions

- Ductal adenocarcinoma
  - Carcinom adenoscvamos
  - Mucinous adenocarcinoma
  - Hepatoid carcinoma
  - Medullary carcinoma
  - Ring cell carcinoma with seals
  - Undifferentiated carcinoma (anaplastic)
  - Undifferentiated osteoclast cell carcinoma
- Acinar cell carcinoma
- Acne cell cystadenocarcinoma
- Intraductal papillary-mucinous neoplasia (IPMN) associated with

invasive carcinoma
- Ductal acinar mixed carcinoma
- Mixed neuroendocrine acinar carcinoma
- Ductal neuroendocrine acinar mixed carcinoma
- Mixed ductal neuroendocrine carcinoma
- Cystic mucosal neoplasia (MCN) associated with invasive carcinoma
- Pancreatoblastoma
- Chistadenocarcinom seros
- Solid pseudopapillary neoplasm

Secondary tumors (breast, lung, malignant cutaneous melanoma and non-Hodgkin's lymphoma).

Cystic neoplasms represent 10% -15% of all cystic lesions of the pancreas. The most common cystic neoplasms include: serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (either cystadenoma or cystadenocarcinoma). Mucinous lesions have the potential for malignancy and / or may be malignant at the time of diagnosis. Non-mucinous lesions have no malignant potential [3, 8, 11] (see Fig. 14).

4 types of cystic pancreatic neoplasms are described:
- Serous cystic tumors
- Mucinous cystic neoplasms (MCNs)
- Papillary-mucinous intraductal neoplasms (IPMNs): of the main duct; of the collateral ducts
- Solid pseudopapillary neoplasms (SPNs)

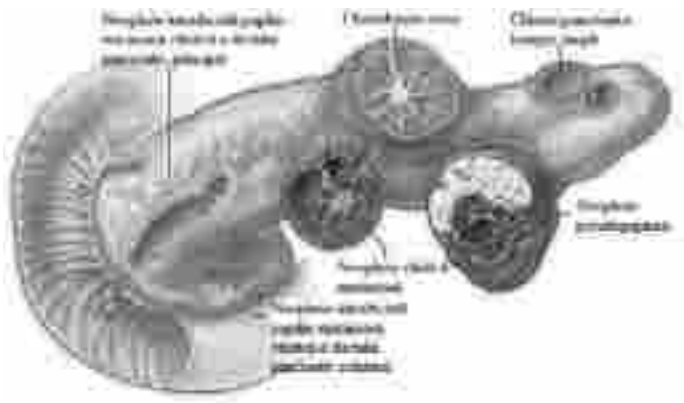

Fig. 14. Cystic pancreatic neoplasms

Neuroendocrine tumors make up about 5% of all pancreatic tumors. These may be functionally inactive cell carcinomas or benign or malignant functional tumors such as insulinomas, glucagon cones and gastrinomas. It is estimated that 40% of pancreatic endocrine tumors are dysfunctional, of which up to 90% are malignant. Insular cell tumors in patients with hereditary syndromes, such as multiple endocrine neoplasia (MEN 1), are less likely to occur in isolation than in patients without these syndromes.

Treatment of pancreatic cancer

The only cure for pancreatic cancer is radical surgery. This approach is mainly appropriate for patients with early stages of the disease, especially stage I and, in some cases, stage II. Age is not a criterion for selecting patients for the surgical approach. Elderly patients benefit from radical surgery. However, comorbidities may be a reason for giving up a resection that would otherwise have been possible, especially in patients over 75-80 years of age.

The European Society of Medical Oncology includes the following treatment recommendations:

– Complete surgical resection is the only potential curative treatment available. However, the overall survival at 5 years is only 10-20%; Long-term survival in tumors with positive lymph nodes is rare.

- Optimal symptomatic treatment has an important role in the management of metastatic disease; these patients may require stenting or bypass surgery for obstructive jaundice or gastric obstruction.

- The role of chemotherapy is limited; gemcitabine was associated with a small survival benefit compared to bolus 5-fluorouracil.

In the case of tumors of the pancreatic head, the treatment of choice is partial **pancreatoduodenectomy**. Cancer of the body or tail of the pancreas is usually treated by **distal pancreatic resection**. In some cases, a full pancreatectomy is required.

Standard lymphadenectomy involves dissection of the lymph nodes in the hepatoduodenal ligament, the common hepatic artery, the portal vein, the right lymph node in the celiac artery, and the lymph nodes in the right half of the upper mesenteric artery. The lymph node ratio (RGL, GL number involved / GL number examined) should be indicated because an RGL $\geq$ 0.2 is a negative prognostic factor (III; B). There is no evidence for the benefits of extensive lymphadenectomy in pancreatic cancer.

Surgical treatment

The volume and nature of the operation depends on the location of the tumor and its stage.

Radical operations:

- In pancreatic cancer of the pancreas, pancreatoduodenal resection (Whipple resection) is indicated (see Fig. 15).
- Subtotal resection is indicated in glandular cancer.
- In tail cancer - left hemisection of the pancreas.
- In choledochal cancer - sometimes segmental resection, one of the derivatives.

Palliative surgeries:

- Internal derivations - cholecystocolangiojejunoanastomoses.
- Gastro-cholangio-entero- and enteroanastomosis.
- External cholecysto-cholangiostomy (external derivation).
- Transcutaneous-transchehepatic external cholangiostomy.
- Endoscopic transtumor ostentation in Vater papilla cancer - endoscopic tumorectomy, RPD, various internal and external derivations.

Radical surgeries

Pancreaticoduodenectomy (Whipple Procedure)

Patients who benefit from this procedure have a tumor located in the head of the pancreas or in the periampullary region. The Whipple procedure is not the strict surgical approach for pancreatic head tumors. Ductal pancreatic tumors, cholangiocarcinoma (cancer of the bile duct) and duodenal tumors will require all this resection. The operation traditionally involves the removal of the pancreatic head, duodenum, gallbladder, gastric cavity, with surgical drainage of the distal pancreatic duct and biliary system, usually performed by anastomosis of the jejunum. The main reason for removing these intra-abdominal structures is that they all share a common source of blood.

Fig. 15. *Whipple surgery*

Pancreatic duodenectomy has been shown to have an overall mortality rate of 6.6%. In pancreatic cancer, extended lymphadenectomy is not recommended. Standard lymphadenectomy for pancreatoduodenectomy should include the following lymph node stations:

•Suprapylorics (station 5)
• Infrapyloric (station 6)
• Anterior-superior group along the common hepatic artery (station 8a)
• Along the common bile duct (station 12b)
• Around the cystic duct (station 12c)
• Posterior superior head (station 13a)
• Inferior pancreatic head (station 13a)
• On the right side of the SMA (stations 14a and 14b)
• Upper anterior (station 17a) and lower pancreatic head (station 17b)

For tumors of the body and tail of the pancreas, dissection of the following lymph nodes is recommended:

• Splenic hilum (station 10)
• Along the splenic artery (station 11)
• The lower edge of the pancreas

Distal pancreatectomy

This procedure has a lower mortality rate than the standard Whipple procedure of 3.5%, but its use in curative resection remains limited. In essence, a distal pancreatectomy may be an effective procedure for tumors located in the body and tail of the pancreas. Unfortunately, the tumor masses located in this area appear later than periampullary tumors and have a higher rate of non-resectability.

The procedure involves isolating the distal portion of the pancreas that contains the tumor, followed by resection of that segment with suturing of the distal pancreatic duct. The main complications for distal pancreatectomy involve pancreatic discharge, hemorrhage and endocrine failure. Again, the best treatment for pancreatic drainage is adequate drainage (see Fig. 16) [1, 7, 11].

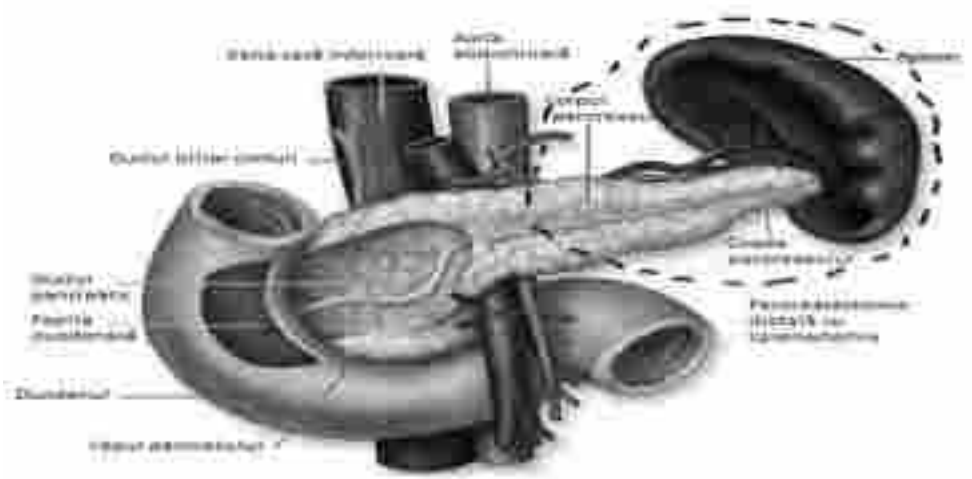

Fig.16. *Distal pancreatectomy*

Total pancreatectomy

Although this procedure is the most common and has the highest associated mortality rate (8.3%), it could still be a valuable tool in the surgical treatment of pancreatic cancer. The indication for the use of total pancreatectomy is in tumors involving the neck of the pancreas.

Chemotherapy

I. Resectable localized disease

Anterograde modular radical pancreatosplenectomy, with lymph dissection of the left hemisphere of the upper mesenteric artery and to the left of the celiac trunk, are recommended to ensure resection of R0. Pancreatico-duodenal resection (Whipple procedure) or Shiu modification includes block resection of the distal portion of the stomach, duodenum, first portion of the jejunum, head, and part of the pancreatic body. The biliary tract anastomoses terminolaterally with the remaining jejunum, and the rest of the pancreas is anastomosed with the remaining jejunum, gastrojejunostomy and vagotomy (1, 5, 6, 7).

For patients with high risk characteristics (very high AC 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain), neoadjuvant chemotherapy is recommended, which requires bioptic confirmation of adenocarcinoma (11) .

Acceptable neoadjuvant regimens include FOLFIRINOX or Gemcitabine + Paclitaxel-albumin. Recommendations for adjuvant treatment after

surgical resection include: Gemcitabine or 5-FU / leucovorin bolus or continuous infusion of 5-FU or Capecitabine. Chemoradiotherapy is not recommended for operated patients. Adjuvant therapy should be administered to patients who have not received neoadjuvant chemotherapy and who have recovered adequately from surgical treatment; treatment should be initiated within the first 12 weeks after surgery. If systemic chemotherapy precedes chemoradiotherapy, imaging must be performed after each treatment.

Patients who have received neoadjuvant chemotherapy or chemoradiotherapy may be candidates for additional chemotherapy after surgical resection and multidisciplinary review. Adjuvant therapy options depend on the response to neoadjuvant therapy and other clinical considerations.

II. Inoperable localized disease

Surgical biliary bypass (cholecystoejunostomy or choledocojejunostomy) is recommended. The mortality rate is 20% and the average survival is 20%. Jaundice can be ameliorated by endoscopic placement of limiting tubes (stents) with a 1-2% reduction in mortality and length of hospital stay. There are no differences in survival between patients operated on and those treated endoscopically with limiting tubes (stents). Recommendations for the treatment of locally advanced disease include the 6-month chemotherapy standard with gemcitabine and chemoradiotherapy at a dose of 45-54 Gy in combination with conventional Capecitabine. Chemotherapy can improve local control and delay the need to resume therapy. Intraoperative radiotherapy or implantation of radioactive sources in the tumor is another therapeutic modality that increases the average survival and relieves pain in 50-90% of patients.

III. Advanced metastatic disease

In biliary obstruction caused by pancreatic tumors, endoscopic placement of a biliary stent is recommended. The endoscopic method is safer than percutaneous insertion and has the same success as surgical hepatojejunostomy. Duodenal obstruction is preferably resolved by endoscopic placement of an expandable metal stent when possible and is more favored than gastrointestinal surgery. Frequent pain in advanced pancreatic cancer should be closely monitored according to standard guidelines for the treatment of pain. Radiation therapy can be used at

this stage to control celiac pain induced by the primary pancreatic tumor. Oral supplementation with pancreatic enzymes has been suggested to help control pain. The introduction of a pain control specialist is often mandatory. Celiac plexus blockage (CPB) can lead to pain control and often a decrease in the total amount of systemic drugs and their side effects.

Radiotherapy

General principles:

- RT recommendations for such patients are typically based on five clinical scenarios: 1) neoadjuvant / resectable; 2) resectable at the limit; 3) locally advanced / inoperable; 4) adjuvant / resectable; and 5) palliative.
- If patients have biliary obstruction (jaundice / direct bilirubin increases), plastic or metal stents should be placed before initiating radiotherapy. Radiation therapy is usually given at the same time as chemotherapy, except for palliative care.

Prognosis

The overall median survival for pancreatic cancer is 4-6 months, and in stages it is: 17 months in stage I; 12 months in stage II; 10 months in stage III and 6 months in stage IV. The median survival is only 28% at 1 year and below 5% at 5 years.

Most symptomatic patients have advanced and incurable disease at the time of diagnosis. Pancreatic cancer progresses rapidly either metastatically or progresses locally in the asymptomatic phase, so only 20% of patients have resectable surgical disease at the time of treatment. Even in individuals with apparently resectable tumors, the prognosis is very precarious. Curative surgical resection is the method of treatment of choice, which offers a median survival of 12-19 months and a 5-year survival rate of only 25-30% for tumors without metastases in regional lymph nodes (negative lymph nodes) and only 8 -10% for tumors with metastases in regional lymph nodes (positive lymph nodes); only 26% in negative resection margins (R0) and 8% in positive resection margins (R1). The resection rate R0 varies between 30-60%.

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COLORECTAL CANCER

Epidemiological-geographical features

High incidence of colorectal cancer - 20-30 per 100,000 population (USA, Canada, UK, France, Austria, Netherlands, Denmark);

Average level - 10-20 per 100,000 population (Scandinavian countries, Latin American and Southern European countries);

Low level - up to 10 cases per 100,000 population (Asian and African countries, for example Kuwait and Senegal, where the incidence is not higher than 0.5-1 per 100,000 population.

Data on colorectal cancer in the Republic of Moldova, on the incidence, show a steady increase for the last years (see fig. 1).

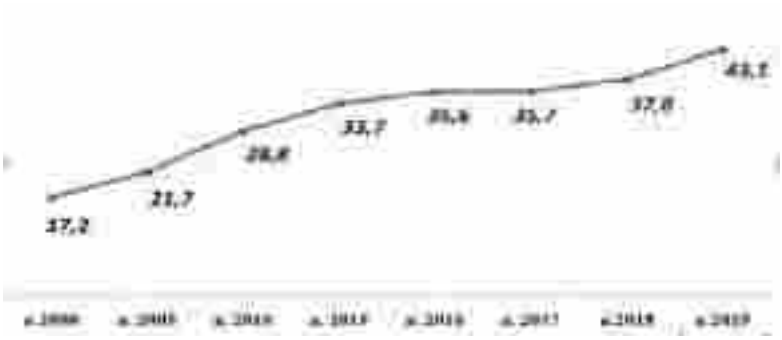


Fig. 1. *Dynamics of colorectal cancer incidence in the Republic of Moldova*

(source - National Cancer Registry, IMSP Oncological Institute)

Data on the prevalence of colorectal cancer in the Republic of Moldova show a positive dynamic for the analyzed period (see Fig. 2).

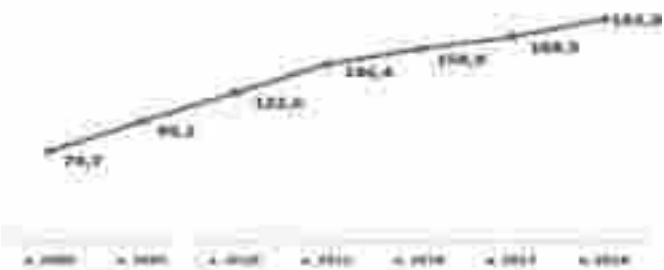


Fig. 2. *Dynamics of colorectal cancer prevalence in the Republic of Moldova (per 100,000 population, source f 35-san)*

However, in terms of mortality, the last three years show a negative trend, so the maximum was recorded in 2016, as later until 2018 decreases to 24.3 per 100 thousand population (see Fig. 3).

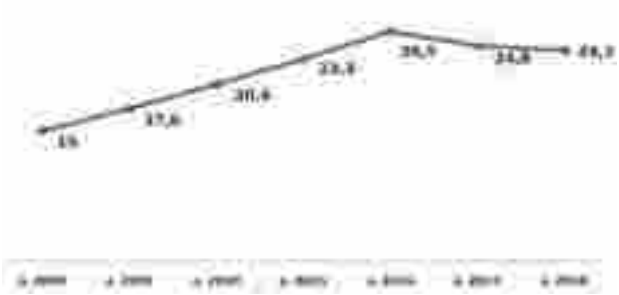


Fig. 3. *Dynamics of colorectal cancer mortality in the Republic of Moldova (per 100,000 population, f35-san source)*

Ethiopatogenesis

Colorectal cancer is a multifactorial disease: genetic factors, environmental factors (including diet) and inflammatory diseases of the colon and rectum are involved in the process of carcinogenesis.

Many data on the genetics of colorectal cancer remain undiscovered, the latest research indicates that genetic factors are predominant for colorectal cancer.

Nutritional factors: The direct link is established between the dietary content of lipids and proteins of animal origin, which under the action of the intestinal flora is transformed into b-glucuronidase, azoreductase, neutral sterols, considered carcinogenic substances and colorectal cancer morbidity.

The use of plant products containing vitamins, antioxidants, pectin and cellulose in the diet activates the fermentation of benzopyrene hydroxylase (produced in the ileum), increases the volume of intestinal contents and decreases the concentration of internal and external carcinogens (benzpyrene, nitrosamines, aflatoxins, etc.).

Age: About 5-10% of people over the age of 40 have rectocolic adenomas, with increasing age and incidence of adenomas, which at the age of 50-59 affect about 35% of the population.

Obesity and lifestyle, such as smoking, alcohol and sedentary lifestyle, have also been associated with an increased risk of colorectal cancer. Smoking has been positively associated with colorectal adenomas, which

are precursor lesions for colorectal cancer. High alcohol consumption is associated with an increased risk of colorectal cancer, the association was significant only for alcohol consumption of 30g or more daily. Compared to non-drinkers with no family history, people who consumed 30 g / day or more and had a family history of colorectal cancer had a relative risk for colon cancer of 2.80.

A meta-analysis of case-control and cohort studies identified diabetes as an independent risk factor for colon and rectal cancer.

The association between body mass index (BMI) and the risk of colorectal adenomas and cancer is reported. The researchers concluded that body mass can increase colorectal carcinogenesis in relatively early stages, especially in men.

***Chronic inflammatory bowel processes**:* ulcerative colitis - the risk of developing colorectal cancer in ulcerative colitis is 5-10 times higher compared to the rest of the population.

Crohn's disease (granulomatous colitis, terminal ileitis) - increases by 20 times the possibility of developing cancer in the same colonic segment, the development of rectocolic cancer against the background of this disease is linked to immune deficiency and chronic inflammation of the intestinal mucosa.

Adenomas: Most research, through numerous clinical, histopathological arguments, demonstrates the malignant transformation of colorectal polyps, considering adenomas as precancerous conditions, which necessarily require surgical treatment in order to prevent colorectal cancer.

Genetic factors: A more detailed description of the molecular-genetic transformation of adenomatous polyps was characterized by Vogelstein and Fearon back in 2004.

The onset is a mutation in the APC gene (adenomatous polyposis gene), which has been found in people with familial adenomatous polyposis (FAP). The protein encoded by the APC gene is important in activating the oncogene c-myc and cyclin D1, which leads to the progression to the malignant phenotype.

Although FAP is a rare inherited syndrome, accounting for only about 1% of colon cancers, APC mutations are very common in sporadic colorectal cancer.

In addition to mutations, epigenetic events, such as abnormal DNA methylation, can also cause tumor suppressor genes to be inactivated or

oncogenes to be activated. These events compromise the genetic balance and ultimately lead to malignant transformations.

Other important genes in colon carcinogenesis include the KRAS oncogene, loss of heterozygosity (LOH) on chromosome 18, which leads to inactivation of the tumor suppressor gene SMAD4 (DPC4) and DCC (eliminated in colon cancer). Deletion of the 17p chromosome and mutations affecting the p53 tumor suppressor gene confer resistance to programmed cell death (apoptosis) and are considered late events in colon carcinogenesis.

A subgroup of colorectal cancers is characterized by poor repair of inadequate DNA (dMMR). This phenotype has been linked to gene mutations such as MSH2, MLH1 and PMS2. These mutations lead to so-called high frequency microsatellite instability (MSI-H), which can be detected by an immunohistochemical test. MSI-H is a hallmark of hereditary non-polyposis colon cancer syndrome (HNPCC, Lynch syndrome), which accounts for approximately 6% of all colon cancers. MSI-H is also found in about 20% of sporadic colon cancers.

Hereditary polypis syndromes

- Adenomatous:
  - with autosomal dominant transmission- Gardner Syndrome; Oldfield Syndrome;
  - with autosomal recessive transmission- Turcot Syndrome.
- Hamartomatous- Peutz-Jeghers syndrome.

Diagnosis of colorectal cancer

Physical examination

The following clinical forms are characteristic of colon cancer:

- Toxic-anemic
- Enterocolic
- Dyspeptic
- Occlusive
- Pseudoinflammatory
- Tumor (atypical)

For rectal cancer are specific tenesmus, the presence of pathological elimination at defecation and pain in the case of localization of the tumor in the lower 1/3 or in advancing the process of higher localization, middle and upper rectum.

Paraclinical investigations

The results of paraclinical investigations will demonstrate homeostatic changes caused by one or another clinical form of the disease. The toxi-co-anemic form will present anemia and signs of intoxication; enterocolic form - essential deviations in the hydrosaline balance; dyspeptic form-protein changes and signs of intoxication; the occlusive form- the disorder of the hydrosaline balance, a hypokalemia and a hemoconcentration; the pseudo-inflammatory form- leukocytosis and the paraclinical detection of a chronic inflammation. In biochemical investigations will be determined disorders of hydrosaline balance, hypodisproteinemia and signs ofintoxication.

The determination of CEA (Carcinoembryonic Antigen) and CA-19 is of relative importance, absolutely nonspecific and cannot be used in the diagnosis of the disease, but is recommended in the surveillance of radically treated patients.

Instrumental diagnostic methods

The diagnosis, clinical protocols for diagnosis and treatment of colorectal cancer have recently undergone radical changes, which have a tendency to minimize the diagnostic process compared to predecessor algorithms. If previously it was recommended in the diagnostic plan abdominal x-ray, then irrigography, rectoromanoscopy and finally colonoscopy, currently for suspicion of colorectal oncopathology, colonoscopy with mandatory biopsy is recommended. Methods such as Ro-graph, USG, Computed Tomography and Magnetic Resonance Imaging are mainly used to assess the spread of the tumor process, staging and application of individualized treatment.

Differential diagnosis with:

- Granulomatous colitis (Crohn's)
- Nonspecific ulcerative colitis (CUN)
- Adenomas
- Hirchsprung's disease
- Familiar polyposis
- Benign non-epithelial tumors: benign tumors that may have the substrate of development in the given area: lipoma, fibroma, myoma, neurinoma, hemangioma and others.

Practically all of them are asymptomatic and are detected by the patients themselves or during the prophylactic control. In most cases they are painless, with no change in the lining (except for the hemangioma, which is gray in color). The swellings are mobile and do not cause pathological elimination. The diagnosis can be established clinically and visually, and the morphological confirmation is obtained after excision of the formation or previously cytologically by transanal and transcutaneous puncture of the tumor.

Specific lesions of the rectum and anus

Anal tuberculosis

1. Anal lupus is characterized by the appearance of tubers of a few millimeters, which are soft, elastic and have a reddish-dark color. The diagnosis is established anamnestically, clinically and morphologically (Pirogov-Langhans cells are detected).
2. Tuberculosis ulcer is the most common form of tuberculosis in the anal canal. These ulcers have an irregular shape, covered with purulent stools that are easily removed, the bottom of the ulcer on contact bleeds. In terms of diagnosis, seeding is of great importance, which, in 70-90% of cases, gives rise to M. tuberculosis.
3. The shape of a wart, which looks like a hard plate, on the surface of which there are growths in the form of keratinized warts. A reddish-purple band is highlighted around them.

Syphilis:In anal area can be found all 3 skin manifestations of this disease (primary, secondary and tertiary syphilis). They are identical to the typical cutaneous manifestations of syphilis.

In this area can be found all 3 skin manifestations of this disease (primary, secondary and tertiary syphilis). We consider that it is not necessary to describe them in detail, as they are identical to the typical cutaneous manifestations of syphilis.

Anorectal actinomycosis

It is an extremely rare pathology. It is manifested by the inflammatory edema of the sphincter, the pronounced pain syndrome, with the presence of muco-purulent pathological eliminations and intestinal occlusion due to the sphincter edema. The diagnosis can be verified cytologically, by analyzing the pathological eliminations, or at the morphological research of the tissue, where mycelium druses are detected.

Differential diagnosis of rectal cancer:

- Hemorrhoids
- Pararectal fistulas
- Fibrous polyps
- Anal papillitis
- Anorectal warts
- Nonspecific ulcerative colitis
- Solitary ulcer syndrome (SUS)
- Bowman's disease
- Pajet's disease (anal)

Classification of colorectal cancer

Colon and Rectum (ICD-O-3 C18-20)

Classification cycling applies only to carcinomas. For this there should be a histological confirmation of the disease.

The following are the procedures for assessing categories T, N and M.

Category T - Physical examination, imaging, endoscopic examination and / or surgical examination

Category N- Physical examination, imaging and / or surgical examination

Category M- Physical examination, imaging and / or surgical examination

Anatomical location

Colon (C 18)

1. Cecum (C 18.0)
2. Colon Ascendant (C 18.2)
3. Hepatic flexion (C 18.3)
4. Transverse colon (C 18.4)
5. Spleen flexion (splenic) (C 18.5)
6. Descending colon (C 18.6)
7. Sigmoid colon (C 18.7)

Rectosigmoid junction (C 19.0)

Rectum (C 20.0)

Lymph nodes considered regional for each tumor location (vascular pelvis attached to the arteriovenous plexus):

Cecum- ileocolic; aa. right colic;

Ascending colon - aa. ileocolic; right colic; medium colic;

Liver flexure - aa. right colic; medium colic;

Transverse colon - aa. right colic; middle colic, left colic (lower mesenteric);

Spleen flexion - aa. middle colic, left colic (lower mesenteric);

Descending colonist - aa. left colic (lower mesentery);

Sigmoid colon - aa. left colic (lower mesentery); upper rectal.

Rectum - all locations (upper, middle and lower) - aa. inferior mesenteric, internal iliac, mesorectal (paraproctal), lateral sacral, presacral, sacral promontory (Gerota fascia).

Metastases in nodules other than those listed above for proper location are classified as distant or distant metastases.

CLINICAL CLASSIFICATION OF COLORECTAL CANCER - TNM

TNM International Classification, 8th edition (revised in 2017 by the International Anticancer Center)

T - Primary tumor

TX - Primary tumor cannot be evaluated

T0 - No evidence of primary tumor

In situ Tis carcinoma: without invasion of the lamina propria (a)

T1 - The tumor invades the submucosa

T2 - The tumor invades its own muscle

T3 - The tumor invades the subserosa or pericolonic or peritonealized tissues

T4 - The tumor directly invades other organs or structures (b, c, d) and / or perforates the visceral peritoneum

T4a - The tumor pierces the visceral peritoneum

T4b - The tumor directly invades other organs or structures

NOTE:

a) the tissue includes the cancer cells in the own lamina of the mucosa (intramucosal) without submucosal and muscular extension;

b) invades the visceral peritoneum with the involvement of a surface;

c) direct invasion in T4b includes invasion of other organs or segments of the colorectum by serosa, as confirmed on microscopic examination or for tumors in the retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extending beyond one's own muscle;

d) the tumor that is adherent to other organs or structures,

macroscopically, is classified cT4b. However, if there is no tumor in the adhesion, microscopically, the classification should be pT1-3, depending on the anatomical depth of the wall invasion.

N - regional lymph nodes

NX - regional lymph nodes cannot be evaluated

N0 - no regional lymph nodes are affected

N1 - metastases in 1-3 regional lymph nodes

N 1a - metastases in a regional lymph node

N1b - metastases in 2-3 regional ganglia

N1c - tumor deposition (deposits note), subserous or peritoneal satellites, dangerous or perirectal soft tissue without regional metastases in lymph nodes

N2 - metastases in 4 or more regional ganglia

N2a - metastases in 4-6 regional ganglia

N2b - metastases in 7 or more regional ganglia

Note- Tumor deposits (satellites) are macroscopic or microscopic nodules of cancer in the area of lymphatic drainage of pericolorectal adipose tissue of a primary carcinoma, which are found primarily and without histological evidence of lymph node residue or identifiable vascular or neuronal structures. If a satellite is identifiable on elastic tissue, it should be classified as venous invasion (V1 / 2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumor deposits does not change the category of primary tumor T, but changes the condition of the nodule (N) in pN1c if all regional lymph nodes are negative on pathological examination.

M - Remote metastases.

M0 - No distant metastases.

M1 - Remote metastases.

M1a - Metastases in a single organ (liver, lungs, ovary, non-regional lymph nodes) without peritoneal metastases.

M1b - Metastases in several organs.

M1c -Peritoneal metastases with or without other organ involvement.

Anatomopathological classification

Categories pT and pN correspond to categories T and N.

pN0 - histological examination of a regional lymphadenectomy specimen will usually include 12 or more regional lymph nodes. If the

lymph nodes are negative but the number of those examined is less than 12, the pN0 classification cannot be applied.

Staging of colorectal cancer
Stadializarea cancerului colorectal

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T2	N0	M0
Stage II	T3, T4	N0	M0
Stage II A	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0
Stage IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
Stage III C	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IV A	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Forms of growth

a) exophyte - polypoid; papillovillous; nodular,
b) endophyte - ulcerative infiltrative,
c) infiltrative - diffuse.

Morphological forms of colorectal cancer

The colon is covered with adenogenic epithelium which is highly prismatic, the degree of differentiation of which increases from the bottom of the crypts to the surface of the villi (see Fig. 5.6).

Fig. 5. *Normal colon (HEx10) Fig 6. Normal line (HEx10)*

Colorectal cancers are of adenogenic origin (see Fig. 7-14) and come in different variants:

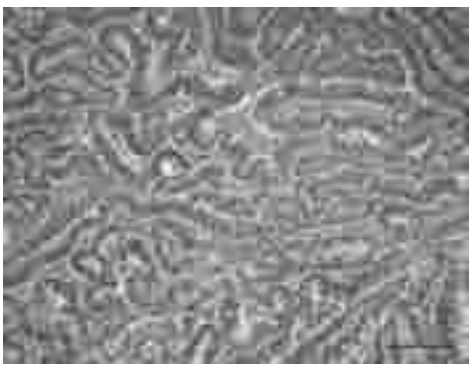


Fig. 7. *COLON, adenocarcinoma with a high degree of differentiation. (HEx10)*

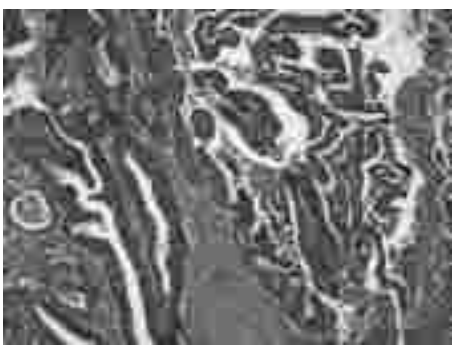


Fig. 8. *COLON, adenocarcinoma with moderate degree of differentiation (HEx10)*

Fig. 9. *RECTUM, low differentiation adenocarcinoma (HEx10)*

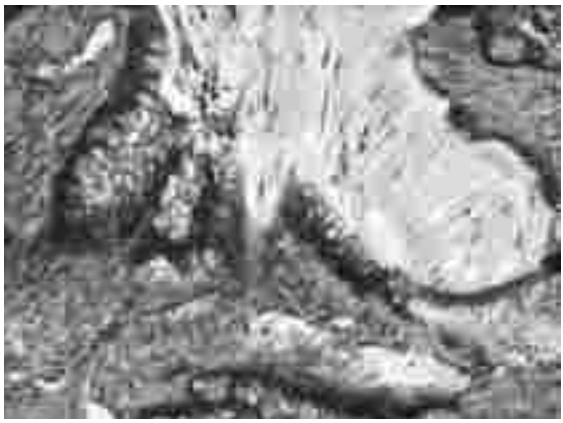


Fig. 10. *COLON, mucinous adenocarcinoma (HEx10)*

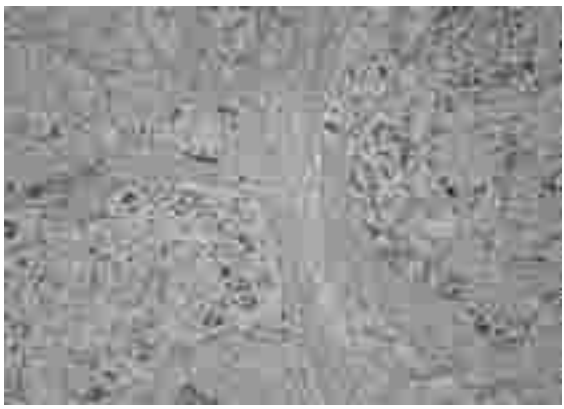


Fig. 11. *COLON, mucinous adenocarcinoma with „signet ring cells" (HEx10)*

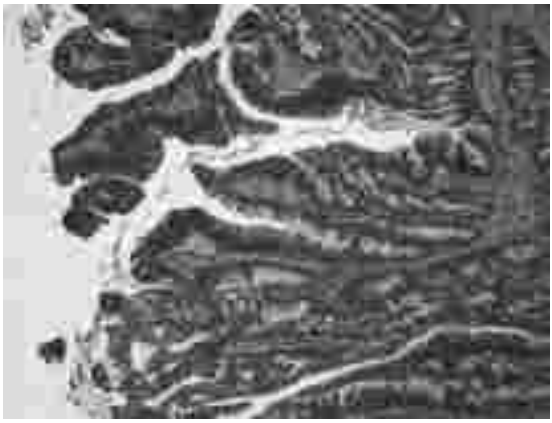


Fig. 12. *RECTUM, papillary mucin adenocarcinoma (HEx10)*

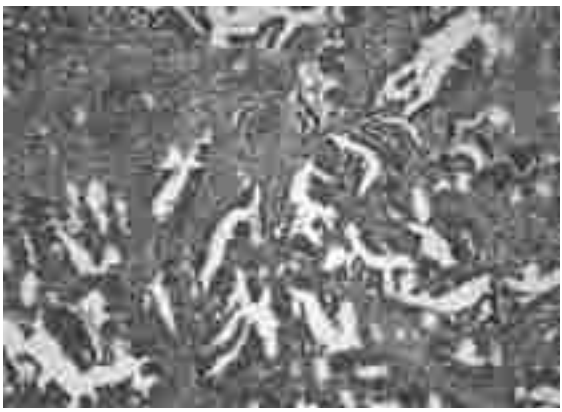


Fig. 13. *COLON. Papillary adenocarcinoma (HEx10)*

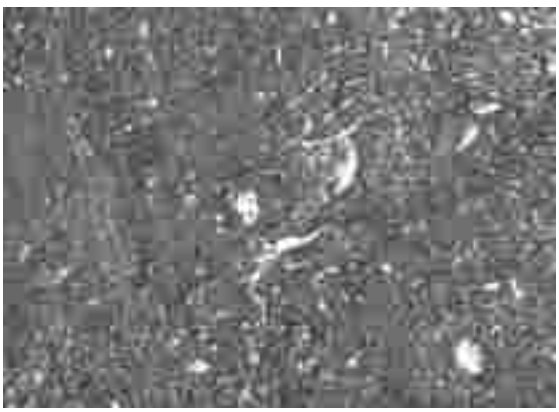


Fig. 14. *COLON. Undifferentiated carcinoma (HEx10*

In the lower and middle rectum, squamous cell carcinoma can be detected as a result of cell ectopia (see Fig. 15).

Fig. 15. *RECTUM, carcinom adenoscuamos. (HEx10)*

Treatment of colon cancer

The treatment of colorectal cancer cannot be considered radical if the surgical component is missing, with the removal of all tumor components. The limits of the minimum resection for colonic tumors, in radical volume are considered 10 cm from the proximal part and min 5 cm from the distal part.

All interventions can be performed by the classical method, by medium-median laparatomy, as well as celioscopic.

Surgical treatment of colon cancer. Depending on the tumor location and possible lymphogenous metastasis, the following surgeries are indicated:

Classic right hemicolonectomy (HCED). (remove the right side of the colon with lymphodissection of the pelvis aa. ileocolic and right colic, with the application of the ileo-colonic termino-lateral anastomosis, or with the application of the terminal ileostomy in case of acute occlusion (see fig. 16).

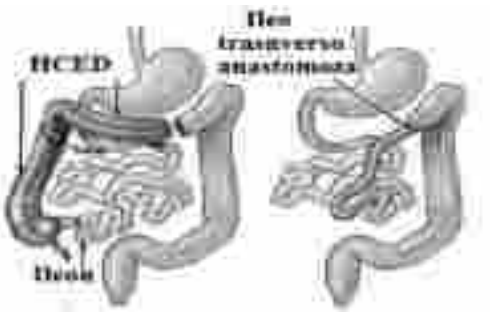


FIG. 16. *Right hemicolonectomy (HCED) with ileotransnversoanastomosis*

Enlarged right hemicolonectomy (HCED): is indicated according to the National and International Protocol, at the location of the tumor in the hepatic flexure or in the right side of the transverse colon. The difference from the classic one is in the lymph dissection and ligation of the middle colic artery, so all the branches are ligated and sectioned a.a. upper mesentery.

Resection of the transverse colon is indicated in the location of the tumor in the middle region of the transverse colon, with lymph dissection of the pelvis of the middle colic artery, with the application of the termino-terminal or latero-terminal anastomosis. In case of insufficient preparation of the intestine, either the terminal transversostoma is applied on the afferent loop or the protective transversostoma, with the formation of the colonic anastomosis (Mayld procedure) (see fig. 17).

Resection of the transverse colon is indicated in the location of the tumor in the middle region of the transverse colon, with lymph dissection in the pelvisoand resection of the middle colic artery, with the application of the termino-terminal or latero-terminal anastomosis. In case of insufficient preparation of the intestine, either the terminal transversostoma is applied on the afferent loop or the protective transversostoma, with the formation of the colonic anastomosis (***Mayld procedure***) *(see fig. 17).*

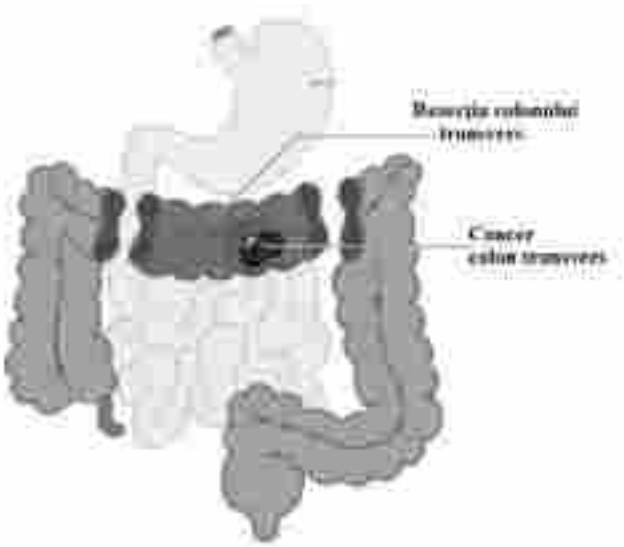


FIG. 17. *Resection of the transverse colon in the malignant tumor of the transverse colon*

Left hemicolonectomy (HCES) is indicated at the location of the tumor in the left mid-lateral region of the transverse colon, spleen flexion, descending colon and proximal sigma, with lymph dissection of the left colonic artery pelvis of the upper sigmoid, with the application of termeno-terminal or latero-terminal anastomosis. In case of insufficient preparation of the intestine, either a terminal transverzostoma is applied on the afferent loop or a protective transverzostoma with the formation of the tremeno-lateral anastomosis (*see fig. 18).*

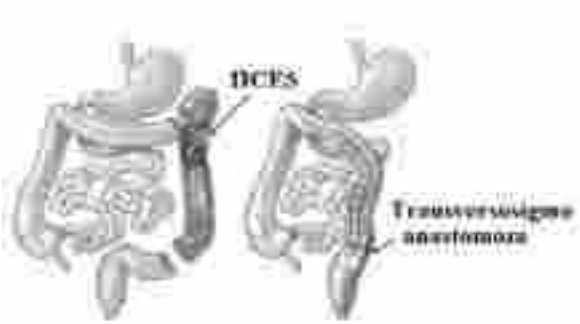


Fig. 18. *Left hemicolonectomy (HCES) with transversosigmoanastomosis*

Obstructive resection of the sigmoid it is indicated for the location of the tumor in the region of the middle sigmoid colon, with lymph dissection of the sigmoid artery to the inferior mesenteric artery, but with the preservation of the superior rectalis artery; with the application of the termino-terminal or latero-terminal anastomosis (the bond is preferably on the distal loop). In case of insufficient preparation and changes in the colon wall, the terminal sigmosome is applied, with the distal bundle placed near the stoma for comfort at the second stage of stoma closure. *(see fig. 19).*

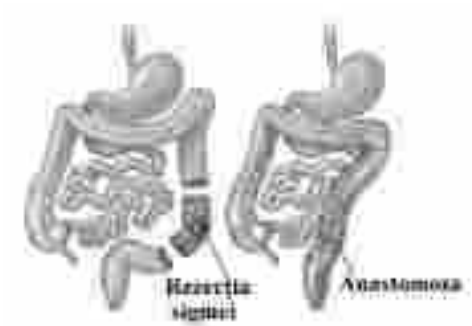


Fig. 19. *Sigma resection in the malignant tumor of the sigmoid colon*

Resection of the distal sigmoid and rectosigma (Hartman's procedure) is indicated in the location of the tumor in the region of the distal sigmoid colon of the rectosigma and al. In case of insufficient preparation and changes of the colon wall, the terminal sigostoma is applied with the placement of the distal abutment under the peritoneal cord *(see fig. 20)*.

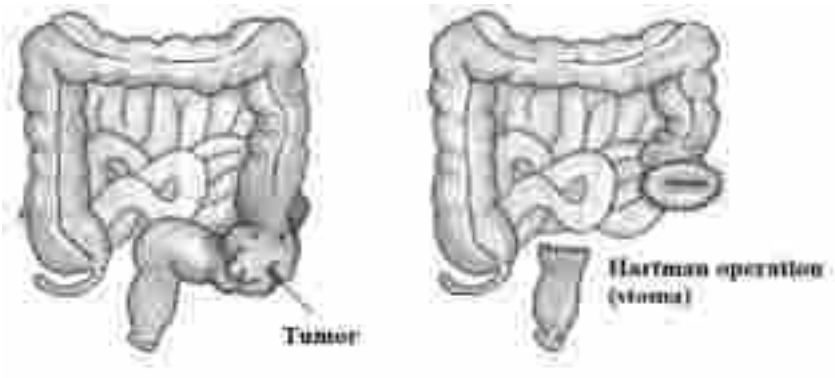


Fig. 20. *Hartman operation*

Obstructive resection Grecov and Miculici. More historical interventions, used at the beginning of the period of development of anesthesia, a period when the list of contraindications for anesthesia were more than indicated, was indicated for elderly patients, or those with concomitant severe diseases. They were indicated for the location of the tumor in the region of the middle sigmoid colon. It was performed without lymph dissection, without the application of an anastomosis. Through the median pararectal incision (m. Rectus abdominis) the sigmoid was externalized with the tumor - Grecov procedure, Miculici differs by the moment of fixing the posterior wall of both intestinal loops. 1-3 days after the operation, the extra-abdominal tumor is excised.

Subtotal colectomy is indicated in multiple primary cancer synchronous with involvement of the colon regions with possible metastasis in both major metastatic basins (upper and lower mesentery). It is also indicated in familial polyposis (in case of the possibility of rectoscopic rectal rehabilitation). The technique combines four interventions: HCED, total resection of the transverse colon, HCES and total resection of the sigmoid and rectosigma with ileo-recto-anastomosis. In some cases, to improve the quality of life of patients, in the absence of adenomas in the check,

ascendo-rectoanastomosis can be applied by reversing at 180 degrees the portion of the check and the ascending to the correct anatomical position.

The total colectomy is practically the same subtotal colectomy, except for the total removal of the colon and rectum up to the lower 1/3 with ileo-recto anastomosis, by the formation of a reservoir in the terminal ileum. In some cases, with Quenu Miles removal of the rectum, with the formation of the terminal ileostoma, preferably with the formation of the reservoir in the terminal ileum.

The Serid-Schloffer Serial Operation. Serial operations are indicated in cases of medical-surgical emergencies and in cases of chronic occlusions, where it is impossible to properly prepare the colon for the application of the primary anastomosis, or the presence of trophic changes in the colon proximal to the tumor. The intervention is performed in three or two stages, if possible. The first stage - laparatomy revision assessment of operability, stoma on the colon related to the tumor, appendicocecostomy or simple cecostomy, transversostomy. The intervention has a curative character, to remove the occlusion and the possible correction of homeostasis faster in the postoperative period. The second stage is performed at an interval of one month or more, depending on the patient's condition. The radical operation is performed for the appropriate location. In the third stage, the stoma raffia is performed, preferably extraperitoneally (without opening the peritoneal sheet), with the placement of the sutured subaponeurotic colon. One of the peculiarities, the preventive stoma on sigmoid in the cancers located below is contraindicated, due to the impossibility of performing an organ-threatening operation in the second stage.

NOTE: All of the above interventions may be both radical and palliative (in the presence of distant, unresectable metastatic changes). Also, the above interventions can be performed with obstruction (with the application of the stoma on both the afferent and the efferent loop. The above interventions can be performed in series .

Palliative surgery in colon cancer

1. *With the application of the stoma on the colon* ***cystostomy*** or appendicocecostomy is indicated in cases of advanced cancer of the ascending colon, liver flexure, and right side of the transverse colon.

Biluminal Transverse stoma is indicated in cases of advanced cancer of the transverse colon located on the right side and up to the anal canal.

Biluminal sigmoidostomy is indicated in cases of advanced cancer of the distal sigmoid colon, rectisigmoid and rectum to the anal canal.

2. *With the application of the ileostomy.* **Biluminal ileostoma** it is applied in cases of advanced cecum cancer, Bauhin's valve and all locations in the presence of diffuse cancer and the impossibility of applying any other stoma.
3. *Without applying the stoma to the colon or ileum*-**By passe**. It is indicated in the case of the advanced local process, with the impossibility of resecting the affected part.

Transverse-ileostomy is indicated in cases of local unresectable advanced cancer of the Baughini check and valve, ascending colon, hepatic flexure, and right side of the transverse colon.

Ileo-sigmoanastomosis is indicated in cases of unresectable advanced local cancer of the Bauhin's valve, ascending colon, hepatic flexure, transverse colon, hepatic flexure, and descending colon.

Transverso-sigmoid anastomosis is indicated in cases of unresectable advanced local cancer of the right side of the transverse colon, hepatic flexion and descending colon.

Chemotherapeutic treatment. Neo-adjuvant chemotherapeutic treatment is administered preoperatively in in suspicious cases for metastases or local spread (T4N1-2M0). It is recommended using, FOLFOX +/- Bevacizumab, Capecitabine, XELOX, XELOX + Bevacizumab, XELOX + Cetuximab, XELIRI +/- Bevacizumab, IROX +/- Bevacizumab, XELIRI +/- Cetuximab, IROX. Adjuvant Chemotherapeutic treatment id administered postoperatively in T4N1-2M0 and in the cases of distant metastases (liver, ovaries, etc.). In the adjuvant chemotherapy is recommended , FOLFOX, Capecitabine, XELOX regimens (6 cures). The first course of chemotherapy should be started at least 25-30 days after operation.

Treatment of rectal cancer

In the radical treatment of rectal cancer there are 3 basic types of surgery currently used with multiple non-essential changes, bearing the name of the authors, who perfected the method and technique of its application.

The first two types, organ-threatening, can be described in common. Technically, the peritoneum is dried on an envelope around the lyre-

shaped rectum, on the opposite side, to the base of the inferior mesenteric artery. Upon finding the local operability, the lymphodissection from the lower mesenteric artery is performed, with its sectioning and ligation more proximal to the branch of the superior rectal artery. Then the rectum is mobilized to the diaphragm of the pelvis, preferably keeping the sacral fascia (allows non-trauma to the sacral nerve plexus and sacral veins), the limit of resection is assessed, the rectum separates from the rectum pararectal tissue to the intestinal wall (mesorectumectomy).

- Anterior resection of the rectum and rectosigma (Dixon)
- Abdominal-abdominal resection of the RAEAR rectum (Bacon, Holdin, Chiricuță-Mandache, etc.)
- Abdominal-perineal removal of the rectum EAPR- (Quenu Miles)

Anterior resection of the rectum and rectosigma (Dixon) is indicated at the location of the tumor in the region of the rectosigma and rectum, except the lower one, with lymph dissection of the pelvis of the inferior mesenteric artery, practically to the level of the aorta and vena cava. Mechanical anastomosis with a circular, thermeno-terminal stapler (sigmorectoanastomosis) is applied, with its separation under the diaphragm of the pelvis. The European Protocol provides for the application of the protective iliostoma for a period of one month. It is possible to perform protective ileopexy for 14 days or trans anal intubation of the intestine for a period of 5-7 days.

Abdominal endanal resection of the rectum RAEAR is indicated at the location of the tumor in the region of the rectosigma and rectum, except for the 2 cm distal portion of the anal canal. With lymph dissection of the pelvis of the inferior mesenteric artery, practically to the level of the aorta and vein. From the sigmoid, a transplant is cut, with the preservation of the paracolar vessels, which is then lowered through the sphincter and extruded.

Procedures:

Chiricuță- Mandache : after mobilizing the rectum below the tumor by 3-5 cm and preparing the transplant from the sigmoid colon, the rectum is resected, which rises with the tumor in the abdomen, the sigma is sectioned above the tumor. Then the sigmoid colon is lowered through the anal orifice and fixed to the outside.

Bacon: Usable for upper rectal tumors. A retractor, such as the drumstick, is inserted through the anal orifice into the rectal to the abdomen. The recluse is ligated transabdominally through the pelvis around the retractor.

The rectum is lowered through the anal orifice, sectioned below the tumor by 2-5 cm and the cexteriorized transfincteric sigma.

Holdin: after mobilization of the transabdominal rectum, the trans anal section above the sphincter is sectioned from the perineal side. The mobilized sigmoid in the abdomen descends transanal and is fixed to the perianal skin for support.

Abdominal-perineal removal of the rectum EAPR (Quenu Miles) is indicated at the location of the tumor in the region of the lower rectum and / or anal canal. From the abdomen, the sigmoid is prepared for the stoma, with its supratumoral sectioning of at least 10 cm. Lymph dissection of the pelvis of the inferior mesenteric artery, practically up to the level of the aorta and vena cava. From the perineal part, the anal sphincter is sutured, the skin and adipose tissue are circularly dissected, the diaphragm of the pelvis is sectioned and ligated on the pelvis. The pelvic cavity is tamped with mesh or connected to vacuum absorption. The pelvic peritoneum is restored, from the abdominal part, the terminal stoma is applied, with the suturing of the parietal defect and the externalized sigma in the form of the stoma.

Palliative surgery in rectal cancer

Application of the stoma to the colon:

- Cecostomy (appendicecostomy) -5%
- Transversostomy -25%
- Sigmoidostomy- 70%.

Combined treatment of rectal cancer

1. Preoperative RT (DSF 20 Gy)- combined program, large fractions 4 or 5 Gy.
2. Preoperative RT (DSF 45-60 Gy)- radical program small fractions 1-2 Gy.
3. Postoperative RT (46-64Gy)- small fractions.
4. Postoperative chemotherapy.
5. Intraoperative cryoapplication.
6. Association of cryo-radio-chemotherapy.

Principles of chemotherapy in the Rectal cancer

Directions for chemotherapy:

- in association with radiotherapy in the preoperative period in the stages I, II, III;
- in association with radiotherapy in the postoperative period ;
- as adjuvant treatment in stages II, III (6 cycles);

- in advanced stages, recurrent forms;
- in patients with hepatic metastases - intrahepatic chemoembolization;
- as adjuvant treatment after resection of metastases located in liver or lungs;
- as neo-adjuvant treatment in cases of hepatic metastases.

Chemotherapy regimens: chemotherapy for recurrent and metastatic disease

- **MAY:** Calcium folinate 20mg/m2 i/v. 1-5 days + 5 FU 425mg/m2 i/v 1-5 days, every 3-4 weeks.
- **LFP:** Lomustin (CCNU) 80mg/m2 per day 1 day + 5FU 400mg/m2 i/v 1-3 days + Cisplatin 120mg/m2 i/v 4 days every 5-6 weeks.
- **MLF:** Mitomycin C 10mg / m2 i / v 1zi + Calcium folinate 30mg/ m2 i/v 2-5 days + 5FU 425mg/m2 i/v 2-5 days, every 4 weeks;
  - Capecitabine 2500mg/m2 per bone 14 days , every 3 weeks;
  - Oxaliplatin 130mg/m2 i/v every 3 weeks;
  - Tegafur 1200-1600mg per os dail;
  - Irinotecan 350mg/m2 i/v, every 3 weeks;
  - Raltitrexed 3mg / m2 i / v, every 3 weeks;
  - Bevacizumab 5mg / kg i / v, every 2 weeks;
  - Cetuximab 400mg / m2 i/v dose initial, then 250mg/m2 i/v each week;

FOLFOX (modified): Calcium folinate 20mg/m2 i/v 1-5 days + 5FU 425mg/m2 i /v 1-5 days + Oxaliplatin 85-130mg / m2 i / v, every 3-4 weeks ;

XELOX: Capecitabine 2500mg / m2 per bone 14 days + Oxaliplatin 85-130 mg / m2 i/v, every 3-4 weeks ; XELOX + Bevacizumab : Capecitabine 2500mg / m2 per os 14 days + Oxaliplatin 85-130mg / m2 i / v, every 3-4 weeks + Bevacizumab 5mg / kg i / v, every 2 weeks ;

XELIRI: Capecitabine 2000mg/m2 for 1-14 days + Irinotecan 100mg/ m2 i/v. 1, 8 days, every 3-4 weeks ; XELIRI + Bevacizumab : Capecitabine 2000mg/m2 for 1-14 day + Irinotecan 100mg/m2 i/v. 1, 8 days, every 3-4 weeks + Bevacizumab 5mg / kg iv , every 2 weeks ;

Irinotecan + Cetuximab: Irinotecan 100mg/m2 i/v 1,8 days, every 3-4 weeks + Cetuximab 400mg/m2 i/v dose initial , then 250mg /m2 i/v , each week;

IROX: Irinotecan 200mg /m2 i/v 1 day + Oxaliplatin 85mg /m2 i/v 1 day, every 3-4 weeks .

Adjuvant Chemotherapy **:** FOLFOX , Capecitabine, XELOX regimens (6 courses) .

Neoadjuvant chemotherapy: recommended practice Mayo regimes; FOLFOX +/- Bevacizumab, Capecitabine; XELOX; XELOX + Bevacizumab; XELOX + Cetuximab; XELIRI +/- Bevacizumab; IROX +/- Bevacizumab; XELIRI +/- 15 Cetuximab; IROX +/- Cetuximab (up to 6 courses).

Peculiarities of administration of some cytostatics drugs: Capecitabine - will be administered orally twice a day; Oxaliplatin - will manage in 400 ml saline or glucose i/v infusion for 2-6 hours with application prior to antiemetics (5HT3 receptor inhibitors) and corticosteroids ; Irinotecan - i /v in saline infusion no longer then 30 min; Bevacizumab - will manage in 100- 250 ml saline in the form of infusion lasting 90 min first infusion , then - 60 min and 30 min; Cetuximab - i/v in 400 ml saline as an infusion lasting 2 hours 1 day , then for an hour every week ; Cisplatin - will be administeed on the background of hyperhydration (prehydration - up to 1l of saline , posthydration - up to 1l of saline) with the application prior to antiemetics (5HT3 receptor inhibitors) and corticosteroids ; Tegafur - will be administered orally in 2-3 doses, no mor than 2g per day, total dose will not exceed 30-40g; Raltitrexed – i/v with saline in the form of an infusion of 15 min.

Evaluation of treatment effectivenes: Assessment methods : subjective, physical (visual, palpation, percussion), radiological, endoscopic , sonographic , CT, MRI , isotopic, biochemical.

Evaluation criteria:

1. Criteria recommended by WHO (Remission complete , Remission Partial, Stabilization, Advancement).
2. According to the RECIST system (Remission complete, Remission Partial, Stabilization, Advancement).

Remote results: Durationof remissions, Survival free of signs of illness, Time until advancement , Survival average.

Contraindications for chemotherapeutic treatment: impossibility to asses morphological features of the disease; general state , which does not allow administration of treatment ; presence of underlying pathologies (decompensated); Laboratory values - out of range; Lack of patient agreement for making antitumor treatment.

Medical treatment issues: 6 cycles of treatment will be performed for adjuvant purposes. In the metastatic forms of disease initialy will

be performed at least 2 cycles of treatment. If the disease is controled, confirmed subjective and objective treatment will be continued with the application of same regime up to 6-8 cycles. In the case of progression of the process after application of treatment lines, will be recommended treatment schemes of line II, III. In the case of unbearable toxicity should be considered the optimization of supportive treatment and/or correction of chemotherapic dosage.

Precancerous conditions of the colon

Precancerous colorectal disease, are defined as cellular changes that make them more susceptible to malignancy, but these conditions are not yet cancer. Untreated , they increase the risk of colorectal cancer. Precancerous lesion are polyps which according to the latter CIM-O classifications may havelow grade dysplasia that denote that the cells are slightly UNUSUAL and severe- dysplasia that means that cells miss their normal appearance, more looking like the structure of cancerous cells .

NB. moderate Dysplasia was excluded from the last morphological classification (2008-2019).

1. Colorectal polyps (according to morphology):
   a. Tubular adenoma - about 70 percent of polyps are adenomatous, the most common type of colorectal polyp. Although a small percentage of tubular adenomas are morphologically confirmed as malignant, virtually all malignant polyps were initially tubular adenomas. An “advantage” is that the process for adenomatous polyps to turn into colorectal cancer usually takes many years (8-12), so population screening can diagnose these conditions, intervene promptly, and eventually achieve the ultimate goal. of screening, decrease specific mortality (by colorectal cancer).
   b. Hyperplastic polyp - is the most “harmless” type of polyp, with a low risk of malignancy, but which are usually diagnosed endoscopically and are resected with histopathological examination.
   c. Adenoma “serous” or “serrated” - has a serrated configuration, similar to a hyperplastic polyp, but with dysplastic epithelium in the upper part of the crypts, are usually flat / flat, difficult to detect, especially if they are located in right hemicolon, have the potential for malignancy.
   d. Inflammatory polyp or pseudopolyp - usually occurs in people with colorectal inflammatory diseases (colitis, rectitis, CUN)

these polyps are not "true" although the endoscopic picture is characteristic of a "classic" polyp. These as a reaction to chronic inflammation of the colorectal mucosa. Inflammatory polyps are benign and generally do not present a risk of developing colon cancer. When treated with the underlying disease (eg CUN), they do not require minimally invasive treatment - endoscopic resection.

e. Adenoma villos (adenoma tubulovilos) - approx. 15% of polyps detected in colorectal cancer screening are hairy / tubulovillous adenomas. The villous / tubulovillous adenoma has the appearance of more fringed projections (visually endoscopic it presents as "seaweed", mobile, soft, fragile) and the tubulo-villous adenoma has a combined tubular and villous structure in proportion of 80/20%, respectively 20/80 %. They have an increased risk of malignancy.

On endoscopic examination, the usual macroscopic classification of polyps determined in the colon and rectum is in accordance with the classification approved in 2000 in Paris, according to which endoscopic colorectal mucosa lesions are divided into:

- 0-I forms of elevated lesions (see fig. 21)
  - 0-Ip pediculated
  - 0-Is sessile
  - 0-Isp semipediculated

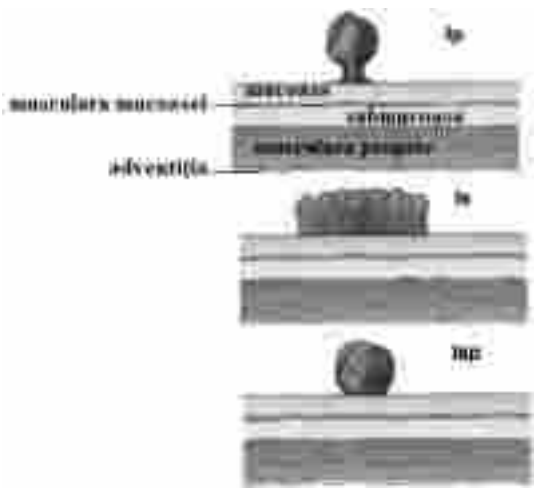


Fig. 21. *Elevated lesions (Paris 2000)*

a. **0-II flat / flat forms of lesions** *(see fig. 22):*

0-IIa plan / Easy elevated

0-IIb complete plan lesion

0-IIc superficial depressive

NB! There can be various combinations of forms described above (example 0-IIa + Is, 0-IIa + c etc.)

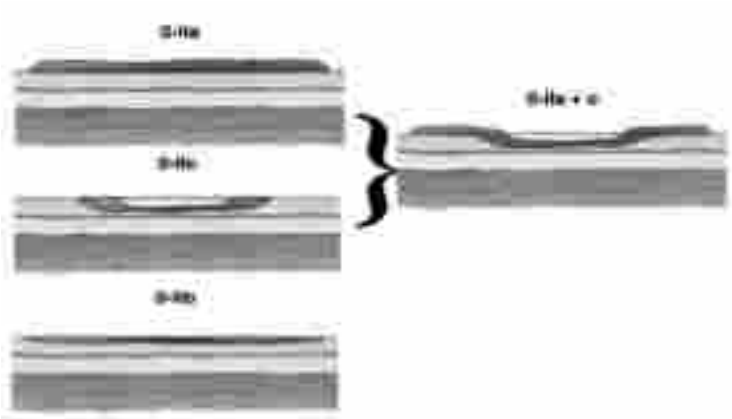


Fig. 22. *Flat / flat lesions (Paris 2000)*

b. **0-III indicates excavated (subleveled) forms of the lesions** *(see fig. 23):*

0-III Excavated / ulcerated

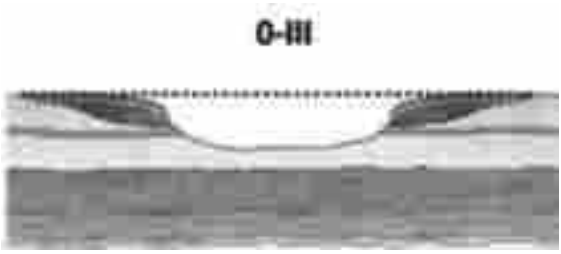


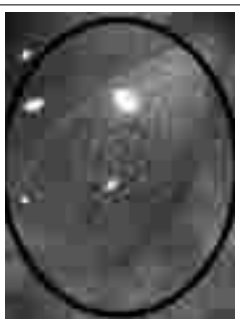
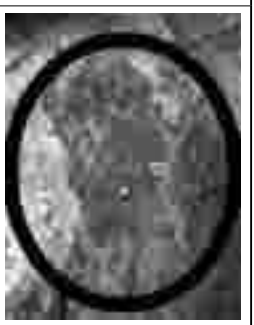
Fig. 23. *Excavated lesions (sublevel) (Paris 2000)*

NB. It is worth mentioning an important moment regarding the classification of colorectal mucosal lesions in Paris, given the lack of accuracy in measurements (the grading scale is missing).

Thus, if an elevated lesion is higher than the open forceps for biopsy (2.5 mm), then it is classified as sessile (0-I), and if the height of the lesions is lower, then it is classified as plan / payment (0-II).

A last classification of colorectal mucosal lesions, but no less important, is the classification given by the endoscopic examination of the mucosa in a special imaging regime, with a narrow band in which the specific blue light allows the appreciation of the capillary pattern (lesion surface). (depending on the endoscope manufacturer) allows differential diagnosis - hyperplastic polyp, adenoma, cancer with increased accuracy during endoscopic investigation (see Table 1).

Table 1. Classification lesion mucosa according to the classification in the band light narrow

Characteristic	**Type 1-SANO I**	**Type 2-SANO II**	**Type 3-SANO III**
color injury	Identical or slightly lighter in color than the background	blue-brown color against the background	Blue-brown color more accentuated with white, asymmetrical linear areas
drawing capillary	Unpronounced or circular, symmetrical present in the whole structure of the polyp	Blue / brown vessels surrounding oval small white segmental areas	Asymmetrical or absent vascular (capillary) pattern
Surface (pattern)	Dark or white «spots» of uniform size, homogeneous	White oval, tubular or branched structures surrounded by blue vessels (capillaries).	amorphous Surface , texture is missing .
endoscopic Conclusion	**Hyperplastic Polyp**	**Adenoma**	**Cancer**
schematic Representation			
Endoscopic picture			

Minimally invasive endoscopic treatment of polyps.

In present, the usual method of minimally invasive surgery in benign colorectal tumors is endoscopic mucosal resection (REM) or the term "popular" endoscopic polypectomy (see Fig. 24).

In general, an endoscopic resection of the mucosa is performed as follows:

- in the first stage, a revision of the oncological lesion (polyp) is performed to assess the shape of the growth (Paris classification), the dimensions and the examination under the NBI regime (as appropriate).
- a solution is applied through a special fine-needle injector to the base of the lesion (circular) to perform a facelift, which allows the removal of the lesion (polyp) from the submucosa (see fig. 25,26).
- with the help of the resection loop it is applied with the help of the usual endoscope, it is fixed and in the cutting and coagulation regime adapted to the dimensions, type and location of the polyp, the endoscopic resection is performed with the extraction of the resected piece
- If necessary, the base of the resection can be coagulated and hemostatic clips applied (closing the defect).
- Subsequently, after reviewing and controlling the hemostasis, the colonoscope is removed and the patient is monitored for at least 24 hours postoperatively.

Fig. 24. *Representation schematic of the resection endoscopic mucosa (REM)*

Fig. 25. Resection endoscopic examination of the rectal polyp with application clips hemostatic (source (IMSP Oncology Institute Screening Center)

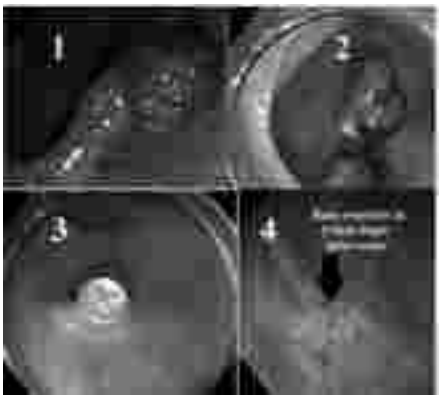


Fig. 26. *Resection endoscopic examination of the polyp pediculate (Paris 0-Ip) and VCS control at 6 months (source (IMSP Oncological Institute , Screening Center)*

2. Hereditary colorectal syndromes - are rare diseases, proven to be colorectal precancerous conditions. These syndromes are caused by a genetic mutation, which can be passed from parents to children.

a. Lynch syndrome (nonpolypodic hereditary colorectal cancer) is the most common type of hereditary colorectal syndrome. A solitary polyp or several polyps develop in the colon or rectum, which malign more rapidly than polyps in cases not affected by Lynch syndrome. The MLH1 gene mutation causes Lynch syndrome. Men and women with a mutation in MLH1 have a 52-82% lifetime risk (up to 70 years) of developing colorectal cancer. Lynch syndrome is associated with a 30% risk of developing second or colon cancer for 10 years after the first cancer. Women have a 25-60% lifetime risk for endometrial cancer and a 4-13% lifetime risk for ovarian cancer. People with Lynch syndrome are also at increased risk for other cancers, including cancer of the stomach, urinary tract, ovaries, small intestine, pancreas or bile ducts, sweat glands, and brain. People with Lynch syndrome also tend to have more precancerous colon polyps that grow faster than individuals without Lynch syndrome. For this reason, people with Lynch syndrome should have frequent colonoscopies (at 12-24 months) even if no pathological condition of the colorectal mucosa has been diagnosed in previous examinations. Mutations in the MLH1 gene are inherited in an autosomal dominant pattern, which means that every first-degree relative, such as sibling

or children, has a 50% chance of inheriting this mutation, and genetic testing is recommended for adult relatives.

b. Familial adenomatous polyposis (PAF) - is an inherited pathology characterized by colorectal polyps (from several tens to several thousand) that implicitly lead to the development of colorectal cancer. People with the classic type of familial adenomatous polyposis have the colorectal mucosa affected by non-cancerous polyps starting in adolescence. These undiagnosed polyps have an increased potential for malignancy, over time they become cancerous. The average age at which an individual develops colon cancer in classic adenomatous polyposis is approx. 39 years old (see fig.27).

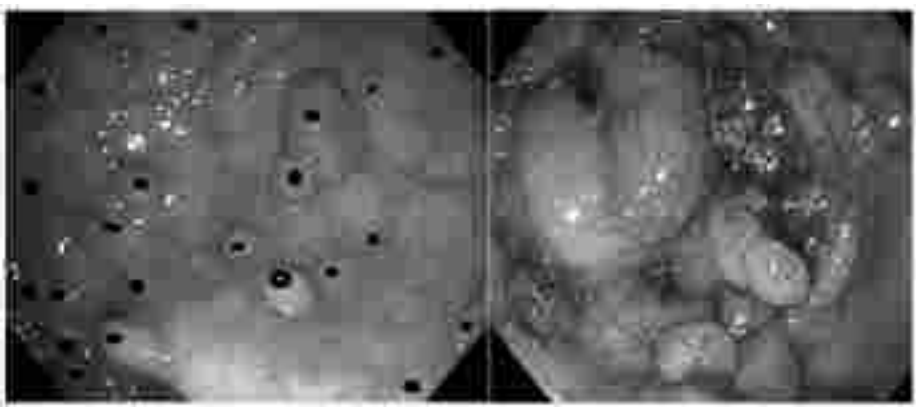


Fig. 27. *30-year-old patient with familial adenoamytoal polyposis in the middle rectum on an area of approx. 5 cm. Over 20 polyps (left figure) in the upper rectum with the involvement of the malignancy rectosigma on the background of adenoma (right figure), photo source IMSP OncologicalFIG. 28. 30-year-old patient with familial adenoamytoal polyposis in the middle rectum on an area of approx. 5 cm. Over 20 polyps (left figure) in the upper rectum with the involvement of the malignancy rectosigma on the background of adenoma (right figure), photo source IMSP Oncological Institute, Screening Center*

b. Peutz-Jeghers syndrome causes the growth and development of non-cancerous polyps called hamartomas in the gastrointestinal tract. These polyps indicate an increased risk of developing certain types of cancer, including colorectal cancer. STK11 gene mutations directly cause Peutz-Jeghers syndrome. The STK11 gene is a tumor suppressor gene, which means that it normally prevents cells from

growing and proliferating uncontrollably. A mutation in this gene alters the structure or function of the STK11 protein, disrupting its ability to restrict cell division. Uncontrolled cell growth leads to the formation of non-cancerous polyps (as a first stage) and later the development of malignant tumors in people with Peutz-Jeghers syndrome.

c. Gardner's syndrome is a form of familial adenomatous polyposis (PAF), which is characterized by the development of multiple colorectal polyps and various types of tumors, both benign and malignant. People with Gardner's syndrome have a high risk of developing colorectal cancer at an early age (under 40). They are also at increased risk of developing other FAP-related cancers (small intestine, stomach, pancreas, thyroid, CNS, liver, airways and gallbladder, adrenal gland). A number of abnormalities in Gardner's syndrome are also described - dental, osteoma, epidermoid cysts, fibroids, lipomas and desmoid tumors. It is caused by changes (mutations) in the APC gene and inherited autosomal dominant.

3. Inflammatory processes of the mucosa - nonspecific ulcerative colitis (CUN) is an inflammatory bowel disease (IBD) is characterized by abnormal inflammation of the inner surface of the colorectal mucosa, against the background of the inflammatory process appear multiple ulcers. Although CUN usually opens by the age of 30, it can develop at any age.

Nonspecific ulcerative colitis is a common form of IBD, and another type of IBD is Crohn's disease (due to an abnormal immune response that causes inflammation), it also causes chronic inflammation of the intestinal mucosa, Crohn's disease can cause inflammation in any part of the system. digestive tract, and the inflammation spreads deeper into the intestinal tissue. Inflammatory bowel diseases are also precancerous conditions, on the background of which pseudopolyps occur, and over time a malignant process can develop.

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KIDNEY CANCER

Epidemiological-geographical features

Renal tumors developed in the parenchyma represent about 90% of all renal malignancies, the rest of the cases having as a starting point the renal pyelocaliceal pelvis.

Worldwide, kidney cancer (KC) is the 13th malignancy (271,000 new cases diagnosed / year), with the highest incidence in developed countries: Australia, North America and Europe. The lowest incidence rates are in African countries or in some Asian countries (India, China, Japan).

The highest incidence rate is in the 6th and 7th decade of life, the average age of diagnosis being 65 years. The incidence is twice as high in males as in females (15.8 compared to 7.1 per 100,000 Europeans). Wilms tumors are most common in children, especially when they are under 5 years of age.

Ethiopatogenesis

The etiopathogenesis of KC is little studied, although experimental clinical work has shown that in its appearance an important role belongs to hormonal disorders (hyperestrogenemia), irradiation, some carcinogens. Some authors support the hypothesis of the appearance of KC against the background of malformations, nephrolithiasis and chronic inflammation of the kidney. It seems that in the appearance of KC the causes are multiple (polyetiological theory).

Risk factors:

RACE - the highest incidence is in African Americans and whites, compared to Africans and Asians who have a low incidence. Possible explanations for these variations are different access to health programs and diagnostic imaging methods, genetic substrate, and exposure to different environmental and occupational factors.

SEX - the incidence and mortality rate for kidney cancer is higher for males. These differences are probably due to different exposure to smoking and certain occupational factors.

AGE - The risk of developing SR increases considerably after the age of 50. Most people diagnosed with this type of cancer are over 50 years of age, with increasing risk the risk increases exponentially.

FAMILY MEDICAL HISTORY - The evidence of a genetic determinism in the appearance of KC came from the existence of familial forms of the disease in a percentage of 4% of all cases. There are 4 well-defined types of hereditary renal cancer: von HIPPEL-Lindau, the familial form of clear cell renal cell carcinoma, hereditary papillary carcinoma type I and type II, and BIRT-Hogg-Dube syndrome with an increased risk of developing KC.

SMOKING - Medical studies have shown that smoking (especially excessive tobacco use) increases the risk of developing KC by 2.3 times.

PHYSICAL ACTIVITY - Sedentary lifestyle, lack of regular exercise, often associated with obesity, increase the risk of KC.

OBESITY - expressed by an increase in body mass index (BMI), is associated with the risk of developing neoplasms. Thus, a 5 Kg / m2 increase in BMI strongly correlates with the risk of kidney cancer in both men and women (relative risk of 1.24 in males and 1.36 in females).

OCCUPATIONAL FACTORS - Category 1 (proven) carcinogens for kidney cancer are: coke (raw material obtained from coal, oil, tar and used in metallurgy, chemical industry or household) and trichlorethylene (solvent used in industry). Perchlorethylene includes probable carcinogens. There are no studies proving the role of renal carcinogen for arsenic, cadmium, chromium, lead, nickel, polycyclic aromatic hydrocarbons and asbestos.

ACQUIRED CHISITIC KIDNEY DISEASE - which is installed in patients with end-stage renal disease and hemodialysis, may be 3-6 times more likely to develop renal cancer.

HORMONAL FACTORS - Extensive prospective studies have shown that hysterectomy is a significant risk factor for kidney cancer and probably the age of menarche and the use of oral contraceptives. The number of births did not correlate with the risk of kidney cancer, although other studies have shown that each birth increases this risk by 15%.

GENETICS IN KIDNEY CANCER - the etiopathogenesis of kidney cancer is determined by the action of environmental factors in the context of genetic susceptibility. An important number of hypotheses have been advanced to outline the genetic profile of kidney cancer, but only 3 mechanisms have been accepted: xenobiotic metabolism, vitamin D receptors and lipid peroxidation.

Diagnosis of kidney cancer

Clinical anamnesis

Most renal tumors develop asymptomatically for a long time. This fact remains characteristic for both benign and malignant tumors, manifesting itself clinically only when reaching considerable size. Often patients go to the doctor presenting the clinic of multiple metastases without accusations regarding the primary tumor. However, kidney cancer is characterized by the triad: hematuria (50-60%), the presence of palpable tumor in the lumbar region (30-40%), low back pain (40-50%). The presence of the triad in most cases demonstrates an advanced tumor process. Hematuria occurs as a result of tumor decomposition, and the pain is due to the involvement of the renal capsule in the process.

Pain and hematuria are not pathognomonic signs of kidney cancer, as most diseases of the parenchyma or pelvis are also manifested by these symptoms. It should be noted that not every palpable tumor is necessarily a cancer. However, the presence of one of the signs described above warns the doctor and suggests a renal neoplasm.

In most cases, a tumor of a hard consistency is detected, with uneven contours, sometimes a little painful, with reduced mobility.

From the triad of renal cancer symptoms, hematuria occurs earlier and more frequently in pelvic tumors. Hematuria is of paramount importance in the early diagnosis of kidney tumors, in that it attracts the patient's attention, while palpable tumors are often diagnosed by a doctor.

So hematuria is the very important basic symptom in diagnosing kidney tumors. It is the result of vessel wear or cancer decay.

Hematuria occurs spontaneously and lasts for 1-2 days, sometimes a few hours only exceptionally is permanent and profuse. For kidney cancer, unlike other kidney pathologies, total hematuria is characteristic, with vermiform clots, short-lived, with pronounced or asymptomatic signs. Renal tumor growth causes hematuria (50-60%), low back pain (40%), the presence of tumor mass on palpation (30-40%) or Wünderlich syndrome. Clinical triad occurs in 10% of patients. The pain is of the neuralgic type and has as mechanism the distension of the renal capsule or the invasion of the anatomical structures of the neighborhood. In the case of hematuria and secondary hydronephrosis, the pain may progress to colic. Tumor progression at the metastatic level according to the sites induces: cough, bone pain, a neurological symptomatology. Tumor extension in the renal

vein and inferior vena cava causes edema of the lower extremity and varicocele.

In KC, the pain is found in 60% of cases and is different in intensity, duration and location. They can be attenuated or acute, very rarely with manifestations of nephritic colic, with frequent irradiation in the external urogenital organs and accompanied by dysuria. The cause of the attenuated pain is the enlargement of the fibrous capsule of the kidney by the growing tumor. Neuralgic pains are probably the result of tumor compression or invasion of the nerve trunks and are usually located in the lumbar region, less often in the iliac and sacral region. Compression of the duodenum and gallbladder causes dyskinesia in the biliary system with the appearance of jaundice and hepatomegaly. Upper polar tumors compress the diaphragm and may be accompanied by dyspnea. Metastatic involvement or primary tumor process of the vessels and nerves causes varicocele (dilation of the veins of the spermatic cord, more often on the left side) and dilation of the veins of the labia majora in women, which do not disappear in dorsal decubitus, are rarely accompanied by pain and can be bilateral.

Sometimes, in addition to the triad, the signs of intoxication appear in the foreground: anorexia, weight loss, fever and hypertension. Considering that long fever(sometimes even a few months) may be the only sign of KC, patients with apparently unmotivated fever should undergo a thorough urological examination.

In patients with kidney cancer, high blood pressure is caused by ischemia of the renal parenchyma and arterial-venous shunting in the tumor tissue.

In the case of chronic renal failure that tends to exacerbate, there are clinical signs of uremic gastritis, enterocolitis, etc. Among the symptoms of distant metastasis of KC that evolve latently, the most common clinically are bone metastases, accompanied by excruciating pain, permanent, with intensification during the night. When the spine is damaged, the pain has a neuralgic character, paresis and paralysis of the lower limbs, urinary incontinence and fecal masses.

Paraneoplastic syndromes

Paraneoplastic syndromes are present in 10-40% of patients with renal neoplasm, being grouped into approximately 15 clinical, endocrinological forms (hypercalcemia, hypertension, polycythemia, Stauffer syndrome, galactorrhea, Cushing's syndrome, altered glucose metabolism) and non-endocrinological (amyloidosis). , neuromyopathy, vasculopathy, anemia, nephropathy, coagulopathy or increased prostaglandins). A

recent study identified a much higher rate of paraneoplastic syndromes, 67.9%, in patients with renal neoplasm, with the most common forms being an increase in ESR (52%), high blood pressure (36%), cachexia. 33%), anemia (31%), pyrexia (23%), impaired liver function (14%), hypercalcemia (6%), polycythemia (6%), varicocele (2%) and neuropathy (1%). The presence of paraneoplastic syndromes in patients with renal neoplasm is an unfavorable prognostic factor and may have a predictive role on survival.

Clinical forms

In the clinical aspect we distinguish 5 forms of manifestation of kidney cancer.

1. ***The hematuric*** form in which the hematuria, although inconsistent, has a revealing character. Blood clots, which can be long and thin, can cause severe dysuria or even acute urinary retention, bladder tamponade.
2. ***Tumor form***. On bimanual palpation, the net contour of the lower pole of the kidney is detected, its consistency being remittent, hard or uneven with softer areas, with a smooth or uneven surface, the palpation being painless. This form has no urinary symptoms and should be differentiated from intraperitoneal tumors.
3. ***The mixed form (hematurico-tumor***) is relatively rare. Clinically, the presence of the tumor is manifested by hematuria and palpation in the flank of the tumor kidney, enlarged in volume.
4. ***Febrile form***. The only and main sign is fever, which in 10% is related to the tumor process, not to superinfection. Fever can mislead your doctor. It has a hectic, recurrent or rhythmic character and correlates with hematuria, being resistant to antibiotics and disappearing with nephrectomy. Fever is explained by the release of circulating protein pyretogenic substances from the tumor formation. This form has a very malignant evolution and a serious prognosis.
5. ***Metastatic form***. The clinical signs of the primary tumor do not manifest and only the appearance metastasis is revealing. Metastases are located in the long tubular bones, spine, lungs, brain, etc. Bone mt are discovered accidentally or through pathological fractures. Radiography reveals metastatic lesions, sometimes fractures, and intravenous urography reveals kidney tumor lesions.

Physical examination

It is based on the following:

1. Clinical signs of general disorders syndrome (weakness, fatigue, dyspnoea on exertion, dizziness, palpitations, weight loss, loss of appetite, fever, etc.);
2. Clinical signs of palpable tumor (tumor location, mobility, size, consistency);
3. Signs of urinary disorders: the appearance of hematuria (its duration, duration, may be macroscopic, total, spontaneous, single or repeated, abundant, painless or painful, or weak, etc.)

Paraclinical and laboratory investigations

Imaging methods detect kidney tumors, differentiate benign from malignant lesions, perform TNM staging, identify different histological subtypes of kidney tumors, actively monitor the progression of kidney tumors and monitor patients after nephrectomy to detect possible recurrence of the disease. Useful imaging methods for assessing renal units are ultrasonography, computed tomography, intravenous urography, and magnetic resonance imaging.

Ultrasonography. Abdominal ultrasound is the main method of assessing kidney damage, being widespread and accessible to doctors and patients. Ultrasonography assesses the presence of renal formations, as well as their size, vascularity and echogenicity, differentiates transonic cystic lesions from iso- or hyperechoic, parenchymal ones, or can monitor tumor growth.

Thus, ultrasonography detects 58% of kidney tumors between 15 and 20 mm, while computed tomography detects 100% of them.

Doppler examination allows exploration of the renal artery and vein with the possibility of objectification of venous tumor thrombi in the renal vein or inferior vena cava (see Fig. 1).

Fig. 1. *Doppler renal ultrasonography*

The use of contrast medium allows exploration even in conditions of small vessels with low flow. The principle of the method is to use contrast agents in the form of microbubbles (gas, air or perfluorocarbon microspheres) that are biodegradable. These bubbles slowly cross the tissue capillary bed and increase the blood's echogenicity.

The advantages of using contrast-enhanced ultrasound are due to the fact that it is a safe, simple method, well tolerated by patients, without irradiation, without nephrotoxicity and with real-time exploration.

Computed tomography. Evaluation of tumor formations by computed tomography with contrast material involves follow-up and acquisition of images in three phases: precontrast, cortico-medullary parenchymal phase and excretory phase.

The precontrast or native phase is useful for identifying areas of fatty tissue or calcification and for setting density measurements (Hounsfield units) that will differentiate cystic (liquid) lesions from solid masses.

The administration of the contrast substance allows the detection of the tumor formation and the exploration of its features: the location, the vascularization of the kidney, the vascularization of the lesion and the venous interest of the tumor.

The excretory phase is especially useful for the detection of small tumors, for the identification of anatomical changes or for the presence of tumor invasion in the pyelocaliceal system.

Computed tomography has a high accuracy for the detection of cortical renal tumors (sensitivity of 100% and specificity of 95%).

Magnetic resonance imaging (MRI) offers advantages over other imaging methods due to its increased ability to highlight contrast between soft tissues and due to its multiplanar imaging capability. Moreover, this technique uses gadolinium as a contrast agent and can be used in patients with kidney failure. Another advantage is the possibility of use for the assessment of tumor growth during pregnancy in women who are known to have tumors in pregnancy.

The advantages of the method are maintained both in the diagnosis (assessment of small tumor masses or establishing the origin of the tumor mass) and in post-treatment monitoring.

In conclusion, any non-adipose tumor mass or renal cyst that concentrates the contrast substance is considered potentially malignant and has a surgical indication. Based on the tumor features recorded

using magnetic resonance imaging, a score with prognostic value can be established: tumor size, peripheral versus central location, intensity in T2 weight and degree of contrast concentration, presence of fat, presence of intratumoral necrosis, presence of vessels collateral retroperitoneal and renal vein thrombosis.

Renal biopsy. In the context of the significant increase in the number of tumors in the T1 stage with indication of nephron sparing surgery and for which the imaging cannot indicate the aggression profile, but also of the development of minimally invasive treatment methods, the role of renal biopsy attracted attention.

The accuracy of the method for differentiating benign from malignant tissue is between 89 92%, for establishing the histological subtype between 78-92% and for establishing the nuclear grade between 70-74%.

Renal tumor biopsy resulted in a change in treatment strategy in 34 to 47% of patients. In the presence of synchronous renal tumors, a biopsy of all lesions is indicated. The risk of malignancy by kidney tumor biopsy is negligible.

The most common is renal puncture guided by ultrasonography.

Renal tissue sampling can be done in two ways:

- *percutaneous biopsy* - this uses a special semi-automatic needle with dimensions of 16-18 G, a needle that will be positioned at the level of the skin projection of the kidney.

- *open biopsy* - renal parenchyma sampling is performed directly from the kidneys during surgery.

Intravenous urography. Estimation of the functional status of the kidneys. The detection of certain signs of alterations in the pyelocaliceal system can be performed by intravenous urography. . In a more superficial location of the tumor, there is an increase in the distance from the edge of the calyx to the renal capsule. Deeper damage shows the deformity of the calyces with their deviation on the opposite side, in the case of the tumor site outside the calyx they are elongated, which is explained by their pull to the periphery, scattered calyx - in the tumor site between the calyx, filling defect or sign abutment (amputation of the calyx) - at their direct infiltration by the tumor. The same sign of the filling or even amputation defect appears in the case of infiltration of the pelvis, which has unclear uneven contours, the ureter being deformed “in bayonet” and

deviated to the midline, almost paravertebral. The latter symptom is more characteristic of lower polar tumors (*see Fig. 2).*

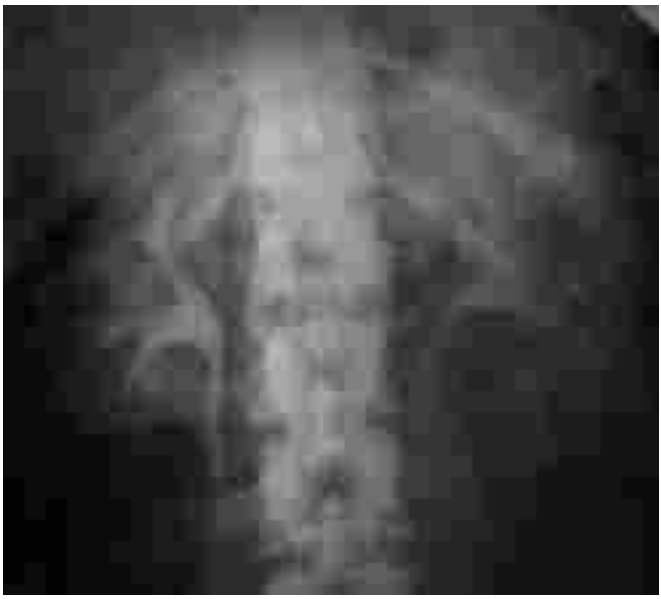

Fig. 2. *Intravenous urography*

Retrograde ureteropyelography is basically the same symptomatic complex and is recommended in cases of functional disorders of the kidneys with urea and increased creatinine, the patient is allergic to iodine contrast agents, when the site of the tumor in the pelvis is assumed. Retropneumoperitoneum is recommended in tumors with peripheral development, which do not affect the pyelocaliceal cavities. In such cases, a deformed kidney shadow is evident.

Bone scintigraphy. It is a non-invasive medical investigation designed to detect oncological conditions.

The correct diagnosis of oncological diseases, as well as the detection of their stage are two essential things for the effective treatment of cancer.

One of the modern imaging investigations recommended for cancer patients is bone scintigraphy, a non-invasive form of scanning of the bone system, which detects various diseases and abnormalities in the bones.

This type of investigation provides valuable information about the existence or evolution of various oncological diseases, but also about inflammation, osteoarthritis or pain whose cause is still unidentified.

Differential diagnosis of kidney cancer

Differential diagnosis of KC is required in:

- Renal tuberculosis
- Renal polycystosis
- Xanthogranulomatous pyelonephritis
- Solitary renal cyst
- Renal angiomyolipoma
- Renal abscess
- Renal lymphomas
- Renal tumors (renal or metastatic adenoma)

Key moments in differential diagnosis

In case of any suspicion of renal tumor or non-tumor disease, subjective and objective (physical) data are not sufficient to differentiate KC from other diseases, in all cases the following research algorithm is recommended: USG uroexcretory system - UIV with descending cystogram - renal CT and abdomen these methods are not competitive, but complementary and need to be performed in all suspicious cases.

Renal tuberculosis. Differentiation is based on; -USG and -UIV, where you can read the signs characteristic of tuberculous kidney damage, upper and lower excretory system; Also signs of renal CT.

Solitary renal cyst. Different types of renal cystic lesions are described, being classified according to: contour, thickness, presence of calcifications in the walls or septa, fluid density, the presence of solid lesions inside or on the periphery of the cyst.

Renal adenoma. The differential diagnosis with other rare kidney tumors is difficult to make, especially with renal adenoma, the relationship between it and KC being mostly pathogenic. Unique benign tumors rarely grow larger than 2 cm (only intra- and postoperatively, eg morphopathologically).

Renal angiomyolipoma. Benign tumors, sometimes of impressive size, are differentiated from cancers by computed tomography examination by cellulo-fat content, with lower densities than water in Hounsfield units.

Renal abscess. It is suggested by fever, low back pain and leukocytosis, with the presence of the source of entry (cutaneous, oral, etc.) in the recent history.

Renal lymphomas. Transitional renal cell carcinomas, adrenal gland cancers and secondary renal tumors (kidney metastases) are other entities

that will be clinically and especially tomodensiometrically differentiated from primitive parenchymal renal cell carcinomas.

Staging of TNM of kidney cancer, AJCC, 8th edition, 2017:

T -Primary tumor

Tx - Primary tumor cannot be evaluated
T0 - No evidence of primary tumor
T1 - Tumor 7 cm or less in maximum size, limited to the kidneys
T1a - Tumor 4 cm or less
T1b - Tumor larger than 4 cm, but not larger than 7 cm
T2 - Tumor larger than 7 cm in maximum size, limited to the kidneys
T2a - Tumor larger than 7 cm, but not larger than 10 cm
T2b - Tumor larger than 10 cm, limited to the kidneys
T3 - The tumor spreads in the major veins or in the perinephritic tissues, but not in the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a - The tumor extends into the renal vein or its segmental branches or invades the pyelocaliceal system or perirenal fat and / or renal sinus (peripelvian), but not beyond the Gerota fascia
T3b - The tumor spreads into the vena cava, under the diaphragm
T3c - Tumor spreads into vena cava above diaphragm or invades vena cava wall
T4 - Tumor extends beyond Gerota fascia (including contiguous extension in ipsilateral adrenal gland)

N - Regional lymph nodes

Nx - Regional lymph nodes cannot be evaluated
N0 - There are no metastases in the regional lymph nodes
N1 - Metastases in regional lymph nodes

M - Distant metastases

M0 - No distant metastases
M1 - Remote metastases present

Histological classification of renal tumors (WHO 2020)

Nephrocellular (epithelial) tumors

- Clear cell nephrocellular carcinoma
- Clear cell multilocular nephrocellular carcinoma
- Papillary nephrocellular carcinoma

- Chromophobic nephrocellular carcinoma
- Carcinoma of the Bellini ducts
- Spinal cord carcinoma
- Carcinomas, associated with Xp11 chromosome translocation
- Carcinoma, associated with neuroblastoma
- Mucinous and fusiform tubular carcinoma
- Unclassified nephrocellular carcinoma
- Papillary adenoma
- Oncocytoma
- Rare tumors

Degrees of tumor differentiation of kidney cancer (after Fuhrman)

Gx - the degree of differentiation has not been evaluated
G1 - high degree of differentiation
G2 - moderate degree of differentiation
G3 - low degree of differentiation
G4 - undifferentiated, anaplastic cancer

Metastatic pathways

KC propagation takes place in different ways. Local spread with the involvement of adjacent tissue organs in the process rarely exceeds the capsule (or at least quite late) invades the perirenal adipose tissue, exceptionally comprising the adrenal and intraperitoneal organs, sometimes the intercostal and abdominal muscles. Lymphogenic metastasis is also relatively late and inconsistent, with kidney cancer not a lymphophilic cancer. First of all, the lymph nodes of the renal hilum, paravertebral along the aorta of the inferior vena cava, are involved in the process. Inguinal, left supraclavicular, iliac, and exceptionally mediastinal ggl may be retrograde metastases. Venous hematogenous metastasis is the most common and exceeds the lymphogenic one over time. From the inferior vena cava, the neoplastic cells reach the small circulation (this moment explains the presence of lung metastases, which are found in 30% of cases), later in the large circulation with liver, brain and especially bone metastases.

Treatment of kidney cancer

Principles of radical treatment in KC

- The radical method of treatment that can ensure healing is surgery.
- The purpose of radical treatment in KC is to completely excise the

tumor tissue - being performed by radical nephrectomy or conservative surgery (partial nephrectomy)

Principles of radical nephrectomy

The standard operation that ensures oncological safety is radical nephrectomy, which consists of the primary ligation of the renal artery and vein, with block excision of the paranefral adipose tissue and adrenal gland outside the Gerota fascia, associated with regional lymphodissection.

The choice of access path depends on the volume of the tumor, its topography, the presence or absence of lymphadenopathy, the age and biological condition of the patient. This type of intervention is usually performed by transperitoneal approach, by median incision, subcostal, Giuleani incision, Shevron.

The advantage of the approach is the wide access with the possibility of primary ligation of the renal artery and vein with the control of possible vascular lesions and performing lymphodissection and tactical or associated operations - colectomy, splenectomy, hepatectomy, resection of the psoas muscle.

Principles of conservative operations

Indications for conservative surgery in patients with KC fall into three categories — absolute, relative, and elective. Absolute indications include the presence of a single congenital, surgical or functional kidney and cases of synchronous bilateral tumors.

Relative indications include patients with unilateral tumors and contralateral kidneys with benign conditions but with evolutionary potential that affect their function in the future: lithiasis, arterial stenosis, diabetes, nephrosclerosis.

Elective indications include patients with normal contralateral kidney with a tumor up to 4 cm, without exceeding the capsule (pT1a), lymphadenopathy (No) and distant metastases (Mo). Compared to radical nephrectomy, conservative interventions require additional investigations for detailed knowledge of renal anatomy and especially vascularization. Spiral CT angiography is usually sufficient.

Partial nephrectomy techniques are:

1. Simple tumor enucleation.
2. Segmental polar nephrectomy.

3. Cuneiform resection
4. Transverse resection.

After palliative surgery:
- Postoperative radiotherapy
- Immunotherapy or systemic chemotherapy
- Hormone and targeted therapy
- Symptomatic treatment.

Principles of palliative treatment

Palliative care is aimed at improving the quality of life and increasing the survival of incurable patients (stage IV).

Surgical treatment:

- Palliative / symptomatic nephrectomy in order to control severe symptoms: major hematuria, retroperitoneal hemorrhage, paraneoplastic syndrome or pain.
- Palliative nephrectomy in patients with metastases in order to regress metastases and prolong survival in combination with chemotherapy, immunotherapy, radiotherapy.

The categories of patients for whom adjuvant nephrectomy may be indicated are:

- patients with surgically resectable single metastases
- selected patients, young people with a primary surgical resectable tumor, and with llimited lung metastases who may be included in systemic treatment, usually immunotherapy.

Symptomatic RT is indicated for the purpose of:

1. Postoperative radiotherapy.
2. Radiotherapy with symptomatic purpose.

Postoperative adjuvant radiotherapy in the treatment of renal cancer has a palliative and prophylactic purpose and is indicated in case of tumor invasion in the renal capsule and the presence of metastases in gl. regional lymphatics.

Postoperative RT radical nephrectomy may improve the outcome of local treatment, especially in T3-T4 tumors. The radiant treatment is applied to TERABALT devices with Co60 energy 1.25 MeV or by irradiation to linear accelerator with high energy 6-15MeV. Postoperatively, the dose of 40-50 Gy is applied in 20-25 fractions in the classic 2 Gy fractionation regimen within 4-5 weeks, including the renal lodge, paraaortal and paracaval lymphatic ggl.

RT is applied after thorough preparation of the patient with organ

topometry and CT scan of the abdominal cavity, the patient's position remains the same during treatment, from 3-4 irradiation fields with dimensions of 14x13cm. The upper limit of the irradiation field is at the level of the intervertebral disc of the thoracic vertebrae Th11-Th12, the lower limit at the level of the intervertebral disc of the lumbar vertebrae L4-L5.

Symptomatic RT is applied in order to control the pain syndrome in case of bone metastases, in a concentrated dose with a dose of 5Gy for 6-7 days, the summary dose being 30-35Gy, which obviously improves the general condition of the patient and improving the quality of life.

Systemic PChT: Patients with stage IV (any T any N M1) of KC, which can be performed according to different schemes

Kidney cancer prophylaxis

The main determinant and preventable causes identified for kidney cancer are obesity, smoking and uncontrolled hypertension, which have a high prevalence in the general population and are attributed to half of all cases of kidney cancer.

*Primary prophylaxis**:***

- monitoring body weight;
- healthy eating: consuming as many varieties of foods rich in vegetable fiber as possible, especially fruits, vegetables, fish and cereals, reducing the amount of animal fats;
- use of dietary supplements with folic acid and calcium;
- reducing the amount of alcohol consumed;
- smoking cessation;
- physical activity dosed for age.
- adequate fluid intake during the day (1.5-2 liters)
- minimizing coffee consumption.

Secondary prophylaxis:

- USG- annually (in patients with chronic kidney disease such as pyelonephritis, glomerulonephritis, benign tumors, cysts, renal angiomyolipoma)
- People after 40 years with a family history (close relatives who have been ill with KC) - urologist consultation, annually.

- General analysis of urine at each referral to the family doctor.
- In the risk group: urethrocystoscopy, once every 3 years
- Timely treatment of urinary tract infections (acute or chronic).
- Surgical and drug treatment of precancerous and underlying diseases.

BLADDER CANCER

Epidemiological-geographical features

Bladder cancer (BC) accounts for ≈5% of the total number of oncological diseases worldwide. Bladder cancer is one of the most common neoplasms of the urinary tract ≈30-50% of cases. In Europe it is the 5th most common cancer in men, in the USA - the 4th, and in the Republic of Moldova - the 6th.

Men get sick 3-4 times more often than women. In the Republic of Moldova, the ratio of men / women is 4: 1. Many researchers explain the phenomenon by the higher frequency of urinary disorders in men - urinary retention due to prostate adenoma, chronic prostatitis, urethritis.

BC can occur at any age, even in children. However, the risk of developing bladder cancer increases with age and it is estimated that approximately 70% of people who develop bladder cancer are over 65 years of age. Young patients diagnosed with BC have a better prognosis because they have more frequent, well-differentiated superficial tumors with low malignancy.

Ethiopatogenesis

The causes of BC have been thoroughly studied. Common risk factors for developing bladder cancer are:

- **Smoking**. Cigarette smokers have up to 4-5 times the incidence of BC than people who have never smoked (Morrison, 1984; Burch et al. 1989). The risk is related to the number of cigarettes smoked per day, the number of years the person has been smoking and the degree of smoke inhalation. This risk was observed in both sexes. Smokers who quit this habit have a lower incidence of BC compared to active smokers.
- **Exposure to various chemicals** (aniline, 2-naphthyl amine, fuel gas, benzidine, 4-aminodiphenyl, aromatic amines, nitrates and nitrites). Aniline dyes, introduced in the late 1800s in the textile industry, have a carcinogenic effect on the urothelium (Rehn, 1895). However,

not only aniline dyes but their metabolites have been shown to be carcinogenic: 2-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, 4-diaminobiphenyl (benzidine), and 2 amino-1-naphthol (Morrison and Cole, 1976). .

- **Ionizing radiation causes bladder cancer**. Patients with TGT treated with radioactive iodine have an increased risk of developing BC. Irradiation of the pelvic region increases the risk of developing BC. Therefore, in patients with cervical cancer and prostate cancer, the risk of developing BC increases 2.5 to 4 times and is proportional to the radiation dose. The highest risk of developing the disease is people who underwent irradiation 5-10 years ago.
- **Diet**. The fluid consumed can influence the onset of vision cancer: 1. Increased fluid intake dilutes urine and increases the frequency of urination, which helps reduce urothelium exposure to carcinogens; 2. The type of fluid consumed may change the risk of urothelial cancer depending on the possible carcinogens it contains (arsenic levels or disinfectants in drinking water). People who consume chlorinated water for a long time have a higher risk of developing BC than people who consume ozonated water.
- **Excess coffee and tea**. Although coffee and tea consumption were included in the studies as an etiological factor of BC, no clear evidence was found that would confirm the risk of BC occurring as a result of consuming these drinks.
- **Various viral, bacterial and parasitic infections**. Schistosoma Hoematobium infection (bilharziasis) is associated with bladder cancer. In 1972, Kunts successfully induced bladder cancer in two primates exposed to Schistosoma Hoematobium infection. In Africa, the Middle East and India, where schistosomiasis is an endemic parasitic disease, BC is the most common type of cancer. According to researchers Hinder and Schiman (1969), Schistosoma was present in the bladder wall in 68% of cases of bladder squamous cell carcinoma.

The involvement of human papilloma virus (HPV) in the occurrence of BC has been studied by several researchers, the results being contradictory. According to Maloney et al. (1994) and Aynand et al. (1998) less than 2% of patients with BC are infected with HPV, and Larue (1995) reported more than 35%.

- **Medications** (cytostatics and analgesics). Patients with Hodgkin's or non-Hodgkin's lymphoma,treated with high-dose cyclophosphamide have a higher risk of developing BC. Lately, drugs have been used to protect the bladder from irritation, reducing the risk of bladder cancer. Prolonged use of analgesics containing phenacetin (a chemical-like substance in aniline dyes) is associated with an increased risk of transient cell carcinoma of the renal pelvis and bladder (Piper, 1985).
- **Urinary tract disorders**:
  - Bladder stones
  - Leukoplakia of the bladder mucosa
  - Chronic urinary retention (prostate adenoma, urethral strictures, chronic infections)
  - Benign tumors (papilloma, adenoma).
- **Genetic factors**. The association of BC with the genetic polymorphism of enzymes such as glutathione S-transferase (GST) and N-acetyl transferase (NAT) has been extensively studied. GST is involved in detoxifying polycyclic aromatic hydrocarbons in tobacco smoke. The enzyme NAT 2 has an active role in the inactivation of aromatic amines. "Fast" and "slow" acetylation indicate the rate at which it is able to inactivate carcinogens in the environment.

Diagnosis of bladder cancer

Clinical anamnesis

The characteristic clinical symptoms of BC are the following:

- **Hematuria** is the most common symptom of bladder cancer, present in 85% of patients. It can be painless, often intermittent. The intensity of the hematuria does not depend on the size of the tumor and the type of growth and may remain the only symptom throughout the clinical course.
- **Pyuria** is rarely found as an isolated sign, but its presence betrays infiltrative tumors, ulcerated, necrotic, with associated suppuration, which often directs the doctor to another diagnosis: urinary tract infection, stones.
- **Polachiuria** occurs in ≈20% of patients with BC, more frequently in infiltrative forms, which diminishes the capacity and suppleness of the organs, is a sign of a late stage in the evolution of bladder tumors.
- **Dysuria** occurs when the tumor is located in the bladder neck, or

infiltrates the bladder neck, or it can occur when the papillary tumors or tumor fringes engage in the neck during urination. Cervical or plunging tumors in the neck may reproduce all obstructive symptoms induced by prostate adenomas.

- **Pelvic pain** is manifested in 5-20% of patients, when the tumor infiltrates the pelvis or metastasizes to the pelvic bones, may be spontaneous or triggered by urination, may have irradiation in the perineum, rectum, glans.
- **Tumor cystitis** is the characteristic syndrome of advanced bladder tumors with late onset, resulting from tumor invasion in adjacent structures, reduced bladder volume and parietal neoplastic infiltrations. In this phase, the frequency of tumor cystitis exceeds 50%, differing from cystitis of other etiology by the predominant hemorrhagic character and the tenacity of pain, resistant to treatment.

BC-induced cystitis in all cases is associated with severe chronic infections. The mechanisms of carcinogenesis are not elucidated, but probably the cause is the formation of nitrites and nitrates in the bladder, as a result of the metabolism of normal components of urine and microorganisms.

Chronic cystitis and other urinary tract infections. Chronic cystitis (CC) in the presence of urinary catheters or stones is associated with an increased risk for squamous cell carcinomas of the bladder (Locke, 1985). Between 2% and 10% of long-term urinary catheter paraplegias have led to the development of BC, of which 80% are pavement.

Physical examination involves rectal or vaginal touch with palpation of the abdomen.

Paraclinical and laboratory investigations

Imaging investigations:

Simple reno-bladder radiography and urography. The bladder tumor looks like a gap in the radiological image. Infiltrative tumors induce changes in the bladder wall, which becomes rigid, inextensible, retracted in pathological areas. Indirect images such as ureterohydronephrosis or mute kidney as a result of invasion and obstruction of intramural ureters induced by solid, infiltrative tumors can also be identified.

Bladder ultrasound diagnoses BC in 80% of cases. Being a cheap and affordable method, USG is frequently used, is a painless, non-invasive

procedure, does not cause side effects, has no contraindications and can be repeated as many times as needed (*see Fig.* 1).

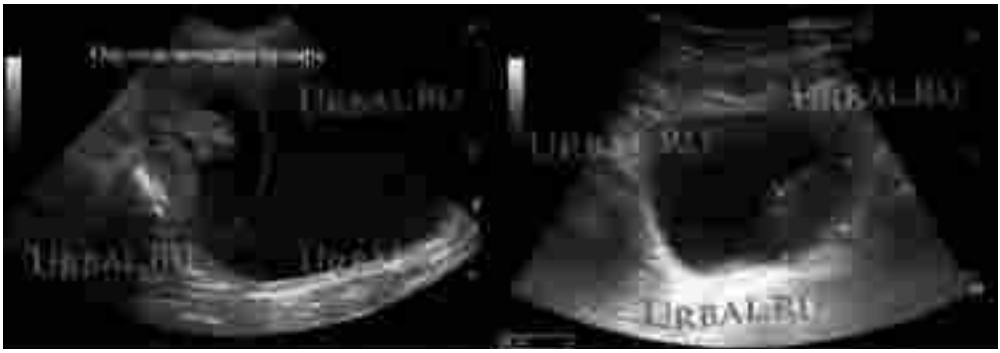

Fig.1. *Bladder ultrasound*

CT is used to determine the size of the tumor and to identify the extension to the lymph nodes. Computed tomography diagnoses up to 85% of tumors and about 90% of pelvic lymphadenopathy (see Fig. 2).

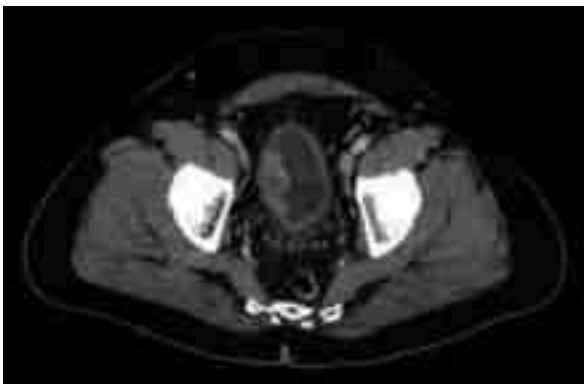

Fig. 2. *CT of the bladder*

MRI - offers several advantages over CT: the tumor tissue is better differentiated from the normal bladder wall, the examination in several planes, the lymph nodes are better individualized, being different from the blood vessels and it is not necessary to administer i.v. of contrast agents.

Both methods (CT and MRI) allow the correct differentiation of infiltrative tumors up to T3 from those with extravesical extension T3b-T4a-b. MRI gives better results, compared to CT, in the detection of regional lymphadenopathy: g / l with a diameter greater than 1.0 cm, almost always invaded by tumor, but also g / l with a smaller diameter, considered reactive, with micrometastases.

Bone scintigraphy is used to identify distant bone Mts, showing bone metastases 9-12 months earlier than their obvious expression on standard radiographs.

Angio-CT - is the standard imaging method for the evaluation of patients with hematuria, as well as patients with infiltrative bladder tumor. The examination is performed by administration of iodinated nonionic contrast agent and capture of precontrast, postcontrast and excretory images. In the post-contrast phase, the lesions of the urothelium are identified, as well as the visceral or adenopathic metastatic masses. In the excretory phase, there are defects of opacification in the urinary tract and delay or absence of opacification of the urinary tract in the context of obstruction (ureterohydronephrosis).

Endoscopic investigations:

Cystoscopy is the fundamental, mandatory and indispensable examination for the diagnosis of bladder tumors, regardless of clinical form and stage, and is recognized by all specialists.

Cystoscopy allows the following clarifications:

- presence of bladder tumor;
- location of the tumor on the endovesical wall;
- the dimensions of the exophyte portion;
- the appearance of tumor fringes;
- number in case of multiple tumors, their distribution;
- location of the ureteral meatus, trigone and bladder neck;
- detection of possible tumors in the prostatic urethra;
- the general appearance of the endovesical mucosa (*see fig.* 3).

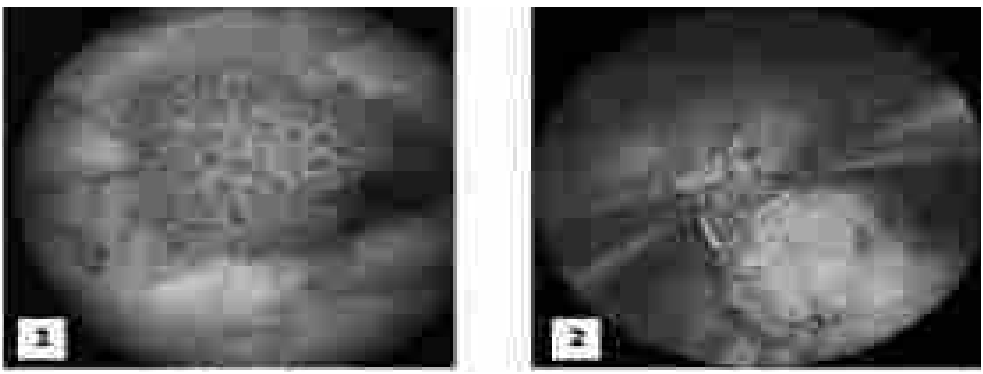

Fig. 3. *Bladder cancer*

Bladder biopsy involves taking cells or tissues for examination under a microscope. The analysis of the cells from the harvested tissue can establish both the diagnosis of the neoplasm and its staging. Bladder cancer biopsy is usually done during cystoscopy.

A study of photodynamic diagnosis (PDI) performed with violet light after intravesical administration of 5-aminolevolenic acid (ALA) and hexaminolevolenic acid (GALA) showed that biopsy and fluorescence-mediated resection are more sensitive to malignant tumors. especially in carcinoma in situ, than in standard manipulations. PDI is recommended for patients with suspected highly differentiated latent tumors, for example, to control biopsies in patients with positive IQ results or the presence of a tumor with a high degree of malignancy in history. The additional costs of FDI equipment need to be taken into account.

In 75-85% of cases, the early diagnosis of superficial UB is established. In 95% of cases these are urothelial carcinomas. Monitoring of patients after RTU-V showed that in 50-70% of patients local recurrences develop, and in 20% of cases the progression of the tumor to an invasive form is established. The unsatisfactory results of traditional endoscopy in the detection of superficial tumors and residual tumors after RTU-V have led to the need to use new diagnostic methods. Very eloquent are the studies of researchers (Korman, 1994, Klana, 1991, Mersdarfa, 1998 and Foreli, 1992) in which it was shown that in 2-6 weeks after RTU-V in 38% -63% of cases residual tumors were detected.

Differential diagnosis

Due to these complex methods of investigation, which determine not only the existence of the bladder tumor, but also the histological nature and the stage of its spread, the possibility of misdiagnosis of bladder tumor seems quite unlikely. The differential diagnosis becomes useless when the tumor, objectified by urethrocystoscopy, has been biopsied or electroresected. For the preendoscopic stage of investigation of bladder tumors, the differential diagnosis will be made with proliferative urinary tuberculosis, bladder lithiasis, prostate adenoma, hypertrophic cystitis, ureterocele, endovesical clots. In the final diagnosis, errors are made in the diagnosis of bladder tumors because clinicians are not informed and do not apply the mandatory national diagnostic protocol.

BC classification according to the TNM - AJCC system, 8th edition, 2017

T - primary tumor

Tx - primary tumor cannot be evaluated
T0 - no evidence of primary tumor
Tis - carcinoma in situ
Ta - noninvasive papillary carcinoma
T1 - the tumor invades the subepithelial connective tissue
T2 - the tumor invades the muscle
T2a - tumor invades the superficial muscle (inner half)
T2b - tumor invades deep muscle (outer half)
T3 - the tumor invades the perivical tissue
T3a - microscopic
T3b - macroscopic
T4 - the tumor invades the prostate, uterus, vaginal wall, abdominal wall
T4a - the tumor invades the prostate, uterus or abdominal wall
T4b - the tumor invades the pelvic wall or the abdominal wall

N - regional lymph nodes (g / l pelvis below the bifurcation of the common iliac artery)

Nx - g / l regional cannot be evaluated
N0 - no metastases in regional g / l
N1 - metastasizes in a single regional g / l
N2 - multiple metastases in regional g / l
N3 - metastases in common iliac g / l

M - distant metastases

Mx - the presence of distant metastases cannot be assessed
M0 - no distant metastases
M1 - distant metastases

Macroscopic forms of BC

1. Noninvasive papillary tumors
2. Invasive papillary tumors
3. Solid papillary tumors
4. Infiltrative tumors
5. Infiltrative-ulcerated tumors
6. Ulcerative tumors

Histopathological classification of BC

- ***Transitocellular (urothelial - 90% of all UB tumors).*** These correspond macroscopically to exophytic tumors, papillary and more rarely, sensory or ulcerated tumors. Exophyte tumors are usually superficial, and the second group is predominantly infiltrative.
- ***Squamous cell carcinoma*** - represents 3-7% of all bladder tumors, being often associated with bladder stones, chronic urinary tract infections or carrier of bladder catheters for long periods of time. This histological variant is common in about 8% of cases in Schistosoma Haematodium infections. Squamous cell carcinomas have an aggressive clinical course.
- ***Bladder adenocarcinoma*** accounts for less than 3% of all bladder tumors. Primitive bladder adenocarcinomas may be preceded by periods of cystitis and urothelial metaplasia and may secrete mucus with a glandular or colloidal structure. Very often, at the time of diagnosis, bladder adenocarcinomas are already invasive in the muscular tunic. The prognosis is unfavorable, although the treatment is very aggressive.
- ***Undifferentiated carcinomas*** are relatively rare tumor lesions, representing about 2% of all bladder tumors, characterized by the lack of mature cells in the tumor, but the predominance of very aggressive small cells.

The degrees of tumor differentiation are:

G1 - highly differentiated, with low degree of malignancy
G2 - moderately differentiated, with low degree of malignancy
G3 - poorly differentiated, with a high degree of malignancy

Metastatic pathways

1. ***The direct local extension*** is made to the ureteral meatus, bladder neck, prostate, seminal vesicles, paravesical fat, peritoneum, pelvic vessels and iliac vessels.
2. ***Lymphatic*** - most often metastases in g / l peri- and retro-bladder, hypogastric, obturator, external and internal iliac, lumboaortic.
3. ***Hematogenous*** - in the bloodstream, with a frequent incidence in the pelvic bones and lumbar vertebrae, lungs, liver.

CVU treatment

Recommended methods for the treatment of superficial tumors of VU (stages T0, T1) are:

1. Transurethral resection of the tumor
2. Instillational treatment with BCG or cytostatics
3. Transvesical electroresection
4. Laser vaporization
5. Other interventions (radical, partial cystectomy)

Endoscopic treatment of bladder tumors

Transurethral resection of bladder tumors (TUR-V) is an endoscopic therapeutic procedure used to completely remove the bladder tumor, but it also provides information needed for diagnosis and staging. Surgery is performed under spinal anesthesia, but in cases of bulky tumors, especially those located on the sides, a general anesthesia is preferred to reduce the risk of obstructive reflex. In some cases it is used to cut the obturator reflex by ultrasound-guided injection of 1% Lidocaine - 20.0 ml and block the normolateral obturator nerve.

From a technical point of view, there are three possibilities for endoscopic resection:

1. Resection based on monopolar cauterization;
2. Resection based on bipolar cautery, with or without thermal vaporization;
3. Laser resection allows intervention in patients whose anticoagulant treatment cannot be interrupted.

Treatment of T0, T1 lesions.

The parameters with prognostic value for recurrence, in descending order are:

- Number of tumors present at the time of diagnosis;
- Recurrence rate: a recurrence every 3 months;
- Tumor size: a large tumor has a higher chance of recurrence;
- Degree of anaplasia.

For the evolution to infiltration, the G and T elements are the most important. Tumors of the bladder neck have a poor prognosis, recurring at 5 years (21%).

Superficial bladder tumors (TVS) are divided based on prognostic factors into:

1. low-risk tumors: single, Ta, G1, less than 3 cm;
2. high risk tumors: T1G3, multifocal or with multiple recurrences, Cis;
3. intermediate: all other tumors Ta-1, G1-2, multifocal over 3.0 cm.

An instillation with cytostatics (epirubicin or mitomycins) less than 6 hours after TUR for TVS decreases the recurrence rate by 50%.

Transurethral resection. Method of choice in the treatment of superficial bladder tumors is transurethral endoscopic resection (TUR-V).

Through the collected tumor specimens, the endoscopic resection allows to obtain the definite diagnosis of malignant tumor, the evaluation of the depth of the parietal invasion - T, therefore the radicality of the resection and the establishment of the histological grading of malignancy - G.

Other benefits of endoscopic resection in the treatment of superficial bladder tumors are:

- convenience for both the patient and the surgeon, especially when performed with video monitor control;
- is well tolerated by the patient;
- excludes the parietal wound with all the complications that derive from it (pain on mobilization, suppuration, dehiscence, fistulas, tumor insemination on the suture tranche, unnoticed tumor arrears, etc.);
- rapid postoperative recovery, allows early mobilization of the patient.

The limits of transurethral endoscopic resection are given by:

- impossibility of passage through the urethra (strictures, false pathways, large prostate tumors, etc.);
- location of the tumor in a hard to reach area (anterior bladder wall in the immediate vicinity of the bladder neck);
- tumor located in the bladder diverticulum (high risk of perforation);
- association of the tumor with other lesions (multiple or voluminous bladder stones);
- pacemaker wearer (risk of heart failure).

TURV complications can be:

- Post-TUR syndrome
- Urinary infection
- Massive bleeding
- Bladder perforation
- Incomplete tumor resection.

A rarer method in the endoscopic treatment of superficial bladder tumors is based on the use of medical LASER, namely vaporization of tumors with LASER.

The advantages of this method are the possibility of performing low-dose analgo-sedation, the use of a finer instrument, which less traumatizes the mucous membranes and the performance of hemostasis while vaporizing the tumor, which would minimize the possibility of hematogenous

dissemination of tumor cells. The most used LASER is Neodymium-YAG. The major disadvantage of this method is the impossibility of collecting a tumor specimen for histopathological examination.

Radical cystectomy

Radical cystectomy is the treatment of choice for locally advanced and infiltrative bladder tumors (see Fig. 3).

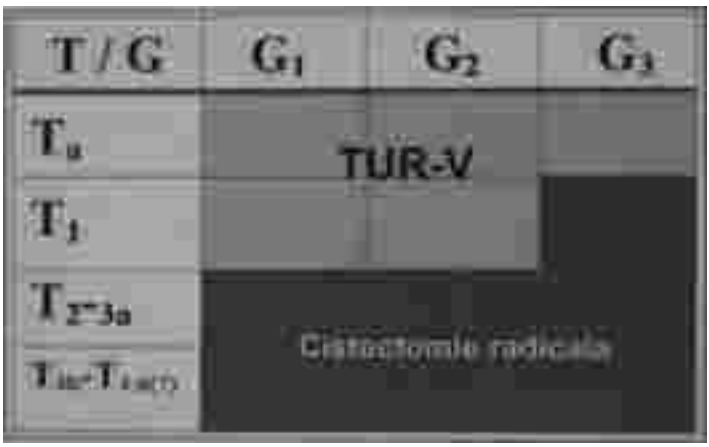

Fig. 3. *Indications for radical cystectomy*

Radical cystectomy involves the removal of the entire bladder, nearby lymph nodes (lymphadenectomy), a portion of the urethra and nearby organs that may contain cancer cells: a) in men - prostate and seminal vesicles, b) in women - uterus , fallopian tubes, ovaries, anterior vaginal wall.

Bricker derivation

Fig. 4. *Bricker type shunt*

Ileal shunting (Bricker) is a commonly used method for redirecting urinary flow after cystectomy (see Fig. 4). The operation involves inserting an isolated ileal intestinal segment between the ureters and an abdominal skin hole.

The advantages are:

1. Protecting the kidneys from ascending infection, from the external environment, which is a advantage over cutaneous ureterostomy.
2. The intestinal segment that opens to the surface of the abdominal skin ensures a rapid evacuation of urine, low pressure in the reservoir, the absence of reflux. One hole in the abdominal skin is easier to care for than two holes. The broad lumen of the cutaneous stoma is less prone to stenosis than the ureterostomy orifice.

Studer derivation (Neobladder)

In 1989, Studer presented the clinical results of a new technique for performing an orthotopic ileal neovesis. It is made of an ileal segment of about 60 cm isolated 25 cm proximal to the ileocecal valve.

The ileum is sectioned on the opposite to mezenteric border in its distal portion, on a length of 40-45 cm, the initial portion of 15-20 cm, remaining intact. The intact proximal portion is rotated 180 degrees anteriorly in the axis of the mesentery, becoming retroperitoneal. The detubularized portion is aplicated and the medial walls are sutured, building the posterior wall of the neovesis.

A 1 cm incision is made in the sloping part of the reservoir and an anastomosis is performed with the urethra (through 5-6 sutures) after the installation of a urethral catheter. The ureteroileal anastomosis is performed by the Bricker technique on the isoperestatic ileal segment.

Urethral implants are protected with externalized stents through the bladder and abdominal wall. The postoperative capacity of the tank initially varies between 150-250 ml, reaching after 6 months 450 ml, an intraluminal pressure of 20-40 cm H2O.

Postoperative complications are rare, their intensity depending on the length of the tank.

An ideal tank has the following characteristics:

- large capacity;
- storage of urine at low pressure;
- protection of the upper urinary tract from obstruction and reflux;
- absence of major metabolic disturbances.

Complications

Complications of urinary tract are:

1. Metabolic (acidosis);
2. Reconstruction of the urinary tract;
3. Infectious;
4. Nutritional and gastrointestinal;
5. Carcinogenesis.

After the reconstruction of the urinary tract, the complication rate is 19.7–55.9%. Intestinal and uretero-intestinal anastomosis are the weak points of the intervention. In the long run, the biggest problems are related to the stoma. Incontinence may occur in patients with continental reservoirs.

Early complications:

1. urinary fistula (nephrostomy is used);
2. infarction of the duct or neovasis;
3. stenosis of the uretero-intestinal anastomosis (ureterohydronephrosis).

Late complications:

1. Complications of the stoma - 15-45%. Dermatitis of the peristomal skin, as a result of the action of alkaline urine. Bleeding. Stenosis of the stoma.
2. Parastomal hernias. More often in the colonic ducts.
3. Uretero-intestinal obstructions. They occur in 8-18% of cases. (ureterohydronephrosis, dysfunctional kidney, ischemia and fibrosis, inadequately drained, infected urine collection, calculus).

Infectious. The increased incidence of bacteriuria in these patients may be explained by the inability of the intestinal mucosa to inhibit bacterial proliferation (as opposed to urothelium):

- Pyelonephritis
- Sepsis
- Kidney failure due to bacteriuria

Nutritional and gastrointestinal.

Early postoperative intestinal complications:

- Complete dissolution of the anastomosis, fistula
- Sepsis secondary to an undrained collection
- Persistent obstruction of the anastomosis
- Urinary fistula.

Late:

- diarrhea and steatorrhea
- vitamin B12 deficiency
- cholelithiasis
- urolithiasis

BC treatment

Adjuvant treatment

Theoretically, T1 papillary superficial bladder tumors can be radically cured by RTUV. However, ≈50% recur in the first 5 years after resection of the primary tumor and 80% in the next 10 years.

Frequently, recurrences have a more aggressive evolution than the primary tumor, towards invasion and / or metastasis. The treatment of superficial bladder tumors, apart from RTU, involves, in most cases, a therapeutic method that aims to:

1. prevention of recurrences;
2. prolongation of the time interval until the occurrence of recurrences;
3. possibly decreasing the grading.

The adjuvant treatment is varied and includes: systemic and instillational chemotherapy, instillational immunotherapy, intravesical chemo-immunotherapy, oral immunotherapy and radiotherapy.

Systemic treatment

- ***Systemic chemotherapy*** is indicated for the treatment of advanced or metastatic disease. The most effective cytostatics proved to be Cisplatinum, which, when used separately, gave favorable results in about 30% of cases. Over time, it has been included in almost all regimens, in various combinations. The most commonly used combinations in the treatment of TVS were: MVAC (methotrexate, vinblastine, adriamycin and cisplatinum) and CMV (cisplatinum, methotrexate and vinblastine).
- In patients with platinum-refractory urothelial cancer, ESMO recommends ***immunotherapy with inhibitors*** of immune response checkpoints (anti-PD-1 or anti-PD-L1 therapy):
  - Pembrolizumab. Data from a randomized phase III clinical trial with KEYNOTE-045 are available

Pembrolizumab has been shown to be the only drug with a significant

increase in the overall survival rate of platinum-refractory urothelial cancer patients (level of evidence 1, recommendation A);

- Atezolizumab. Phase III randomized clinical trial with IMvigor211 and a number of Phase I-IV studies, including an actual practice study with SAUL (test level 2, recommendation grade B);
- Nivolumab. The Phase II CheckMate 275 study evaluated the activity and safety of the PD-1 inhibitor nivolumab and demonstrated its efficacy (level of evidence 3, recommendation grade B);
- Avelumab or Durvalumab. Phase Ib and I / II studies (proof of confidence level 3, degree of recommendation C). However, experts note that at the date of the most recent working group meeting on 22 August 2019, both medicines were not approved for use by the European Medicines Agency (EMA).

Intravesical treatment

Intravesical chemotherapy. Recurrences occur in 60-80% of patients operated for superficial bladder tumors, presumably due to the implantation of neoplastic cells in the urothelium during resection. Based on this hypothesis, the concept of post-TUR-V intravesical chemotherapy was developed. It is used for stages Ta and T1 with an excellent 5-year survival rate (90%).

The indications for intravesical therapy are as follows:

1. Multiple primary tumors
2. Multiple tumor recurrences
3. Large tumor grading - G3
4. T1 stage tumors
5. Post-TUR-V positive urinary cytology
6. Dysplasia or Cis in randomized biopsies.

Aims of intravesical therapy:

1. Prevention or delay of recurrence
2. Eradication of the possible presence of residual microscopic cancer or Cis
3. Prevention of tumor progression
4. Reduction of indications for radical cystectomy
5. Maintaining quality of life or prolonging life.

The most commonly used substances for this type of chemotherapy are: Mitomycin C, Doxorubicin, Epirubicin.

Bladder immunotherapy

The first experience in the treatment of intravesical instillation with Calmette-Guerin bacillus (BCG) for bladder tumors was published by Marales in 1976. At present, BCG therapy is adjunctive therapy for cases of non-invasive muscle tumors with intermediate risk (G2) or increased (G3) in order to reduce the rate of recurrence or tumor progression. BCG therapy is superior for reducing the recurrence rate ≈40% and also has the effect of reducing the rate of tumor progression ≈27%. Compared to patients who underwent only RTU-V, patients who also benefit from instillational therapy with BCG have a 40% reduction in tumor recurrence rate, and can be considered the first-line therapy for superficial bladder tumors.

Bladder immunotherapy has shown clearly superior results in the treatment of superficial bladder tumors, regardless of stage. The most commonly used medications are: BCG (Calmette-Guerin Bacillus), interferon and IL-2 (interleukin-2).

Indications for BCG therapy:

1. Prophylaxis of recurrence and progression of the tumor after surgery
2. Cis treatment
3. Ablative therapy of residual or multifocal disease

BCG contraindications. BCG treatment is contraindicated in patients with active tuberculosis, women who are breastfeeding, in the presence of other carcinomas - Hodgkin's disease, leukemia, HIV.

PROSTATE CANCER

Epidemiological-geographical features

Prostate cancer (PC) is a malignant disease, being one of the most common cancers in men over the age of 50, accounting for ≈21% of male cancers and ≈10% of deaths from malignancies. among men. PC is the second leading cause of cancer death after lung cancer. A total of 600,000 cases of PC are reported worldwide each year.

Prostate cancer is the most common type of cancer among the male population in Europe and ranks third in the structure of cancer. In 2012, approximately 417,000 new cases of cancer were diagnosed, of which PC accounted for 12% of the total number of cases [1]. Castration-resistant prostate cancer (CRPC) is the second leading cause of death from malignancy in males [2].

Prostate cancer usually progresses slowly, often occultly. Many patients die from other conditions before these cancers appear clinically and are occasionally detected by a morphopathologist at autopsy.

Ethiopatogenesis

The etiology of PC has not yet been elucidated, but there is indisputable evidence to suggest that genetic and environmental factors play an important role in the appearance and evolution of the tumor. At least 4 groups of factors responsible for the occurrence of PC are highlighted:

Genetic factors. Some PCs may be genetically inherited. Men who have had a first-degree relative diagnosed with PC have a double risk of developing prostate cancer, while the presence of two or three such patients in the family increases the risk by 5 or 11 times, respectively.

Hormonal factors. The appearance of PC and its evolution are certainly influenced by androgen hormones. In men whose total testosterone is above 50% of the average level, the risk of developing prostate cancer is 2.34 times higher (Wilding G., 1995).

Dietary factors. Diet plays an important role in the development of prostate cancer. Several epidemiological studies have shown that there is a relationship between a high-fat diet and the occurrence of PC. These foods also have a high concentration of calcium and zinc. Excess calcium can be a contributing factor to PC.

According to some researchers, selenium, vitamin E (α-tocopherol) and lycopene (carotenoid with a strong antioxidant effect, present in tomatoes) can reduce the incidence of PC by 30-40%. Soy isoflavones (a food widely used in the Asian diet) and green tea have the same role. Higher levels of vitamin D in the blood can prevent the onset of PC, and excess vitamin A can increase the risk of developing this type of cancer.

Infectious factors. According to many researchers, infectious agents of a microbial and viral nature can be the cause of PC.

Pathogenesis. Almost all cases of PC are adenocarcinomas, which develop from prostate acinar cells. The prostate normally atrophies between the 5th and 7th decade of life. Malignant transformation has been found to occur in these atrophic and postatrophic glands. At the same time, multiple atypical and hyperplastic changes take place in the prostate.

According to pathological studies, prostate cancer has a long period of asymptomatic development. It sometimes takes several decades for a clinical manifestation to form. According to Sakr W. A. et al., Small outbreaks of histological cancer were found in 27% of men in their 40s and 34% in men in their 50s. According to researchers Breslow N. et al. (1977) and Barry M. J. (2001), prostate cancer occurs in 60% -80% of men over 70 years and only 0.1% of people under 50 years. The great urologist surgeon E. Proca said: if men lived 120 years, they would all get prostate cancer.

According to the location, 70% of the PC develops from the peripheral area, 15-20% from the central area and 10-15% from the transitional area. Most prostate cancers are multicenter.

Prostate cancer diagnosis

Clinical anamnesis

In the early stages, prostate cancer is asymptomatic. Due to the fact that most adenocarcinomas start at the periphery of the prostate gland, the local symptoms of PC usually appear late. The presence of symptoms and signs already betrays the advanced local stage of the disease or even the metastatic stage.

Local ***clinical manifestations*** are represented by:

a) obstructive symptoms, manifested by: decreased strength of the urinary stream, difficulty in starting urination, interrupted urinary stream, which gradually lead to:
   - incomplete urinary retention without bladder distension;
   - incomplete urinary retention with bladder distension;
   - complete urinary retention;
   - false urinary incontinence due to "too full" (ischuria paradoxa).

Dysuria is caused by tumor infiltration of the bladder neck, which, once it appears, becomes permanent, progressive and without remissions.

b) irritative symptoms, manifested by: nocturnal and diurnal pollakiuria, urinary urgency. These symptoms are caused by the direct influence of the tumor near the neck and bladder triangle, but also indirectly by changes in the detrusor in the face of the cervicoprostatic obstruction.

c) hematuria is relatively rare and indicates neoplastic invasion of the trigone or complications following bladder distension.

d) hemospermia, decreased ejaculate sperm volume or impotence are consequences of local tumor progression in the ejaculatory ducts and neurovascular bands in the vicinity of the prostate.

e) locoregional pain, rarely encountered, is manifested by stings, foreign body sensations or frank pain, located in the perineum, rectum, with irradiation to the hypogastrium or penis. It occurs in the late, extracapsular, invasive stages in the surrounding tissues.

General clinical manifestations. As with other neoplastic diseases, patients with PC have associated general symptoms: loss of appetite, irritability, asthenia, adynamism. Depending on the location of the metastases, different clinical manifestations may occur:

a) bone - lumbar or pelvic pain, anemia due to bone marrow damage;

b) lymphatic - edema of the lower limbs by compression of the iliac veins with or without deep thrombophlebitis;

c) hepatic - pain or obstructive jaundice in hepatic mts;

d) cerebral - headache, intracranial hypertension syndrome.

Other symptoms, such as nausea, vomiting, low back pain, occur in bilateral ureteral obstruction with the onset of acute renal failure.

Paraclinical and laboratory investigations

Rectal palpation (RP). Rectal examination is a common clinical procedure of urological examination that can provide valuable information for the diagnosis of prostate cancer. PC is usually located in the peripheral

area and is accessible for clinical examination. TR clinically identifies about 50% of prostate tumors (volume over 0.2 mm).

According to the data presented by some researchers, the prostate puncture-biopsy indicated on the basis of RT had a positive histological result in ≈40% of cases. The positive predictive value (PPV) of TR is dependent on the PSA level, as follows:

PSA - 2.5-4.0 ng / ml, PPV - 22-30%,
PSA - 4.1-10.0 ng / ml, PPV - 41%,
PSA> 10 ng / ml, PPV - 69%.

Prostate specific antigen (PSA). PSA was first identified and characterized by Wang et al. in 1979 as a glycoprotein monomer with a protease activity with a molecular weight of approximately 30 kDa and 237 amino acids, after which it was widely implemented in the diagnosis of prostate cancer.

PSA is a glycoprotein-serine protease produced exclusively by prostate epithelial cells. PSA is a specific organ marker, but it is not specific for prostate cancer, with elevated levels in other prostate conditions such as benign prostatic hyperplasia, prostatitis or other non-malignant conditions. PSA reference values are:

a) 0-4 ng / ml - Standard;
b) 4-10 ng / ml - "gray" area, suspected PC;
c)> 10 ng / ml - pathological values. PC probably, positive predictive value - 50-80%.

To improve the specificity of PSA in early diagnosis and therapeutic monitoring in PC, other serum PSA indices have been introduced:

a) PSA density (PSA density), refers to the ratio between the PSA level and the prostate volume. The PSA value increases by approximately 0.12 ng / ml per gram of BPH tissue. The value of this index is controversial. Deficiencies are related to individual variations in PSA production and errors in calculating prostate volume (25%);
b) PSA velocity index (PSA velocity), refers to the rate of increase of the serum PSA level. Patients with PC show a rapid increase in PSA levels before diagnosis. A PSA rate of 0.75 ng / ml / year indicates an increased risk of developing PC;
c) molecular forms of PSA. Approximately 90% of PSA circulates in the protein-bound blood of alpha-1-antichymotrypsin. A smaller fraction is the alpha-2-macroglobulin-bound and free PSA forms of PSA. The ratio of free PSA to total PSA can differentiate between prostate cancer and benign hypertrophy.

PCA3 (Prostate Cancer gene 3). Recently, more and more cases of PC are found in patients with normal PSA levels and vice versa, there are a large number of negative results in PBP prostate biopsies-punctures in men with high PSA levels. Urine PCA3 gene assay is a new test with greater accuracy in detecting PC. PCA3 analysis can reduce the number of unnecessary biopsies. Prostate cells have been found to contain PCA3 genes, which are the basis for the synthesis of a particular type of protein, which they produce in greater amounts than other cells in the body. When the level of PCA3 protein is increased, it is detectable in the urine. In over 90% of prostate tumors, overexpression of the PCA3 gene occurs in tumor cells, with 60-100 times higher levels of PCA3 RNA than normal prostate cells.

Prostate biopsy. PC is suspected by clinical examination (TR), PSA and TRUS. The definite diagnosis is established anatomopathologically and is mandatory before starting therapy. Fine needle aspiration cytology, prostate biopsy-puncture or examination of the endoscopic resection of the prostate TUR are used.

Imaging diagnosis

Imaging investigations play a very important role in completing the diagnosis of prostate cancer, for the correct staging and for planning the treatment strategy.

Transrectal ultrasound (TRUS) is an ultrasonographic technique that can assess the appearance, size of the prostate and the relationship with adjacent tissues (see Fig. 1). Transrectal ultrasound examination allows:

a) imaging identification of suspicious lesions;

b) improving the accuracy of prostate biopsy.

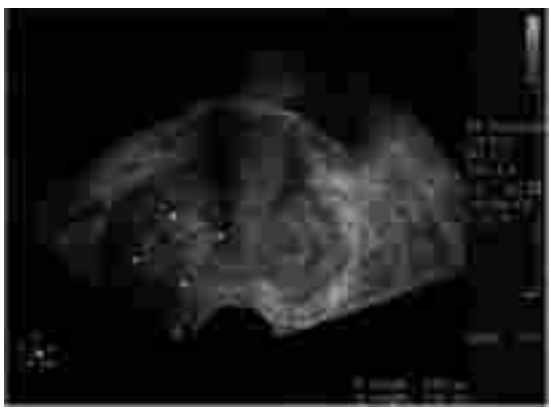

Fig. 1. *TRUS Prostate Cancer*

The classic image of hypoechoic lesions located in the peripheral area of the prostate is not always present, but in over 30% of cases the lesions are noted ultrasound as isoechoic areas, being detectable only by systematic biopsies. Elevated PSA levels, palpable lesion on TR or ultrasound detected (TRUS) are indications for prostate biopsy. All three indices present make the biopsy rate positive in 56-72% of cases.

Standard radiography is useful in confirming lesions suspected to be bone metastases found on bone scintigraphy. Thoracic-pulmonary radiography is required to stage the process. Often the diagnosis of metastatic PC is established on the basis of standard radiographs performed for other conditions, detecting specific bone or lung lesions.

Computed tomography (CT) has not proven its potential to distinguish architectural changes inside the prostate, although it can detect changes in its size. CT is not recommended as a routine examination in newly diagnosed PC staging.

Magnetic resonance imaging (MRI) is a complex and highly accurate method that allows a better view of the boundaries of the gland and tumor. It is often used for the correct staging of the disease in order to determine the appropriate treatment.

The Prostate Imaging-Reporting and Data System (PI-RADS) is used to evaluate prostate lesions in patients with clinical suspicion of prostate cancer to determine if a biopsy is required. The evaluation of the prostate according to the PI-RADS criteria uses a five-point scale that indicates the probability that a combination of predefined MRI findings correlates with the presence of clinically significant cancer (score from 1 to 5, depending on the risk of malignancy, where 1 - more likely benign, and 5 - highly suspected of malignancy). The PI-RADS score is applied for each lesion identified in the prostate gland. An extremely useful quality of MRI is its high negative predictive value for clinically significant cancer, which means that men with a negative test result can avoid unnecessary biopsies. In practice, a binary model of classification of MRI results was introduced - negative or positive, to determine the need for biopsy. Results with PI-RADS score 1 and 2 were defined as negative, and those with PI-RADS score 3, 4 or 5 - positive. For the detection of clinically significant prostate cancer, it has been shown that this binary model for evaluating MRI results has a high sensitivity (0.91; 95% CI: 0.83, 0.95) and low specificity (0.37; 95 CI %: 0.29, 0.46). False-positive results have been shown to occur

predominantly in PI-RADS scores 3 and 4, and less so in PI-RADS 5 lesions.

Bone scintigraphy (BS) is a very sensitive method for detecting skeletal metastases, superior to standard radiographs, serum alkaline phosphotase levels, and clinical examination. PSA has been shown to be a direct factor proportional to the presence of bone metastases. As a result, for patients with PSA levels below 20 ng / ml, bone metastases can be ruled out with a probability of 99.2%, and in cases with PSA <10 ng / ml, with a probability of 99.5%.

Due to its high sensitivity, this method often gives false positive results, managing to detect not only metastases, but also old fractures, arthritis, bone infections and a lot of other inflammatory bone diseases.

PC classification according to the TNM - AJCC system, 8th edition, 2017

T - primary tumor

Tx - primary tumor was not evaluated
T0 - there is no evidence of primary tumor
T1 - clinically inapparent tumor, impalpable, undetected by imaging investigations
T1a - the tumor discovered accidentally histologically, affecting a maximum of 5% of the resected prostate tissue
T1b - tumor discovered incidentally histologically, affecting more than 5% of resected prostate tissue
T1c - tumor discovered by prostate puncture-biopsy (performed to detect elevated PSA values)
T2 - tumor limited to the prostate
T2a - tumor limited to a single prostate lobe
pT2a - tumor of interest ½ or less from a prostate lobe
T2b - the tumor affects more than ½ of one lobe, but does not affect both lobes
pT2b - unilateral tumor involves ½ from one lobe and more
T2c - the tumor affects both prostate lobes
pT2c - tumor spread in both lobes
T3 - extracapsular enlarged tumor
T3a - extended tumor extracapsular (sometimes bilateral)
pT3a - extended extracapsular, determined microscopically

T3b - the tumor involves the seminal vesicles
pT3b - the tumor invades the seminal vesicles
T4 - the tumor is fixed or invades adjacent structures other than the seminal vesicles
pT4 - the tumor invades the rectum, the anal lift muscles and / or is fixed to the pelvic wall

N - g / l regional

Regional Nx - g / l could not be evaluated
N0 - no metastases in regional g / l
pN0 - regional g / l are not affected
N1 - metastases in regional g / l
pN1 - metastases in regional lymph nodes

M - distant metastases

M0 - no distant metastases
M1 - distant metastases present
pM1a - non-regional metastases in g / l
M1b - bone metastases
M1c - distant metastases with different locations

Histopathological classification of PC

Histological PC is divided into: Adenocarcinoma; Cr transitocellular; Cr pavements.

By **degree of cell differentiation** (G): G1 - well differentiated; G2 - differentiated environment; G3 - poorly differentiated; G4 - anaplastic.

The Gleason classification takes into account the degree of histological differentiation G and how the tumor grows. There are 3 main degrees:

1. Well differentiated: Gleason 2-4
2. Differentiated environment: Gleason 5-7
3. Poorly differentiated: Gleason 8-10.

Histological grading G is one of the most important prognostic factors in the clinical course of prostate cancer. Well-differentiated prostate adenocarcinomas (G1) have a favorable clinical course and a better prognosis, while undifferentiated adenocarcinomas have a better prognosis.

Metastatic pathways

PC invades local g / l generally late in the advanced stages, but aggressive forms - G3 and G4 with a Gleason score of 8-10 can cause

neoplastic lymphadenopathy in the early stages - obturator, hypogastric and iliac g / l. PC metastasizes to long, wide bones, lungs, and liver. The most common bone metastases are found in the pelvic bones, vertebrae, femur, skull bones, shoulder blade, ribs. More than 80% of these metastases are osteoblastic, the rest being osteolytic. Metastasis is made either by the perineural lymphatics or by the Batson anastomoses between the pelvic venous network and the perivertebral venous plexuses.

The presence of bone metastases is accompanied by an increase in acid phosphatases (PAPs) and prostate-specific antigen (PSA), which thus become hormonal markers for the determination of bone dissemination.

PC treatment

PC is recognized worldwide as one of the most important medical and social problems of the male population. Optimal therapy at various stages of the disease remains a widely studied topic, in terms of biological and metastatic evolutionary possibilities and, on the other hand, multiple therapeutic options, with the intention of prolonging life and improving patients' quality of life.

The general principles of PC treatment are:

1. Curative visa treatment - radical prostatectomy and curative radiotherapy;
2. Palliative visa treatment - hormone therapy, palliative radiotherapy or chemotherapy;
3. Treatment of complications - endoscopic resection of cervicoprostatic release, nephrostomy or cutaneous ureterostomy, epicystostomy.
4. Watchful Waiting

Radical prostatectomy (PR)

PR is the fundamental therapeutic option for patients in the curative stage, with a long life expectancy and good biological status.

The first radical perineal prostatectomy was performed in 1904 by Hugh Hampton Yaung. Later, in 1945, Millin popularized the extravesical retropubic approach and in 1949, together with Memmeloar, described retropubic PR. Surgery has long been unpopular due to the increased risk of specific complications: bleeding, urinary incontinence and loss of appetite.

The optimal surgical treatment for PC is radical prostatectomy - the removal of the entire prostate between the urethra and the bladder and both seminal vesicles. The retropubic or perineal surgical approach and the laparoscopic approach are used.

The indications are:

1. T1a, when life expectancy exceeds 15 years or a high degree of anaplasia;
2. T1b-T2 (standard treatment) with long life expectancy;
3. T3 - with limited unilateral extracapsular extension, Gleason score below 8 and PSA below 20 ng / ml.

Today, radical surgery can be considered a therapeutic option for patients with T3a stage with a long life expectancy, low PSA, no clinical lymph node dissection (CT) and no invasion of the seminal vesicles (MRI). Some authors have found that the survival rate with undetectable PSA at 5 years postoperatively exceeds 60% if the preoperative PSA level is below 10 ng / ml.

Radical prostatectomy combined with adjuvant hormone therapy achieves a specific survival rate of 80% at 10 years. Patients with positive lymphadenopathy on definitive histopathological examination may receive immediate adjuvant hormone therapy.

Retropubic radical prostatectomy

Retropubic radical prostatectomy involves the removal of the prostate and seminal vesicles as a whole from the periprostatoseminal cell-adipose tissue, followed by vesicourethral anastomosis. The extraperitoneal retropubic procedure allows simultaneous access to the prostate and lymph nodes, but is at increased risk of bleeding. The intervention is performed 6-8 weeks after PBP or 12 weeks after TURP, for remission of inflammatory phenomena and resorption of hematomas resulting from the previous procedure.

Laparoscopic PR. The transperitoneal or retroperitoneal route can be used.

Robotically assisted radical prostatectomy

Robotic assisted prostatectomy is surgery performed using a robotic system controlled by a doctor, through small incisions in the abdomen. The robotic system was developed by Intuitive Surgery (USA) and is a complex consisting of a console with the operator and three surgical arms connected to a three-dimensional (3D) camera and the necessary tools

for intervention: forceps, scissors, coagulation hook, etc. . Although it involves high costs, this type of minimally invasive intervention has an assured future, due to its indisputable advantages: maximum accuracy, flexibility, control, fewer risks and complications.

Complications of prostatectomy:

Early complications of prostatectomy are: deep vein thrombosis, pulmonary embolism, urinary fistula, prolonged lymphatic drainage, pelvic lymphocyte, wound suppuration, urinary tract infection, hemorrhage.

Late complications are: urinary incontinence, erectile dysfunction, urinary fistula, urethral stricture and vesicoureteral anastomosis, urinary tract infections.

Definitive radiotherapy (RD)

Definitive radiotherapy is recommended for patients who are not suspected of having metastatic disease. RD in some cases competes with PR curatively, but ensures a better quality of life.

External radiotherapy in curative doses is considered an alternative to localized surgical treatment (T1-2N0M0). Radiation fields include tumor volume, prostate, and in some cases seminal vesicles and pelvic lymph nodes. The maximum dose is 65-70Gy. The duration of treatment is 6-7 weeks. The long-term survival rate (10-15 years) without a clinically detectable tumor is 70-90%.

Patients are divided into 3 risk groups with changing doses of radiation therapy:

1. Low risk T1a-2a and Gleason score ≤6 and PSA <10;
2. Intermediate risk T2b or Gleason 7 score or PSA 10-20ng / ml;
3. Increased risk of T2c or Gleason score> 7 or PSA> 20 ng / ml.

The main prognostic factors for therapeutic benefit are Gleason score and serum PSA level before treatment. Clinically advanced local disease (T3-4N0M0). According to statistical results, the 10-year survival rate after external radiation therapy is 35%. Many authors have concluded that long-term or short-term hormone therapy is welcome before radiation therapy.

Three-dimensional external radiotherapy (R 3D)

R 3D allows to increase the doses on the target tumor tissue with the care of the surrounding normal tissues and to reduce the therapeutic toxicity: radiotherapy with nodular intensity.

Postoperative adjuvant radiotherapy is indicated for patients who are

diagnosed in the pathological stage of pT3 after radical surgery. In these cases, the local recurrence rate is estimated at 25-68%. Postoperative radiotherapy reduces the rate of local recurrence and PSA levels.

Brachytherapy is a curative therapeutic method, used in the treatment of localized PC and involves the implantation of radioactive sources in the target tissue. The aim of the technique is to generate high doses of irradiation in the prostate, with the care of the surrounding healthy tissues. In recent years, the technique of brachytherapy has been improved by the placement of ultrasound-guided, transrectal and computerized dosimetry radioactive implants.

The method was first described by Pasteau and Degrais in France, when radium needles, I125, were used.

Cryotherapy is a technique for destroying tissues affected by freezing, causing cell death by:

1. Protein dehydration and denaturation;
2. Direct rupture of the cell membrane by ice crystals;
3. Vascular stasis and microthrombosis with consecutive ischemia;
4. Induction of apoptosis.

The cryotherapy needles are placed under the TRUS guide. A temperature of -40 ° C is obtained in the central part and of the neurovascular strips.

Cryotherapy is the right option for patients up to 40 years old, with enlarged prostate glands, from the low risk group (T1a-2a, PSA <10, Gleason score <7) with a life expectancy of less than 10 years. Treatment results are inferior to radical prostatectomy.

Complications of cryotherapy: erectile dysfunction ≈80%, tissue edema - 3%, incontinence - 4.4%, pelvic pain - 1.4% and urinary retention - 2%.

Hormone treatment. Although it has no tumorigenic role, testosterone is essential in the evolution of PC. It is well known that prostate adenocarcinoma is hormone-dependent in most cases, and that 70-80% of patients with metastatic CA respond to one of the forms of androgen deprivation.

In 1941 Huggins C. et al. described the favorable effect of orhidectomy and estrogen administration on the course of metastatic disease, demonstrating for the first time the therapeutic response of PC to androgenic deprivation. Testosterone, the major circulating androgen, is produced mainly by testicular Leydig cells: 5% of circulating androgens are derived from the adrenal secretion of androstedione and dihydroepiandrosterone

(minor precursors). Although 98% of serum testosterone is protein bound, free testosterone enters the prostate cell and is converted to DHT dihydrotestosterone, the major intracellular androgen. It binds to a cytoplasmic protein receptor and the complex enters the cell nucleus, where it modulates DNA transcription.

Thus, prostate cells, including neoplastic cells, grow under the influence of DHT. Hormone treatment aims to lower the tissue level of DHT or prevent it from binding to specific receptors.

The most commonly used forms of primary androgen blockade are LHRH agonists and orhidectomy.

Total androgen blockade associates primary androgen blockade (LHRH agonists, orhidectomy) with an antiandrogen, with the suppression of both testicular and adrenal androgens in order to achieve a better and longer-lasting initial therapeutic response without significantly increasing the incidence of adverse effects. Although not curative, hormone treatment reduces the size of the prostate tumor and metastases and slows the growth rate. Hormone treatment results depend on tumor stage and grading at diagnosis, PSA level, and Gleason score.

The average survival is 30-53 months, but ≈10% of patients survive 10 years or more.

Bilateral orchidectomy is a cheap, easy procedure, well tolerated by the patient, with insignificant morbidity, the anesthesia is local or spinal. Due to its safe and immediate therapeutic efficacy, the treatment is suitable for patients diagnosed in late stages with generalized bone metastases and a significant risk of fractures or spinal cord compression. Therapeutic response is expected in 80% of cases, and the average duration of therapeutic efficacy is 4-5 years.

HRH analogues. They were recently introduced as a hormonal treatment of chemical castration in metastatic disease. The efficacy is similar to DES, but there is no risk of severe cardiovascular side effects. On the other hand, treatment is preferred to orchidectomy by most patients. The survival rate of patients treated with LHRH analogues is similar to those treated with orhidectomy.

LHRH agents are Leuprorelin, Gaserelin, and Buserelin, given monthly and at 3 months. LHRH analogs have a chemical structure similar to that of the hormone released by the hypothalamus and interfere with the feedback mechanism that controls testicular testosterone production.

Serum testosterone levels similar to orhidectomy are obtained after 21-28 days.

LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The answer is direct and fast on the release of LH and FSH and, consequently, on the secretion of testosterone, without flare-up phenomenon. But, for example, the monthly drug Abarelix has been shown to be ineffective and has serious side effects due to allergic reactions.

Antiandrogens. Suppression of androgen stimulation on the prostate remains the "test stone" in the management of locally advanced and metastatic disease. Androgenic deprivation can be achieved by castration (chemical or surgical) or by inhibiting the action of androgens in the prostate cell, by competition of androgen receptors.

Alternatively, the two treatment modalities can be combined to achieve maximum hormone suppression, called maximal androgen blockade (MAB) or complete androgen blockade (CAB).

Antiandrogens are classified into steroids (cyproterone acetate, medroxyprogeeiterone acetate) and non-steroids (nilutamide, flutamide and bicalutamide).

Non-steroidal antiandrogens: Nilutamide 150-300 mg / day. Flutamide 250 mg 3 times a day. Bicalutamide 150 mg / day.

Steroid Antiandrogens: Cyproterone Acetate - 250 mg daily, has progesterone properties that lead to the suppression of LH and testosterone production.

Combination therapies

Complete androgen blockade (CAB) has failed to demonstrate therapeutic value in the management of PC. Although numerous comparative studies have been performed with chemical or surgical castration as monotherapy, only in some have the significantly superior efficacy of CAB been argued.

Discontinued antiandrogenic treatment. Metastatic disease becomes insensitive to hormonal treatment, with increased PSA levels, on average after 2 years of treatment. Second-line endocrine therapy has a short-term clinical response in 20-40% of cases. Discontinuation of Fluzamide in patients with clinical signs of relapse under CAB provides significant therapeutic benefit for 4-6 months in one-third of patients.

This phenomenon (antiandrogenic discontinuation syndrome) is

common to antiandrogens and is the first-line therapy in case of failure of hormone therapy.

Bone complications treatment

Hormone treatment and the progression of PC increase the risk of bone complications, such as pain, fractures and spinal cord compression, with profoundly negative effects on quality of life. The following medicines are indicated:

Bisphosphonates - show significant inhibitory effects on prostate tumor cell proliferation, local invasion and the ability to metastasize in preclinical stages. Increase survival by 3-5 months.

Chemotherapy. This therapeutic method involves the use of various chemicals in order to destroy malignant cells.

Taxanes are among the most active agents in the treatment of metastatic cancer.

Prognosis of prostate cancer

The prognosis and the chances of cure depend on the type of prostate cancer, the time of diagnosis, the degree of invasion of the surrounding tissues, the general health of the patient, the body's reaction to the treatment administered.

The prognosis of PC generally depends on the spread of the process and the degree of tumor differentiation (Gleason Score). In cases of localized cancer, 10-year survival reaches 90-95%. In conservatively treated patients, the prognosis depends on the T category, the Gleason score and the PSA level until the start of treatment. After radical treatment (radical prostatectomy) the results depend on the PSA level until the intervention, the pathomorphological stage pT, the Gleason score and the presence or absence of tumor cells at the surgical edges. Indications for hormonal treatment in asymptomatic patients should be excluded. Metastatic PC treatment is palliative, as it cannot lead to the patient's healing, but it can improve his condition by cutting the pain, reducing the tumor and the level of the infravesical obstruction, prolonging the time of clinical remission of the disease. Genetically dependent forms of PC are found in 5-10% of cases and only in men younger than 55 years. These tumors usually have a low degree of differentiation and an increased Gleason score, with a lower survival rate.

Prostate cancer prophylaxis

Well-known risk factors for PC are: age, hereditary predisposition, race, diet, hormonal background, ultraviolet rays, vitamin deficiency or excess. Reducing risk factors may play a key role in PC prophylaxis.

Dietary factors play an important role in the development of prostate cancer. A diet high in meat and animal fats leads to altered cholesterol metabolism, contributing to prostate cancer. Excess calcium and vitamin A also promote PC. While selenium, vitamin E, lycopene, isoflavones, green tea, products rich in vitamin D reduce the risk of PC.

Reducing the inflammatory processes of the urogenital system reduces the risk of PC. The appearance and evolution of PC are influenced by endogenous and exogenous androgens. In men with a testosterone level increased by 5%, the risk of developing PC is 2-3 times higher. Most cells in the structure of prostate cancer are androgen-dependent and grow rapidly under the influence of these hormones. This indicates the importance of maintaining a normal androgenic background for the prevention of the given disease.

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MALIGNANT TUMORS OF THE SKIN

Malignant tumors of the skin are divided into non-melanocytic skin tumors that include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and melanocyte skin tumors that include malignant melanoma. Non-melanoma skin cancer is the most common type of cancer worldwide.

Epidemiological-geographical features

Basal cell carcinoma is the most common form of cancer, accounting for about 15-20% of all cancers, with a reduced mortality of 1 in 1,000 cases and a very low risk of metastasis of about 0.028-0.55% of cases, or no metastasis. The incidence of BCC in Australia is the highest of 3,253 new cases per 100,000 per year and in Eastern Europe - 1785 per 100,000 population. In comparison, CCS accounts for approximately 30-40% of skin cancers, with an incidence of 25 cases per 100,000 population in Europe and approximately 250 cases per 100,000 population in Australia and a mortality rate of 0.1% of all deaths. caused by cancer. BCC is more common in men than women, it can develop at any age on average to 40 years, compared to SCC which frequently affects the elderly population, with an average age of 60-70 years. BCC is most commonly found on the face - 75% on the forehead, eyelids, nose and cheeks, but also on the neck, torso and limbs. The development of SCC takes place both on healthy skin or mucous membranes 67% and on precancerous lesions 33%. It can frequently affect the cephalic extremities and genitals - 80%, back, extremities in the dorsal parts of the hands, palms, soles.

Etiopathogeny

Risk factors. The predominant risk factor for skin is UV radiation, characterized by its cumulative appearance, frequent exposure, which explains the location of this type of skin cancer in the exposed parts of the body (face, including lower lip, neck, shoulders, limbs, etc.).

Skin cancer patients were divided into risk groups: people with phototype I and II, people with white skin, people with blond hair, blue or green eyes, people working in the field, workers in metallurgy, glassmaking, farmers and fishermen. The genetic factor in the development of skin cancer is quite rare, it is more common in malignant melanoma.

Other important risk factors are ionizing radiation, chemicals such as arsenic, tar, mineral oils, aromatic hydrocarbons, potassium, etc. Recently, the action of human papillomavirus (HPV) in the development of skin cancer has been constantly discussed, especially in the mucous membranes of the mouth, nasal cavity, cervix and anal region.

X-rays and thermal radiation: these are less common factors, but they are recognized as risk factors, especially for some groups of people, such as radiologists, radiotherapists, engineers, doctors and patients treated with Grenz rays.

Skin cancer can occur on both healthy skin and pre-existing lesions - keratosis cheilitis, actinic keratoses, chronic trophic ulcers, scars, skin horn, seborrheic wart, chronic radiodermatitis, keratoacanthoma, lupus erythematosus, etc.

Skin anatomy and structure

On the outside is the *epidermis* which is composed of several cell types - keratinocytes, melanocytes, Langerhans cells. The *dermis* is the central part of the skin's supporting tissue. It consists of many collagen fibers, blood vessels that allow healing, nerve endings, hair follicles, sebaceous glands and sweat glands. The *hypodermis* is the deepest part of the skin and is made up of fat cells, which produce fat that is rich in veins and arteries. The hypodermis protects us from shocks and pressure. The skin also contains hair follicles that produce hair. Their base is sac-shaped and in the dermis. It contains the orifices of the sebaceous glands and can be lifted by the erector muscle. The skin also contains sebaceous glands that open into the hair follicle. They secrete sebum, which lubricates the skin and protects it. The nerve endings of the skin are made up of Meissner corpuscles (perceive the movements of objects on the skin), Ruffini corpuscles (perceive skin stretch), Pacini corpuscles (fine vibrations on the skin surface), Merkel discs (detect skin deformities as long as stimulation persists, and shape objects, free nerve endings: perceive temperature (thermoreception) and perception of pain (nociception).

Skin functions: protective role, tactile sensitivity, touch receptors, vitamin D production, sebum secretion.

Precancerous skin conditions

The first group includes bowenoid papulosis, Bowen's disease, Queyrat's erythroplasia and Paget's disease. These precancerous lesions are similar to "in situ cancer."

Group II includes precancerous lesions, with the potential for malignancy from 25% and in some cases up to 100%, such as: xeroderma pigmentosum, various types of dermatitis, keratosis cheilitis, actinic keratosis, cutaneous horn, keratoacanthoma, leukoplakia, and so on.

Group III is considered heterogeneous, and the precancerous conditions in this group have a very low malignant potential: hypertrophic, postoperative and keloid scars, radiodermatitis, trophic ulcer, etc.

Diagnostic methods

Clinical anamnesis

Table 1. Comparative diagnosis of BCC and SCC

	Basal cell carcinoma (BCC)	**Spinocellular cancer (SCC)**
Evolution	Slow - may take months or years.	Fast - a few months to a year
Affectation	Only skin	Skin, semi-mucous membranes and mucous membranes
Simptoms	It is often asymptomatic, itching, disconfort in the tumor, rarely local pain.	Frequently asymptomatic, pruritus, the presence of a tumor that has grown in dynamics, the presence of affected regional lymph nodes.
Macroscopic growth form	Nodular, ulcerative, mixed	Ulcerative, nodular, warty (cauliflower), ulcerous, mixed
Local skin signs	Skin lesions such as macula, papule, nodule	Any type of lesion: papule, skin nodule, various sizes and shapes, with blurred edges, with a tendency to ulceration.
Clinical forms	Nodular, Vegetative, Ulcerated, Multicenter superficial, Erythematous, Pigmented, Scar plan, Pagetoid, Sclerodermiform, Basal cell neuromatosis (Gorlin-Goltz Syndrome)	Epithelioma cuniculatum, Nodular, Ulcerative, Ulcerated, Keratosis Warty, rare forms: infiltrative type, actinomycotic, fissured, erysipiloid, erosive, cystic, squamous cell carcinomatosis.

The diagnosis of skin cancer is based on the history of the disease, its evolution over time, clinical and cytohistological diagnosis.

Physical examination

An important role in the diagnosis of skin cancer is the physical examination - inspection of the skin and tumor which may have irregular contours, various shapes and sizes, hard consistency, immobile over time, mandatory palpation of regional lymph nodes. Examination with an old magnifying glass, but the most commonly used method, to be able to accurately describe the macroscopic shape of the tumor.

Clinical-paraclinical and laboratory investigations

The laboratory test - which includes general blood tests that may indicate late-stage leukopenia and biochemical blood tests - may reveal information in the presence of distant and elevated metastases of bilirubin, ALT, ASAT, urea, creatinine, phosphatase. alkaline.

The thermographic examination method allows the assessment of the local temperature level at the level of the tumor. In the case of malignant tumors where the temperature is 2-4.5 degrees Celsius higher in the case of SCC, and in BCC it will be 1.5-2 degrees Celsius. This is due to the fact that atypical cells multiply rapidly, increasing metabolism and releasing energy, which is locally appreciated by high temperature.

Cytodiagnosis - performed by scraping in „dry" tumors or fingerprint for ulcerated forms. If regional lymph nodes are affected, we can perform aspiration puncture at this level to confirm the lymphogenic spread of the tumor process. The most effective and safe method is the histological method, performed by the method of incisional or exceptional biopsy, which gives us information about the type of tumor or its histological subtype, the degree of differentiation, the level of tumor invasion or lymphatic or vascular invasion.

Considering distant metastasis, we will perform imaging methods such as in the lungs R-fia of the chest or chest CT, and in the abdominal organs - abdominal USG, abdominal CT with / without contrast, bone scintigraphy in case of bone metastases.

Table 2. TNM classification of BCC and SCC - AJCC, 8th edition, 2017

TNM classification of basal cell carcinoma	**TNM classification of squamous cell carcinoma**
1. Primary tumor (T) Tx - the examinations performed do not allow the assessment of the extension of the primary tumor; T0 - the primary tumor is not detectable; Tissue - intraepithelial or in situ tumor; T1 - tumor up to 2 cm in size; T2 - tumor with a diameter over 2 cm; T3 - tumor that invades the maxilla, mandible, orbit or temporal bone; T4 - tumor that invades the axial skeleton (spine or has perineural invasion of the base of the skull);	1. Primary tumor (T): Tx - the examinations performed do not allow the assessment of the extension of the primary tumor; T0 - the primary tumor is not detectable; Tissue - intraepithelial or in situ tumor; T1 - tumor up to 2 cm in size; T2 - tumor with a size between 2 and 4 cm; T3 - tumor larger than 4 cm; T4 - invasive tumor (cartilage, muscle, bone);
2. Regional lymph nodes (N) Nx - the performed examinations do not allow the appreciation of the regional metastases; N0 - no signs of regional metastases; N1 - metastasis in a single lymph node, ipsilateral up to 3 cm in size; N2 N2a - metastasis in a single ipsilateral lymph node (size ≥3 cm, but <6 cm); N2b - metastases in several ipsilateral lymph nodes, all smaller than 6 cm; N2c - metastases in bilateral or contralateral lymph nodes, all smaller than 6 cm; N3 - lymph node metastasis larger than 6 cm.	2. Regional lymph nodes (N): Nx - the performed examinations do not allow the appreciation of the regional metastases; N0 - no signs of regional metastases; N1 - metastasis in a single ipsilateral lymph node up to 3 cm in size; N2 - metastasis in a single ipsilateral lymph node (size ≥3 cm but <6 cm) in several ipsilateral lymph nodes (all <6 cm) or bilaterally or in the contralateral lymph nodes (all <6 cm); N2a - metastasis in a single ipsilateral lymph node larger than 3 cm but smaller than 6 cm; N2b - metastases in several ipsilateral lymph nodes, all smaller than 6 cm; N2c - metastases in bilateral or contralateral lymph nodes, all smaller than 6 cm; N3 - lymph node metastasis larger than 6 cm;
3. Distant metastases (M): Mx - are not sufficient data to estimate distant metastases; M0 - there are no signs of distant metastasis; M1 - distant metastasis (lungs, liver, bones, etc.)	3. Distant metastases (M): Mx - are not sufficient data to estimate distant metastases; M0 - there are no signs of distant metastasis; M1 - distant metastasis

BCC and SCC complications

Nonmelanocyte skin tumors have a tendency to ulcerate associated with secretions from the tumor and the presence of a foul odor, hemorrhage, may increase in volume, the tumor becomes immobile and hard palpable.

Metastatic pathways

Basal cell cancer does not metastasize, or rarely metastasizes. Squamous cell carcinoma can metastasize to the lymph nodes in the regional lymph nodes, perineural and hematogenous into organs and tissues - lungs, bones, liver, brain, etc.

Treatment methods

The treatment of skin cancer can be radical - for example, surgical treatment can be complex and combined. But in all cases, the treatment of skin cancer will depend on the stage of the tumor.

In stage 0 and I when the tumor affects the skin superficially and locally, the most effective method is surgery . It is important to keep the excision limits of the tumor - 1.5 cm from the edge of the tumor and deep to the muscle fascia, to prevent the risk of recurrence and subsequent metastasis. Nitrogen cryotherapy, electrocautery, laser therapy, topical ointments with 5-Flouracil or Imiquimod can also be performed.

In stage II, surgical treatment is indicated, keeping the excision margins of the tumor 1.5-2 cm from the edge of the tumor and deep to the muscle fascia, and to affect its removal of the muscle fascia.

In stage III, when the tumor is larger, with local infiltration into adjacent tissues and regional ganglion metastases are present, the treatment becomes combined, consisting of: Electroexcision of the tumor with axillary radical lymphadenectomy + adjuvant PCHT, or complex treatment that includes surgical treatment + PCHTadj + postoperative RT . Cervical lymph node lymphadenectomy (Crille surgery) is characteristic of metastasis of tumors located in the head and neck region, and for tumors on the lower limbs will be performed inguinal lymphadenectomy (Duken surgery) or lymphadenectomy of the femoral lymph nodes.

For stage IV the treatment is the palliative one - by palliative chemo / radiotherapy, the symptomatic treatment, and from the surgical point of view when the tumors are located on the limbs - amputations and exarticulations will be performed .

The most successful treatment is MOHS micrographic surgery, which allows the tumor to be determined and consists of step-by-step histological analysis during surgery. It is unique in accuracy and gives a 99% chance of cure, all possible methods. The advantage of this procedure is that it can eradicate the tumor by accurately preserving healthy tissue, all performed under local anesthesia and on the same day of surgery.

In addition to conventional treatment methods, ***photodynamic therapy*** can also be used as a method of treatment - which is a combined method of treating CCS by applying a local drug - photosensitizing agent and subsequent irradiation of this tumor area, with laser light radiation or a special lamp. After applying the cream and the laser, the place will be bandaged with material to prevent light from penetrating at this level. The interaction of the photosensitizing cream and the lamp transforms the oxygen present into singlet oxygen, superoxide anion, free radicals, representing reactive substances, which ultimately have the property of locally destroying the tumor.

Chemotherapy is applied only in case of lymph / hematogenous metastasis and depending on the stage of the disease, it can be both neoadjuvant and adjuvant. The most common method of chemotherapy is systemic, very rarely using topical. Most protocols use combination chemotherapy with the following chemotherapeutics - cisplatin, doxorubicone, paclitaxel, bleomycin, 5-FU.

Radiation therapy - is a method with very good results because most histological forms are sensitive to RT and become less effective, with increasing tumor thickness and the degree of deep invasion of the tumor. The summary dose is applied from 1.5 to 2.5 Gy to the tumor.

Evolution and prognosis

The evolution of basal cell carcinomas is slow, with exceptional metastasis, a favorable prognosis but with an increased risk of recurrence. The risk of recurrence is individual, based on some forms of BCC and the treatments used. With proper treatment, the prognosis for most BCC patients is favorable. The risk of developing a second BCC is 36-50%.

The peculiarities of rapid evolution, metastasis and localization of CCS result in an unfavorable prognosis compared to BCC. Faster evolution and potential for faster metastasis are for mucosal tumors, and compared to skin tumors. As a disease it is considered as a cancer with aggressive

potential and unfavorable prognosis in the cases of stages III and IV .

The evolution of regional lymph node metastases, which have not been treated in time or radioresistant, subsequently form lymph node blocks, which infiltrate the surrounding adjacent tissues as well as the neighboring vascular-nervous bundles, the bone damage.

Skin cancer prophylaxis

Periodic examination, sun protection, consultation with a doctor in the early stages is of major importance. The prophylaxis of the development of skin cancer is the exclusion of risk factors and the treatment of precancerous skin lesion. Given that UV radiation is a major factor in the occurrence of skin cancer, it is important to avoid exposure to sunlight, between 10.00-16.00, to artificial rays for the tanning effect, maximum coverage of skin surfaces with accessories and clothing from natural material, use of protection creams with factor SPF 30-80. It is also important to highlight the people in the risk group, through regular visits to the oncologist-dermatologist, a diet rich in vitamins, antioxidants and adequate water intake .

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MALIGNANT MELANOMA

Malignant melanoma (MM) is a form of skin malignancy that starts in melanocytes, cells that produce melanin, the pigment that colors the skin and can appear in any area of the body. MM is considered the most dangerous, very aggressive, with a rapid evolution and an unfavorable prognosis due to the fact that it has the highest rate of metastasis and death.

Epidemiological-geographical features

Global melanoma rates have risen rapidly over the past three decades. Although melanoma accounts for less than 2% of skin cancers, it also has an increased mortality rate. The incidence of malignant melanoma has increased rapidly worldwide. The annual incidence of malignant melanoma in the world is 10 per 100,000 inhabitants. The incidence of MM in the European Union is 10 cases / 100,000 per year. Australia has the highest incidence rate of MM in the world - 17 cases per 100,000 population per year. In the Republic of Moldova the incidence through MM is 2 cases / 100,000 annually. It is more frequent in women, more often in the extremities of the body, in men more frequently in the trunk (see fig. 1). MM can be found at any age, but more often it is attested in the average age of 50 years.

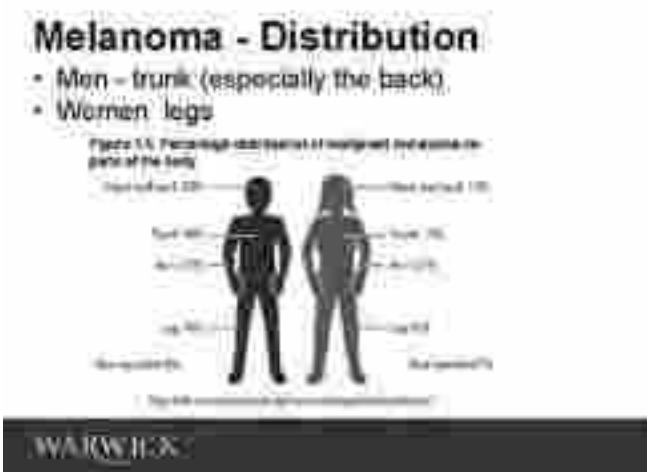

Fig. 1 *MM frequency by sex and location*

More often it is determined in people with phenotype I and II of the skin, blue, green and gray eyes, in people with blond and red hair.

Ethiopatogenesis

There are 3 categories of risk factors that influence melanoma morbidity - these are genetic factors, environmental factors and phenotypic expression factors of the gene-environment interaction.

UV radiation - frequent sun exposure is considered a major factor in the development of MM with an increased incidence in Australia, North America, Eastern Europe. Repeated sunburn is a well-established risk factor for the development of MM. The harmful effect of UV rays is the cumulative one, which can be considered from childhood. Thus, according to some studies, it has been shown that children exposed to the sun from childhood, who have been subjected to sunburn, have a high rate of development of MM in adulthood.

Phototypes I and II - sun or sun exposure in small doses can cause mild skin burns.

Trauma. Trauma to the developing nevus, if not excised immediately, has a very high potential for malignancy.

The presence of melanocytic nevus - dysplastic nevus make up nevus with high risk of development in MM.

Age - MM increases with age. The incidence gradually increases after 20 years, with a maximum between the ages of 40-60 years.

Personal history of melanoma - a person who has had melanoma is at risk for other melanomas.

Family aggregation - higher incidence of families in which melanomas were detected in several family members, in different generations.

Hormone factors are related to long-term use of hormones - oral contraceptives, hormone replacement therapy, pregnancy.

Immunosuppression - represents people with HIV / AIDS or drug-induced transplant patients.

Diagnosis of malignant melanoma

Clinical anamnesis

MM often develops asymptomatically, rarely may have insignificant itching. The signs are only the objective ones. A nevus becomes suspicious

of melanomatous transformation when its color changes - from light brown to dark brown to black or vice versa from brown to white, the color may also become uneven, the contour becoming irregular, rapidly increasing in size, a luster on the surface of the affected nevus, there may be an edematous halo around the nevus, satellites around the nevus, or even nodules on the surface of the nevus that acquire a brindle appearance of the nevus, and damage to the regional lymph node (see Fig. 2) [18,19].

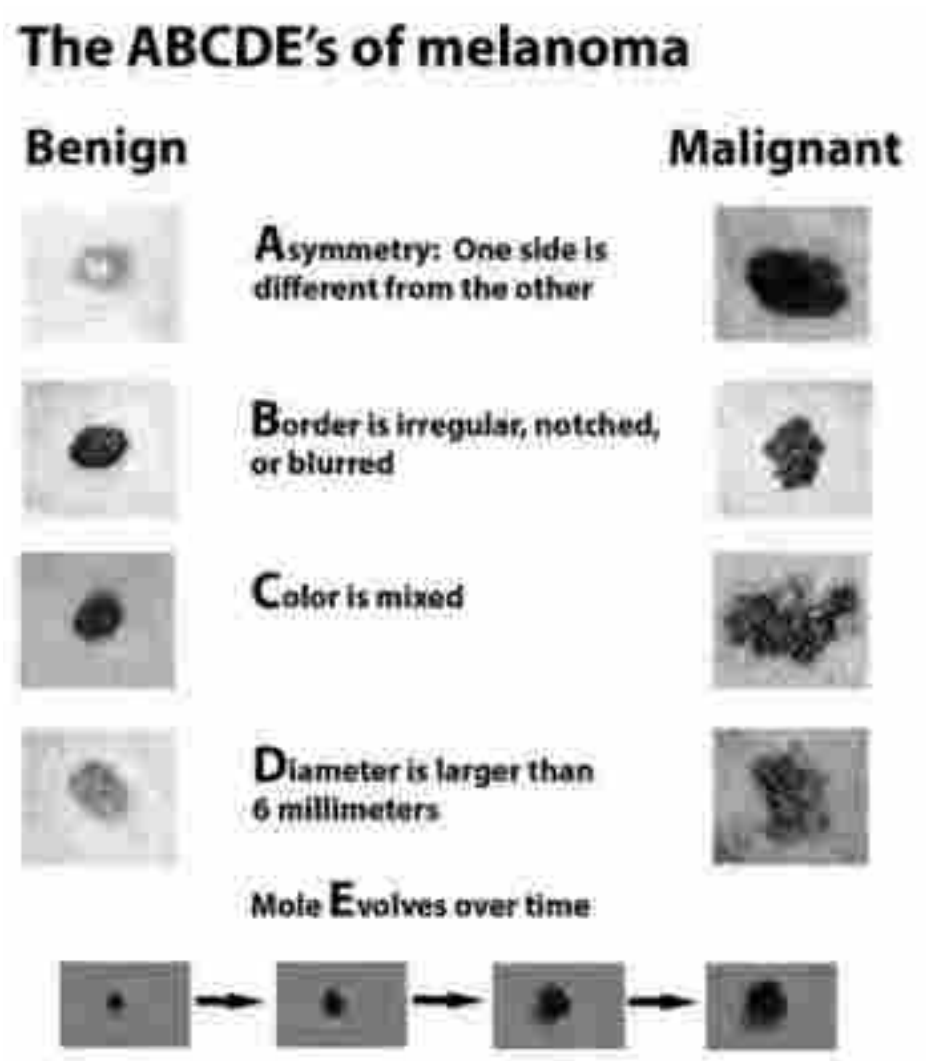

Fig. 2. *Signs of malignancy of the nevus according to the ABCDE classification*

MM has several clinical forms: surface enlargement - it is the most common form of MM, nodular form, lentigo-melanoma, lentigo-acral melanoma and rare forms: mucosal melanoma, ocular melanoma, amelanotic melanoma, melanoma with complete regression, soft melanoma, desmoplastic melanoma.

The diagnosis is based on the history of the disease, **the physical examination** - with the appreciation of the signs of malignancy of the nevus (according to the ABCDE classification), the **examination with a glass**, the palpation of the regional lymph nodes. **Laboratory investigations**: in the general analysis of the blood, there will be no changes that indicate the presence of MM. In the biochemical analysis of blood in the presence of distant metastases, the indices of ALAT, ASAT, bilirubin fractions, urea, creatinine, alkaline phosphatase will be increased. In the general analysis of urine - may be the presence of melanuria. The specific tumor marker for MM is S-100.

Paraclinical investigations

Thermography by determining the temperature level at the level of the nevus, which in the case of MM will be increased from 2.5- to 5 degrees Celsius.

Computerized dermatoscopy - can more accurately assess changes in the surface of the suspect's nevus. The changes that characterize melanoma are asymmetry, the presence of several overlapping colors. Subsequently, the dermatoscopic score is determined, which facilitates the diagnosis. It is a non-invasive and painless method.

Confocal microscopy and SIAScan also determine changes that may occur at the nevus level, neural architecture disorders, in in vivo time, and is close to the histological result. Radiography of the affected region is performed in all cases when the growth of the tumor in the bone or cartilage is clinically suspected [2,28].

Cytological examination will be performed only by fingerprint is allowed only in the case of ulcerated tumors. In case of regional lymph node involvement, aspiration puncture can be performed at this level, with confirmation of the diagnosis of melanoma metastasis.

Excision biopsy - which is the same surgery, when the tumor is completely excised, respecting the edges of the excision 2.5-3 cm from the edge of the tumor and deep to the muscle fascia. It is important to perform this procedure with the protection of general anesthesia, because by infiltrating the local anesthetic we can spread the tumor cells in different parts of the tumor with increasing the risk of recurrence.

Additional methods for the detection of distant metastases include chest chest X-ray, chest CT, USG g / regional lymph and abdominal organs, abdominal CT or angio CT / abdominal MRI, lymphography, lymphoscintigraphy, bone scintigraphy, brain MRI, PET CT.

Once the histological material is obtained and on the basis of additional examinations, we can determine the stage of the disease. The determination of category T is based on the microstadialization system according to Clark, which includes 5 levels of tumor invasion and the determination of tumor thickness according to Breslow. Breslow thickness is measured in millimeters, the classic levels being: <0.75; 0.76 - 1.50; 1.51 - 4.0 and> 4 mm (see fig. 3). It has recently been proposed to change these limits (ASCO-2000): TI <1.0 mm, T2: 1-2 mm, T3: 2-4 mm and T4> 4 mm.

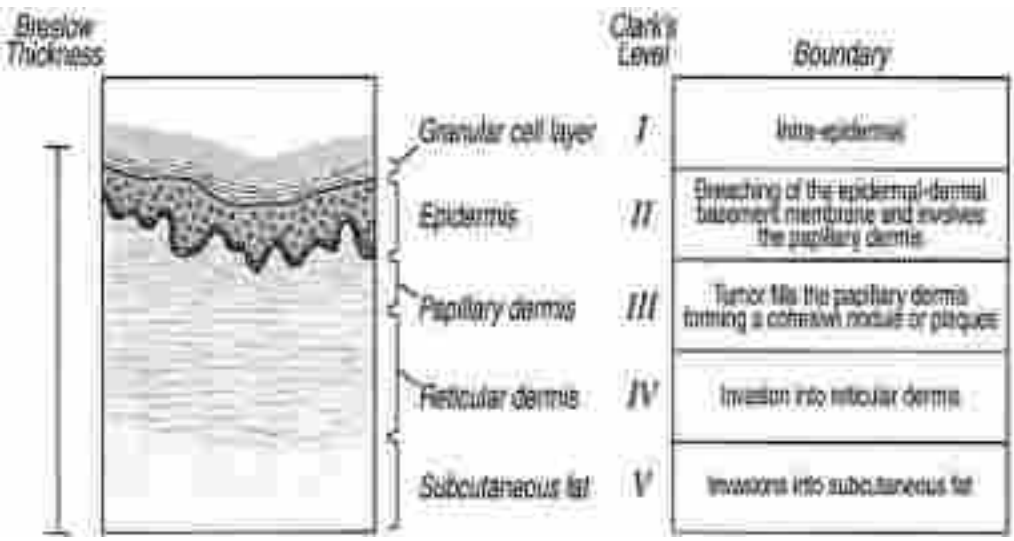

Fig. 3. *Klark and Breslow classification*

Table 1. TNM staging of malignant melanoma, AJCC, 8th edition, 2017

Clasification T	Tumor thickness	Ulceration
T1	< 1mm	a) No ulceration, Clark II-III level. b) With ulceration or Clark IV-V level
T2	1,01-2,0mm	a) No ulceration b) With ulceration
T3	2,01-4,0 mm	a) No ulceration b) With ulceration
T4	>4 mm	a) No ulceration b) With ulceration
ClasificationN	No. metastatic lymph nodes	Type of metastases
N1	1	a) Micrometastases b) Macrometastases
N2	2-3	a) Micrometastases b) Macrometastases c) Metastases in satellite transit without lymph node involvement
N3	>4 or metastases in satellite transit with lymph node involvement	
Clasification M	Localisation	LDH serum
M1a	Cutaneous, subcutaneous, lymph node, pulmonary	Normal
M1b	Viscerals with other locations	Normal
M1c	Any localisations	increased

Complications of malignant melanoma

Following the spread of the pathological process, MM can be associated with eliminations from the ulcerative tumor with/without smell, as well as bleeding. From the complications of the surgical treatment: intraoperative hemorrhages, trauma of the peripheral nerves, and postoperatively: suppuration of the wound, hemorrhages from the main vessels, marginal or total necrosis of the flap, lymphorea.

Metastatic pathways

The metastatic pathways of MM are lymphogenic - in the regional lymph nodes, hematogenous pathway in organs (lungs, liver, brain, bones, etc.), perineural, cutaneous.

Treatment of malignant melanoma

The treatment of MM will depend on the stage of the disease, it can be radical, combined and complex. **Surgical treatment**. Stage I melanoma patients have a favorable prognosis and 10-year survival. The radical and optimal method is considered *Electroexcision* of the primary tumor. Other methods are known, such as: tumor *cryodestruction*, laser therapy, *hyperthermotherapy*, *radiotherapy.*

In the case of in situ melanoma and lentigo-melanoma, it is recommended to perform *electroexcision* of the tumor at a distance of 1 cm from the tumor, regardless of it's location, because the chances of recurrence are minimal.

Duken surgery is performed on lower limb skin melanoma and involves highlighting the inguinal lymph nodes as a whole with the adipose tissue. Crille surgery is performed for lymphatic metastasis in the cervical lymph nodes of the skin melanoma of the head and neck region. In case of damage to the skin of the upper limbs or, in some cases, of the trunk, lymphadenectomy of the axillary lymph nodes is performed. The effectiveness of prophylactic lymphadenectomy is confirmed by the fact that metastases in the regional lymph nodes are found in every third patient.

Chemotherapy treatment. Chemotherapy for MM is quite limited. It is used more frequently in patients after surgical treatment for stages IIC, IIB, IIIC, in case of process elimination or tumor recurrence. Polychemotherapy is welcome, such as: Cisplatin + Dacarbazine, Dacarbazine + Tamoxifen, Cispaltin + Dacarbazine + Tamoxifen, Carboplatin + Dacarbazine + Tamoxifen, etc.

Immunotherapy - is the adjuvant method of choice, or can be combined with systemic chemotherapy. Interferon -α2b is widely used, at a dose of 20 million IU / m2, daily, 5 days a week for 4 weeks, with evidence of the patient's dynamics, if repeated treatment is required. At the moment the treatment of choice in Europe, the USA is the target therapy, with the use of Nivolumab preparations. Interferon as a method of immunostimulation

is no longer used in highly developed countries and demonstrates its ineffectiveness in the treatment of MM.

Radiation therapy treatment. Most often the radiotherapy treatment is the postoperative one, and the treatment schemes depend on the location of the tumor, on the thickness, on the positive resection edges, on on the primary performed treatment. Several radiotherapy treatment schemes are known, the most common being the following schemes:

- DS 32Gy, 4 fractions of 8 Gy, for 4 weeks;
- DS 50Gy, 20 fractions of 2.5 Gy each, for 4 weeks (18, 23.30)

Criteria for hospitalization of patients with MM. All patients with histologically or cytologically confirmed MM require specific treatment and hospitalization in the specialized department of the Oncological Institute.

Prognosis

The survival rate of a carrier of malignant melanoma depends on a number of factors such as sex, age, location, macroscopic appearance, clinical stage, histological type, mitotic index, level of invasion, tumor size, volume, size and thickness, etc. . With the spread of the malignant process in the lymph nodes, survival suddenly decreases. Survival at 5 years in patients with MM and metastases in the lymph nodes is 48% (37% at 10 years).

Follow-up of patients with MM

It consists of the follow-up of localized and loco-regional disease, patients with dysplastic nevi considered at high risk require follow-up throughout life, follow-up for 5 years in local stages with a thickness of <1.5 mm and for 10 years in other forms is considered as sufficient, anamnesis, general examination including assessment of regional lymph node status, skin examination, and palpation of the removed primary tumor region will be recommended every 3 months for the first 2 years and thereafter every 6-12 months. Patients will be instructed in the need to avoid excessive sun exposure and artificial ultraviolet radiation without adequate protection and regular examination of the skin and peripheral lymph nodes. In the process of specific medical treatment, patients with recurrent or metastatic melanoma will be supervised in the clinic and inpatient IMSP IO with the necessary investigations and therapeutic procedures. Specific examination is indicated only when the clinical situation so requires.

Prophylaxis methods

Primary prophylaxis consists of observing a healthy lifestyle, protection from the sun's rays, avoiding contact with environmental pollutants, and the use of protective clothing and equipment.

Secondary prophylaxis includes preventive surgical excision of pigmented nevi with a high risk of trauma, as well as traumatized and inflamed patients, referral of patients with benign pathologies and precancerous conditions to dermatologists, surgeons and supervision in the treatment indicated by these specialists. The computerization of the population about this disease, self-control in the mirror, about how important is the annual control of patients at high risk of developing MM, of people in the risk group, of people working outdoors, about the importance of application protective creams, natural quality clothing, glasses, cap.

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LOWER LIP CANCER

History *- first descriptions*

The first description of lower lip cancer belongs to the ancient physician Aulus Cornelius Celsus (1st century AD), and the oldest method of surgical treatment of cancer at this site was cuneiform lip resection. The method proved to be ineffective because the recurrence rate was very high. In order to improve the results, a series of researches were carried out, various methods of treatment were developed, both surgical and radiotherapeutic, medicinal, etc.

Epidemiological-geographical features

Epidemiology of lower lip cancer in southern areas (India, Middle Asia, Sri Lanka, Burma, South America), less in the Nordic countries, in the USA, Central Europe. From the second half of the twentieth century, when the epidemiological research of lower lip cancer was based on scientific clinical-experimental statistics. In the Republic of Moldova, lower lip cancer ranks 5th to 7th in the structure of cancer. The incidence is 5 - 5.5% of the locations of the head and neck region. In the Republic of Moldova, 180 primary patients are registered annually, the vulnerable age is 50-70 years, a male preference. A true prediction of the dynamics of morbidity and mortality from lower lip cancer has become possible as a result of the organization of the Republican Cancer Registry. In recent years, there has been a decline in mortality rates from lower lip cancer, which demonstrates an improvement in the diagnosis and treatment of cancer at this location.

Ethiopatogenesis

Lower lip cancer, like many other cancers, has a polyetiological etiopathogenesis. Several etiological factors are involved in its appearance, such as:

Internal factors:

- compromised immunity;
- genetic predisposition.

External factors:

- physical: insolation (UV), ionizing radiation, chronic microtraumas (sharp, decayed teeth, poor quality prostheses, blade cuts, etc.), microfuels (with cigarette butts);
- chemicals: various harmful chemicals (petroleum products, agricultural chemicals), including alcohol and tobacco;
- biological: viral infections (VHZ, HPV), bacterial.
- Lifestyle factors such as tobacco and alcohol abuse in combination negatively affect survival, accurate smoking record, number of packs per year, and alcohol, number of drinking days per week and number of drinks per day . Tobacco history should be reported as a demographic and may be included in future prognostic groups. From a practical point of view, the standard classification should be as follows: non-smoker; <10 packages; > 10 but <20 packages a year; > 20 packs. Nutrition is an important prognostic factor and will be measured indirectly by losing more than 5% of your body weight in the last six months. Depression negatively affects quality of life and survival. The previous or current diagnosis of depression should be recorded in the medical record.

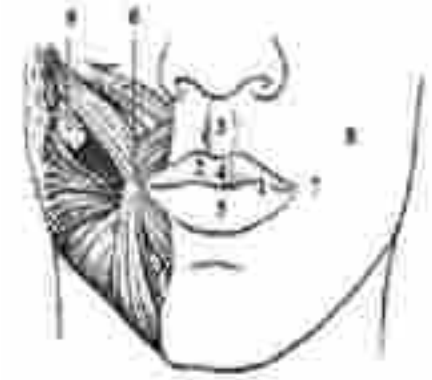
Harmful factors from the external environment, acting for a long time on the background of an internal predisposition cause pathological changes in the tissues of the respective organ, in this case on the tissues of the lower lip. The changes are many and varied, but are generally referred to as „precancerous conditions" or „precancerous conditions." Along the way, various classifications of these precancerous conditions have been developed. We present one of the classifications, which is relatively simple and shows the morphological character of the changes.

Topographic anatomy of the lower lip, physiology and vascularization

The lower lip (labium inferius) has a mucous-muscular-cutaneous, mobile structure that delimits the buccal orifice in the lower part.

The lip starts at the junction between the edge of the vermilion and the skin and includes only the surface of the vermilion or that part of the lip that comes in contact with the opposite lip. The rest of the vermilion

is staged in the skin chapter. It is subdivided into the upper and lower lip, joined at the corners of the mouth *(see Fig. 1)*.



1. Rhyme oris
2. Upper lip
3. Filter
4. Tuberculum
5. Lower lip
6. The labial commissure
7. The angle of the mouth
8. The cheek
9. Adipose tissue

Fig. 1. *Anatomy of the lower lip*

It consists of 3 parts: cutaneous; intermediate (red border); mucosa. The lips, including the lower lip, have the following functions: retaining food in the oral cavity, sucking, forming the food bowl, participating in mastication, contributing to the aesthetic appearance, mimicry, forming bilabial consonants („b", „m", „p"), labiodental („f" and „v"), the pronunciation of the vowels „o" and „u".

Precancerous conditions:

I. Precancerous conditions with a low incidence of malignancy (optional precancerous)

1. Diffuse dyskeratosis (chronic cheilitis)
   - proliferative
   - destructive

II. Precancerous conditions with a high incidence of malignancy (mandatory precancerous)

1. Nodular dyskeratosis
   a) destructive (chronic fissure);
   b) proliferative
      - cutaneous horn
      - leukoplakia
      - papilloma
      - teratoacanthus

For destructive forms, erosive, ulcerative processes are characteristic, and for the proliferative ones - formations with proliferative character and cornification with acanthosis.

Among the most common forms of proliferation is keratoacanthoma.

Keratoacanthoma is a tumor formation very similar to early stage lip cancer. It usually develops under the influence of harmful environmental factors (sun, wind). It can occur as a result of chronic lip trauma or microcombustion. Lately, more and more insistently there is talk about the role of the virus in the etiogenesis of lip cancer, and traumas, burns are just cocancer, predisposing factors. Keratoacanthoma usually develops on the central segment in the lateral one and never develops in the area of the labial commissure.

Clinical signs characteristic of keratoacanthoma are the epithelial „collar" formed on the perimeter of the formation and the hard sponges adhering to this „collar". Subsequently, the surface of the formation keratinizes from the center and there is another sign characteristic of keratoacanthoma - a ditch around the focus of keratinization, which is also called pseudoulcer, because it does not bleed, unlike the true ulcer.

Keratoacanthoma can often become malignant and one of the signs of malignancy is the acceleration of the growth of keratoacanthoma and its induration. For these reasons keratoacanthoma is considered a mandatory precancer.

Precancer treatment is performed by different methods: conservative, surgical, radiotherapy and combined:

CONSERVATIVE - application of natural ointments (butter, sea buckthorn oil, etc.);

SURGICAL – usual or electric excision of the tumor;

RADIOTHERAPY – this is the method of choice in late stages;

COMBINED METHOD - consists of 2 steps:

Stage I - irradiation of the outbreak

Stage II - Vanach's operation

After a longer evolution, the precancer can become malignant, this transformation usually begins with the acceleration of the growth of the formation, with the appearance of accentuated induration and surface roughness. A dense plaque forms under which small, slightly bleeding papillomatous growths can be seen.

This tumor infiltrate grows in size, becomes rough, and at its periphery a initially better delimited sponge is formed, and as it evolves the boundaries become blurred.

Diagnosis of lower lip cancer

Clinical anamnesis

The clinical diagnosis of lip cancers is mostly based on history (history) and physical examination (visual and palpable). A biopsy is required to confirm the diagnosis, and is usually done from the primary tumor. Lymph node biopsy is performed by fine needle aspiration or cytological examination (smear) when indicated. The results of diagnostic biopsy of primary tumor, regional lymph nodes and distant metastases can be included in the clinical classification. The diagnosis of ENE should be based almost entirely on physical examination, rather than imaging studies. Examination of the lips and oral cavity usually reveals the largest diameter of the cancer, although palpation is essential for the evaluation of DOI and submucosal extension. The extent of the cancer in the mucosa reflects its true linear size. The induration that surrounds the cancer usually occurs as a result of peritumor inflammation. The DOI must be differentiated by the thickness of the tumor, and its determination is based on the invasion below the plane defined by the surrounding normal mucosa. Any exophytic appearance should be noted, but the assignment of the stage is determined by what is manifested at / below the surface (defined by the adjacent normal mucosa). Clinical evidence of bone destruction should be noted and its depth estimated (eg, in bone versus cortex in the spinal cord). Dysphagia is suggestive of a tumor that has sufficient invasion of the oral structures to produce dysfunction. Likewise, salivation or inability to swallow fluids without difficulty suggests a tumor with substantial DOI. Trismus, when not caused by pain, is associated with a deeply invasive lesion. Numbness of the lips and / or teeth is often associated with nerve invasion.

Thick lesions are often defined by computed tomography (CT) or magnetic resonance imaging (MRI) depending on availability, patient tolerance, contrast allergies, and costs. CT examination provides an advantage over MRI in assessing cortical bone erosion, although the latter appears to be more sensitive but less specific for detecting bone marrow invasion. MRI provides the added benefit of evaluating perineural tumor invasion. Positron emission tomography (PET) / CT is performed primarily for lymph node staging of the disease or when distant metastases are suspected, unless the CT component is performed as a post-contrast examination with imaging evaluation of the neck. Ultrasonography does

not allow an adequate assessment of the location of the primary tumor of the lip, but may be additional for lymph node evaluation with other otherwise equivocal results of lymph node imaging.

Cancers on the background of diffuse or nodular proliferative dyskeratoses, manifest as papillary forms of cancer, which being located on the lower lip have the appearance of prominent formation of various forms, with poorly pronounced boundaries, painless and hard to palpate. The multiple forms look like small, multiple growths that fuse into a large, swollen tumor. Although the tumor is extensive, it is superficial due to the biological peculiarities of the lip tissues.

The ulcerative form of lower lip cancer initially presents a lesion, covered with a dense crust, at the detachment of which an ulcer with irregular edges appears. The edges of the ulcer are twisted, hardened, irregular. The bottom of the ulcer is hard, it is dry, without elimination.

Initially, the ulcer is painless and only later is the inflammatory process associated, pain and purulent discharge appear.

The ulcer form has a rapid evolution, in a short time all the layers are involved in the process: the skin, the muscles, the mucosa. In advanced stages it spreads to adjacent tissues and areas.

Extranodular extension (ENE)

ENE is defined as an extension of metastatic carcinoma in the lymph node, which extends beyond the capsule and extends into the surrounding connective tissue, regardless of the associated stromal reaction (see Fig. 2). The histopathological aspects for ENE are as follows:

1. Infarorbitaly LN
2. Buccal LN
3. Mandibulary LN
4. Submandibulary LN
5. Submentonians LN
6. Deep cervicaly LN
7. Pretrahealy LN
8. Jugulo-omohioidians LN
9. Superficialy LN
10. Jugulodigastric LN
11. Occipitaly LN
12. Retroauricular LN

13. Preauriculary LN
14. Parotidians LN

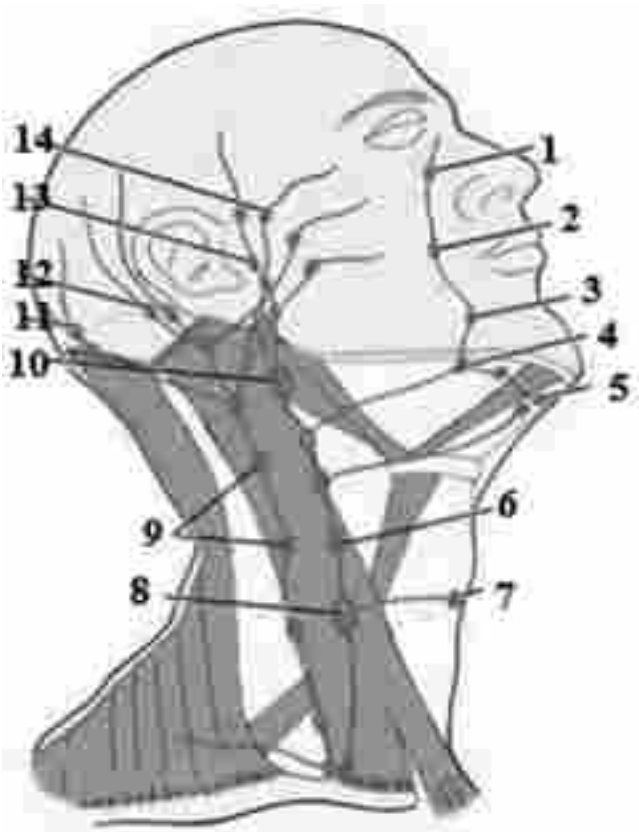


Fig.2. *Diagram of lymphatic drainage of the head and neck region*

• ENEmi (microscopic ENE less than or equal to 2 mm)
• ENEma (ENE greater than 2 mm or macroscopic ENE)

Depth of invasion (DOI)

DOI assesses the degree of invasion of a carcinoma, regardless of its exophytic composition. It is first measured by identifying the „horizontal line" of the basement membrane in the adjacent squamous mucosa. From this horizontal line, a „vertical line" is established at the deepest point of the tumor invasion, which is DOI. The depth of the invasion is recorded in millimeters. Measurements in millimeters can be easily made by printing lines on acetate foils, which can be stacked on top of glass slides.

TNM - AJCC classification, 8th edition, 2017
Definition of primary tumor (T)

Categorie T	Criteria T
TX **T0** **Tis**	The primary tumor cannot be evaluated The primary tumor is not detectable Carcinoma in situ
TI	Tumor <2 cm, with invasion depth (DOI) <5 mm DOI is invasion depth, not tumor thickness
T2	Tumor <2 cm, DOI> 5 mm and <10 mm or tumor> 2 cm, but <4 cm, DOI <10 mm
T3	Tumor> 4 cm or any tumor with DOI> 10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease (lip) The tumor invades the bone cortex or affects the lower alveolar nerve, the floor of the mouth, or the skin of the face (eg, cheek or nose) (oral cavity). mandible or jaw or affects the maxillary sinus or facial skin) Note: Superficial erosion of the bone / alveolus (alone) by a primary gingival tumor is not sufficient to be classified as T4.
T4b	Highly advanced local disease The tumor invades the masticatory space, the pterygoid plaques or the base of the skull and / or circumferentially invades the internal carotid artery.
Categorie N	Criteria N
NX **NO**	Regional lymph nodes cannot be evaluated No metastases in the regional lymph nodes
NI	Metastasis in a single ipsilateral lymph node J <3 cm in maximum size, ENE (-)
N2	Metastasis in a single ipsilateral lymph node> 3 cm, but <6 cm in maximum size and ENE (-) or metastases in multiple ipsilateral lymph nodes, none> 6 cm in maximum size and ENE (-) or metastases in bilateral lymph nodes or contralateral, none> 6 cm in maximum size and ENE (-)
N2a	Metastasis in a single ipsilateral ganglion> 3 cm, but <6 cm in maximum size and ENE (-)
N2b	Metastases in multiple ipsilateral ganglia, none> 6 cm in maximum size and ENE (-)
N2c **N3**	Metastases in bilateral or contralateral lymph nodes, none> 6 cm in maximum size and ENE (-) Metastasis in a lymph node> 6 cm in maximum size and ENE (-) or metastases in any of the lymph nodes and ENE (+) clinically evident

Definition of distant metastases (M)

CategoryM	Criteria M
M0	No distant metastases
M1	Distant metastases

AJCC prognostic groups

T	N	M	Stady
Tis	N0	M0	0
T1	NO	MO	I
T2	NO	MO	II
T3	NO	MO	III
T1,2,3	NI	MO	III
T4a	N0,I	MO	IVA
T1,2,3,4a	N2	MO	IVA
Any T	N3	MO	IVB
T4b	Any N	MO	IVB
Any T	Any N	M1	IVC

Histological grade (G)

G	G
GX	The degree cannot be assessed
Gl	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Staging of lower lip cancer

St. I - tumor or ulcer with Ø 1-1.5 cm, within the mucosa and submucosa of the red edge of the lower lip, without Mt;

St. IIa - tumor or ulcer larger than 1.5 cm, but only ½ of the lip surface within the mucosa and submucosa;

St. IIb - tumor or ulcer of the same size or smaller with 1-2 Mt mobile in the regional ganglia;

St. IIIa - tumor or ulcer spread with invasion in all layers of the lip or with spread in the cheek, soft tissues of the submental region;

St. IIIb - tumor or ulcer identical to IIIa or less with Mt partially fixed in the regional lymph nodes;
St. IVa - tumor extended in the phase of decomposition with invasion in all layers, with spread in the labial commissure, the chin region, Mt fixed regionally;
St. IVb - tumor of any size with Mt at a distance.

Treatment of lower lip cancer

In the treatment of lower lip cancer, the stage of the tumor process (degree of spread) and the clinical form of the tumor are always taken into account. The basic principle of cancer treatment in this location is to perform it in 2 stages: treatment of the primary focus and treatment of regional metastases.

Stage I-II is usually performed with enlarged resections of the lower lip with plastic tissue of the local tissues (see Fig. 3).

Fig. 3. *Enlarged resection of the lower lip with local plasty*

1. Radiotherapy method - telegamatherapy in a summary dose of 60 Gy.
2. Surgical method - trapezoidal resection with subsequent plasty according to the method of N. Blohin, A. Paces (see fig. 4).

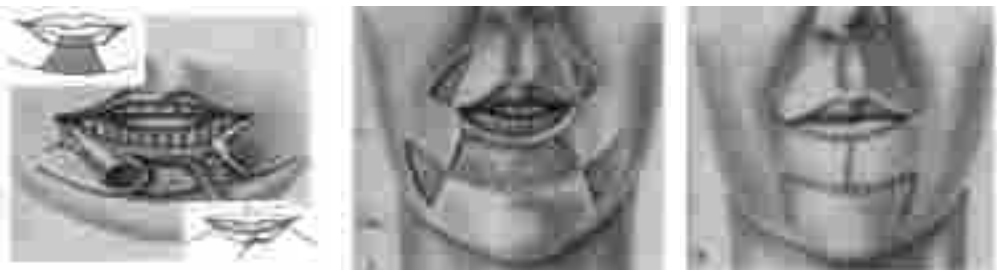


Fig. 4. *Diagram of trapezoidal resection of the lower lip*

3. The method of cryodestruction in exophyte forms.

Treatment st. III:

- Combined method: preoperative radiotherapy (40-50 Gy) + trapezoidal resection of the tumor with subsequent plasty of the defect
- For ulcerative-infiltrative forms: combination radiotherapy (40 Gy telegamotherapy + contact X-ray or brachytherapy)

Treatment st. IVa:

Complex method:

- telegamatherapy cure (50 Gy);
- one week after radiotherapy, a combined operation is performed (enlarged resection of the lower lip in block with the soft tissues of the chin region, the buccal floor, if necessary with resection of the mandible and secondary plasty);
- postoperative chemotherapy (methotrexate 5-Fluoruracil, Bleomycin, Cisplatin according to special protocols).

Stage IVb treatment:

Palliative treatment:

The treatment of regional lymph node metastases is performed by the surgical method in different variants.

- Vanach type operation, which consists in highlighting the submandibular lymph nodes in block with the submandibular salivary glands.
- Highlighting the fascicolo-fascial ganglia, the superior variant, which consists of the Banch type operation + the removal of the soft tissues from the lateral cervical triangle.
- Cryle-type surgery - highlighting the lymph nodes in block with the cervical soft tissues, removing the cervical portion of the internal jugular vein and the sterno-cleido-mastoid muscle.

Prognosis

Stage I-II - 100% healing;

Stage III - 50-60% healing can be achieved;

Stage IIIb-IVa - cure in about 15% of cases.

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THYROID CANCER

History - first descriptions

Thyroid surgery techniques are described for 100 years. Theodor Kocher of Bern. 1872 - first thyroidectomy. 1901 - or 2,000 thyroid procedures performed. 1901 - post-surgical mortality 50% 4.5%. 1909 - won the Nobel Prize for this work.

Epidemiological-geographical features of thyroid cancer

Thyroid cancer morbidity rates have risen significantly in recent decades. This increase is explained by the increase of longevity, by the improvement of the early diagnosis, the accentuated pollution of the environment, especially with radioactive substances, the insufficiency of Iodine in water, soil. The number of primary thyroid cancers, registered in the Republic of Moldova, increases by about 3% per 100,000 population.

Thyroid cancer mainly affects women, the ratio of women to men reaches 10: 1. The most vulnerable age is 34-45, but the incidence of children has increased in recent years. According to WHO data, thyroid cancer morbidity has doubled in the last 20 years.

Thyroid cancer mortality accounts for 1% of all cancer deaths in the same period.

Ethiopatogenesis

In the etiology and risk of thyroid cancer, 2 groups of etiological factors are recognized: exo- and endogenous.

Among the exogenous factors we mention:

- food factor - Iodine deficiency in the diet;
- cattle deficit. A and C, protein;
- chronic trauma;
- Gussogenic foods from the brassica family that contain profiltiuracil, progotrine, they have an antithyroid activity stimulating TSH that lead to an increase in the volume of the thyroid gland. (Cabbage, radish, etc.).
- some medicines such as resorcinol, thyrostatics, phenobarbital, etc.;
- exogenous radioactive factor from the environment and iatrogenic

(irradiation for diagnostic or curative purposes).

An explosive increase in thyroid cancer was recorded after the catastrophe at the Chernobyl nuclear power plant. An example is the incidence of thyroid cancer in Ukraine, where until the Chernobyl damage the index was 0.6% 000, and after (1991) it was 2.1% 000.

In the Republic of Moldova, the indices of morbidity due to thyroid nodular pathologies increased 5 times, the ratio of women / men reaching 14: 1, the most affected ages being -30- 40-50 years.

The increase in mortality rates is explained to some extent by early diagnosis, especially due to ultrasound examination, which allows the detection of thyroid nodules below 1 mm.

Among the endogenous factors we mention:

- hereditary predisposition (family history, multiple neoplasms MEN IIA, MEN IIB);
- Hormonal disorders in the body (contraceptive use, early menarche, early pregnancy, first late pregnancy).

A special place in the etiology of thyroid cancer is occupied by the stress factor, which can act in two ways: as an exogenous and endogenous factor.

Precancerous conditions of the thyroid gland

Cancer of the thyroid gland, as well as cancers of other organs, develops on a prepared ground, against the background of pathological processes with slow evolution. Some of the predecessor processes initially with benign evolution may turn into malignant tumors under certain conditions. But their latent and lasting evolution masks the onset of malignancy. For these reasons, thyroid cancer, although located in a visible organ, is often diagnosed in advanced stages.

Out of the multitude of thyroid precancers, the following nodular pathologies have a higher risk of malignancy:

- thyroid adenoma;
- autoimmune thyroiditis (Hashimoto);
- toxic nodular goiter.

Thyroid gland adenoma is one of the most common benign tumors of the thyroid gland. Adenomas can be follicular and papillary. It mainly affects women (13: 1). It develops slowly, the symptoms are insignificant and it refers to disorders of the function of the thyroid gland.

Autoimmune thyroiditis (Hoshimoto's manure)

Struma is part of the group of chronic thyroiditis. It mainly affects women after the age of 40. The gland enlarges in moderate volume, hardens, is painless, with a tuberous or smooth surface. The evolution is faster than in ordinary grooves, the gland tissue degenerates, the lymph nodes are not involved. At the moment, an active approach to this problem is needed, namely - mandatory surgical treatment due to the major risk of malignancy.

Nodular toxic goiter

The diffuse form of toxic goiter develops in thyrotoxicosis, and the nodular one - in case of edemic or sporadic goiter.

It occurs against the background of iodine deficiency, resulting from hypofunction of the gland. It can also occur in normal concentrations of iodine, but when it cannot be assimilated by the body. Endemic and sporadic goiter, although of different etiology, has an identical clinic and pathogenesis.

Clinically, toxic goiter is manifested by insomnia, chronic fatigue, irritability, tremor of the upper limbs and even the whole body.

Conservative treatment has proved ineffective, which is why an active surgical tactic has been used lately.

Topographic anatomy of the thyroid gland, physiology and vascularization

The human thyroid gland is one of the largest glands with internal secretion. It has a flattened, reddish formation, is composed of 2 lobes, joined by the isthmus and weighs 20-60 g. It is located on the anterior surface of the neck, below the thyroid cartilage, the lobes are located on both sides of the trachea. The right lobe is usually slightly larger than the left lobe. The upper edge of the gland reaches the upper edge of the thyroid cartilage, and the lower reaches the tracheal rings 2-3-4, sometimes 6 (see Fig. 1).

The thyroid gland has 2 capsules: internal and external. The inner one envelops the gland, adhering intimately to the parenchyma of the gland, from this capsule inside the gland penetrate fibers, which divide the gland into lobules. The outer capsule is thicker, enclosing the entire gland in a block with a portion of the larynx. From the thickening of this capsule,

a fixation ligament is formed, which connects the gland to the trachea and larynx. Thus the thyroid gland moves during the act of swallowing. Between these 2 capsules pass the blood vessels.

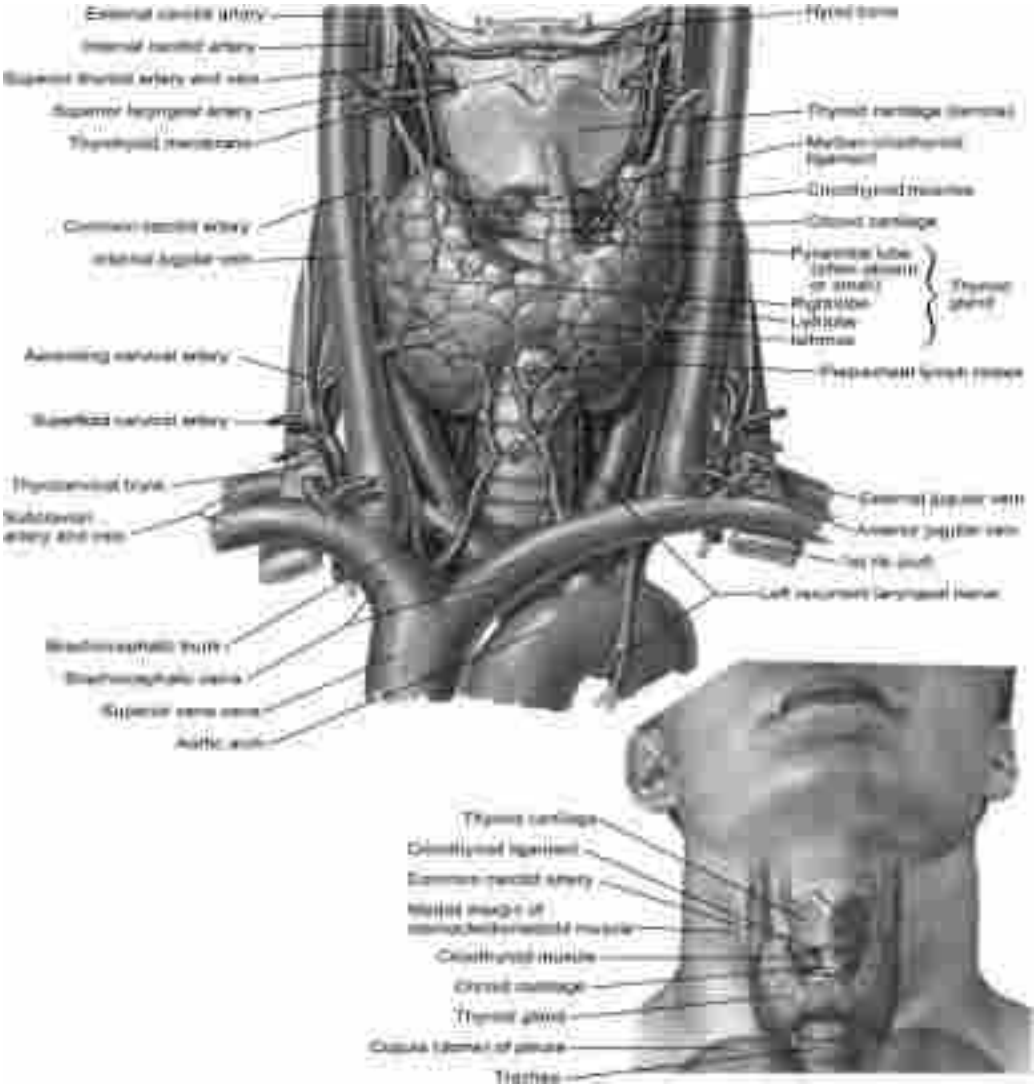

Fig. 1. *Anatomy of the cervical region*

On the posterior surface of the lateral lobes between the inner and outer capsules are the parathyroid glands, the number of which varies from 2-3 to 5-6, sometimes up to 12.

The upper parathyroid glands adhere to the thyroid capsule more closely than the lower ones.

The thyroid gland is one of the most vascularized organs, the blood vessels forming multiple anastomoses not only between their own blood vessels, but also with the vessels of neighboring organs (pharynx, larynx, trachea, esophagus).

Blood supply is provided by two superior thyroid arteries, 2 inferior and one odd artery (fig.2).

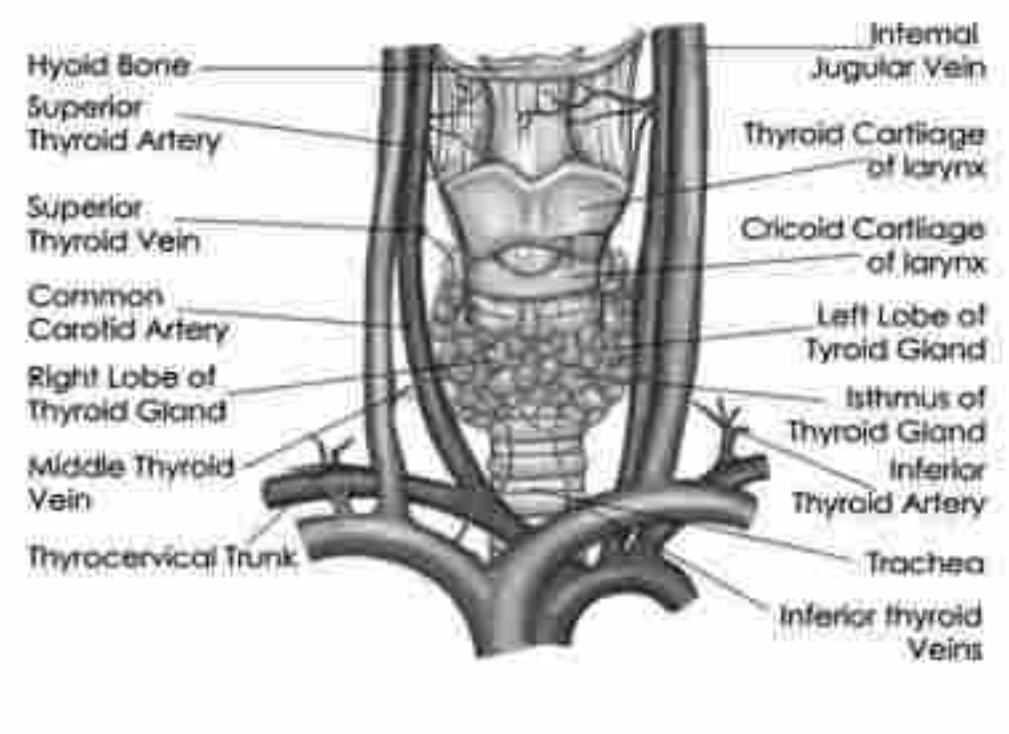

Fig. 2. *Anatomy of the thyroid gland*

The recurrent nerve passes through the thyroid gland, which enters the larynx through a single trunk, which branches before penetrating the larynx. This nerve provides phonation, so it is important not to be traumatized during surgery, which would lead to phonation disorders, up to total aphonia.

The venous system of the thyroid gland is very vast and forms many anastomoses. Venous blood from the upper and middle thyroid veins flows into the internal jugular vein, and the lower vein into the brachifacial vein.

The thyroid lymph vessels collect lymph in the prelaryngeal, para- and pretracheal ganglia, and in the jugular ganglia. Several researchers have

established the regional lymphatic collectors of the thyroid gland as a result of his studies:

1, 2, 3) the deep (jugular) chain, formed by the upper, middle and lower ganglia along the jugular vein, from the angle of the mandible, the mastoid process and the pole inferior of the parotid gland to the level of the entrance of the jugular vein into the subclavicular vein, the inferior jugular ganglia are also called supraclavicular;

4) the chain of the prelaryngeal ganglia (the latter are located along the recurrent nerve, spreading in the thoracic cavity);

5) lymph nodes in the antero-superior mediastinum (retrosternal);

6) paratracheal or dolphin nodes, mediastinal to the aortic crutch. There is a difference of opinion regarding the existence of anastomoses between the lymphatic and venous vessels, although some authors claim that in the thyroid gland the lymphatic vessels form synapses with the venous ones, which contributes to a rapid metastasis (see Fig. 3).

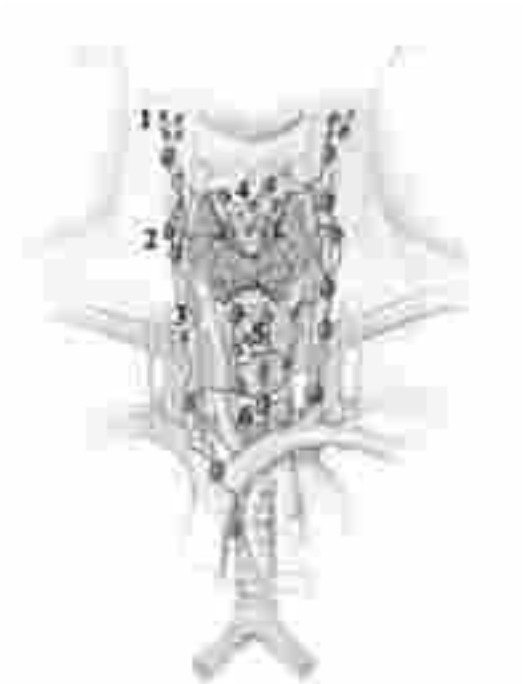

Fig. 3. *Cervical lymphatic chains*

The lymphatic system of the thyroid gland forms extensive anastomoses

with the lymphatic system of the root of the tongue, of the laryngeal and pharyngeal lymph rings.

Physiology and functions of the thyroid gland

The thyroid gland is involved and directly responsible for the metabolism of iodine in the body.

Depending on the iodine saturation we distinguish monoiodothyronine, diiodothyronine, triiodothyronine (T3) and thyroxine (T4, tetraiodothyronine).

The most important compounds are T3 and T4, while T1 and T2 are the initial stages of biosynthesis.

The specific thyroid hormone - thyroxine - is a regulator of intracellular oxidation processes. It was discovered in 1915 by Kendall, and in 1952 researchers I. Cross and A. Pitt-Rivers discovered the hormone triiodothyronine. The action of these hormones is to stimulate all types of metabolism.

The thyroid gland contains 3 types of cells:

"A" - follicular cells - thyroxine-producing;

"B" - parafollicular cells (so-called Askinazy or Hürthle cells) accumulate serotonin, which regulates the function of the thyroid gland and maintains homeostasis in the body;

"C" - parafollicular cells - producing calcitonin (the hormone that regulates the level of calcium in the body.

The anterior lobe of the pituitary gland regulates the function of the thyroid gland through thyroid hormone.

A regulator of thyroid function is the microelement "I" (iodine), the deficiency of which stimulates the function of the thyroid gland and inhibits the excess.

The functional activity of the thyroid gland depends on the concentration of thyroid hormones in the bloodstream.

It has been shown that thyroid hormones also have an impact on the activity of the central nervous system, and through this mechanism it is performed and interacts with the other endocrine organs: the sexual organs, the adrenal cortex, etc.

This explains the higher incidence of thyroid disease in women, in whose body there are considerable physiological fluctuations during life (puberty, menstrual cycle, pregnancy, births, abortions, climax, etc.).

Diagnosis of thyroid cancer

Clinical anamnesis

Thyroid cancer is a unique disease in that it retains its function. Thyroid cancer does not manifest in its early stages due to some pathognomonic or specific symptoms of this disease, it occurs almost asymptomatically or against the background of the symptoms of chronic background pathologies.

Malignancy of the pretumor process can be suspected by the following signs:

- sudden and rapid increase in volume of the gland;
- the appearance of induration and tuberosity;
- fixation of the tumor node.

Initially these symptoms refer only to the tumor nodule, later the whole lobe or the whole gland is involved. At the beginning, the patient only complains of a state of discomfort or sensations of compression. The general condition is satisfactory, the patient does not complain of pain.

The advancement of the tumor process in a short time causes the appearance of worrying symptoms: worsening of general health, sudden weight loss, severe asthenia, dyspnea, hoarseness, dysphagia, pain in the area of the humoral and cervical plexus.

As late symptoms we mention accentuated pain with irradiation in the occipital, supraorbital region and in the ear.

If the tumor process spreads in the mediastinum, compression and displacement of the organs and vessels take place, located in the mediastinum, a network of dilated veins occurs, asphyxia and elimination of bloody sputum may occur.

Therefore, the symptoms of thyroid cancer depend on the degree of tumor progression and the direction of its spread.

Functional disorders in thyroid cancer are rare, which is explained by the strong compensatory mechanism of thyroid adaptation.

In order to improve the preoperative diagnosis of thyroid cancer in the clinic “Surgery of tumors of the head and neck region” of the Oncological Institute of the Republic of Moldova, an algorithm was developed to diagnose nodular pathologies of the thyroid gland, including thyroid cancer.

This algorithm consists of:

1. Clinical examination (anamnesis, visual examination, palpation of the gland and lymph nodes).

From the anamnesis we find out the history of the disease, the treatment applied previously, the accusations at the time of the address.

General accusations include: severe irritability, tachycardia, asthenia. exophthalmos, insomnia, cardiac pain, diarrhea, dysmenorrhea, decreased work capacity.

From the local accusations we mention: the presence of the nodular formation on the anterior surface of the neck, difficult swallowing, hoarseness or dysphonia.

These symptoms vary from case to case.

Physical examination

Visually, the increased volume of the gland, symmetry, surface (tuberous, smooth), the presence or absence of exophthalmos, the condition of the skin, tremor, etc. are appreciated.

The boundaries of the tumor, the mobility of the nodule or the classic gland, the pain syndrome, etc. are palpably determined. The altered cervical ganglia can also be detected by palpation.

Paraclinical and laboratory investigations

For a more accurate diagnosis, special instrumental methods of investigation are applied.

Scintigraphy of the thyroid gland, which is based on the difference in uptake of radioactive iodine by normal and tumor tissue. “Cold” areas indicate the presence of tumor tissue.

Ultrasonography of the thyroid gland is widely used, being a relatively inexpensive and quite informative method. It allows the detection of nodules less than 1 cm in diameter (microcarcinomas).

Among the ultrasound signs specific to some malignant formations we mention: irregular contour of the nodule, different density and echogenicity of the normal tissue compared to the tumor, the presence of calcinates, the integrity of the nodular and / or glandular capsule, asymmetrical shape of the gland.

Sonoelastography is a new non-invasive method, which is based on

determining the tumor process by the degree of elasticity. The elastogram is associated with the color Doppler phenomenon:

- knot colored in green - elastic (SE-1);
- predominantly green node with blue inclusions - medium elasticity (SE-2);
- blue knot with small green sectors - low elasticity (SE-3);
- full blue knot - hard knot (SE-4).

SE means “elasticity score”. SE-4 indicates the malignant character of the nodular formation.

Computed tomography in the diagnosis of thyroid cancer is used less and only in less clear cases to detect the integrity of both the nodular capsule and the entire gland. Penetration of the capsule is a sign of the spread of the tumor.

The cytological method by thin needle dotted biopsy is currently one of the most informative methods in the differential diagnosis of benign and malignant nodules and is recognized as the “gold standard”. Aspiration puncture biopsy can be performed under both palpation and ultrasound control.

The sensitivity of this method varies between 65 and 98%, and the specificity of the method is 92%. The accuracy of the method does not depend on the size of the tumor, only to some extent - on the histological structure. The method was less informative in solid tumors (6-8%).

Aspiration biopsy can develop complications: minor bruising, pain instead of sampling, very rarely can develop edema with compression of the trachea and dyspnea. Gland abscesses can rarely develop.

Fine needle aspiration biopsy is also used to assess the condition of the cervical ganglia.

In the preoperative period, the lymph nodes from levels II, III, IV and V are evaluated, which showed signs of suspected malignancy on ultrasound.

The histopathological examination is the most informative, but it is postoperative, except when it is applied intraoperatively “ex temporaneu” in cases of difficult diagnosis.

Histopathological examination allows the determination of the histopathological type of thyroid cancer (follicular, papillary, medullary or undifferentiated carcinoma).

Classification of thyroid tumors according to TNM - AJCC, 8th edition, 2017

Category T	CriteriaT
TX	The primary tumor cannot be evaluated
T0	There is no evidence of primary tumor
T1	Tumor ≤2 cm in maximum size, limited to the thyroid
T1a	Tumor ≤1 cm in maximum size, limited to the thyroid
T1b	Tumor> 1 cm, but ≤2 cm in maximum size, limited to the thyroid
T2	Tumor> 2 cm, but ≤4 cm in maximum size, limited to the thyroid
T3	Tumor> 4 cm and limited to thyroid or macroscopic extrathyroidal extension invading only infrahyoid muscles
T3a	Tumor> 4 cm, limited to the thyroid
T3b	Macroscopic extrathyroidal extension that invades only the infrahyoid muscles (sternohyoid, sternothyroid, thyroid, or homohyoid muscle)
T4	Macroscopic extrathyroid extension
T4a	Tumor of any size with macroscopic extrathyroidal extension that invades the subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
T4b	Tumor of any size with macroscopic extratyroid extension invading the prevertebral fascia or circumferentially invading the carotid artery or mediastinal vessels

Definition of regional lymph nodes (N)

Category	Criteria N
NX	Regional lymph nodes cannot be evaluated
N0	There is no evidence of metastases in the loco-regional lymph nodes
NOa	One or more benign lymph nodes confirmed cytologically or histologically
NOb	There is no radiological or clinical evidence of metastases in loco-regional lymph nodes
NI	Metastases in the regional lymph nodes
NIa	Metastases in the lymph nodes at level VI or VII (pretracheal, paratracheal or prelaryngeal / dolphin, or superior mediastinal). The damage can be unilateral or bilateral.
NIb	Metastases to the lymph nodes in the lateral cervical compartment unilaterally, bilaterally or contralaterally (levels I, II, III, IV or V) or to the retropharyngeal lymph nodes

Definition of distant metastases (M)

CategoryM	Criteria M
MO	There are no distant metastases
Ml	Distant metastases

AJCC GROUPS PROGNOSTIC STAGE Differentiated carcinoma

When the age at	And T	And N ...	And M	Then the stage is
<55 years ≥	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
≥55 years	T1	N0/NX	M0	I
≥55 years	T1	N1	M0	II
≥55 years	T2	N0/NX	M0	I
≥55 years	T2	N1	M0	II
≥55 years	T3a/T3b	Any N	M0	II
≥55 years	T4a	Any N	M0	III
≥55 years	T4b	Any N	M0	IVA
≥55 years	Any T	Any N	M1	IVB

Anaplastic carcinoma

When T	And N ...	And M	Then the stage is
T1-T3a	N0/NX	MO	IVA
T1-T3a	N1	MO	IVB
T3b	Any N	MO	IVB
T4	Any N	MO	IVB
Any T	Any N	Ml	IVC

Complications in the treatment of thyroid cancer

Complications in surgical treatment:

a) general:

- bleeding;
- hematomas;
- inflammatory processes in the wound;

b) local complications:
- recurrent nerve trauma;
- trauma of the sympathetic nerve with the installation of Horner's syndrome (ptosis, exophthalmos, narrowing of the pupil);
- trauma to the accessory nerve;
- trauma of the parathyroid glands with the installation of hypoparathyroidism.

Treatment of thyroid cancer

Selecting an optimal method of treatment for thyroid cancer is a difficult task, given the polymorphism of tumor structure, rapid and massive metastasis, the difficulties of early diagnosis, the debatable problems of complex treatment. Although some successes in radiotherapy have been achieved in recent years, the drug and hormone treatment of thyroid cancer, as a basic method remains surgery - radical surgery.

In choosing the optimal variant of intervention, not only the principle of radicality is taken into account, but also the principle of functionality.

The treatment is planned strictly individually for each patient, based on the degree of spread of the tumor, the histological structure, the character and direction of spread, but also the age and sex of the patient.

Within the treatment of thyroid cancer, 3 types of surgery have been developed:

1) typical operations;
2) extended operations;
3) combined operations.

Typical operations

1. Thyroid gland resection is indicated in pretumorous conditions, thyroid adenomas, toxic nodular goiter, autoimmune thyroiditis, thyroid cancer T1N0M0, st. Takes.

It is performed in case of tumor node less than 1 cm in diameter within the parenchyma. It consists of excision of the lobe affected by the isthmus. In this type of operation, only the degree of local spread is taken into account, regardless of the patient's age and sex. The principles of ablation and the preservation of the function of the gland and the recurrent nerve are strictly observed.

2. Subtotal resection - is indicated in case of tumor nodules larger

than 1 cm, without capsule invasion, T2a-3aN0M0. It consists of resection of the affected lobe, isthmus and partially of the unaffected lobe.

3. The maximum subtotal resection - it is indicated in tumors 2-4 cm - consists in the excision of the affected lobe in block with the contralateral lobe and of the isthmus. Keep healthy glandular tissue in place of the recurrent nerve in the larynx (about 3-5 g). The parathyroid glands are preserved if they are not affected.

If the tumor has spread to the immediate vicinity of the parathyroid glands, they are transplanted into the sterno-cleido-mastoid muscle.

4. Thyroidectomy - is indicated in case of damage to both lobes and penetration of the capsule, st. T2b-3bN0M0. Tumor 2-4 cm in size the largest within the gland. Total excision of both lobes and isthmus is performed, keeping the recurrent nerve and parathyroid glands unaffected. Thyroidectomy also does not take into account the histological shape of the tumor, the presence or absence of metastases.

Only the extent of the parenchyma of the gland is taken into account. The volume of the thyroidectomy may be changed intraoperatively if necessary.

5. Minimally invasive organ management operations. The method of minimally invasive operations is a relatively new method. It has the same indications as in other typical operations. It aims to reduce the postoperative pain syndrome, to obtain favorable cosmetic results, to reduce the hospitalization term, to reduce the cost of treatment.

There are special instructions for this type of operation:

- affecting a single lobe;
- the tumor nodule should not exceed the volume of 2.0-2.5 cm;
- lack of regional metastases;
- without penetration of the capsule;
- is not performed in patients with short necks.

The incision on the anterior surface of the neck is 2.5 - maximum 4.5 cm.

The postoperative period is uncomplicated, patients do not require postoperative treatment. It has a great cosmetic advantage, especially for young women.

Enlarged operations

1. Enlarged thyroidectomy with excision of the cervical soft tissues and adjacent muscles (T3aN0M0) (T3aN1M0).

Type 2 - with minimal spread in the muscles, in the soft tissues, with the involvement of the recurrent nerve.

Total removal of the block gland with the cervical soft tissues and muscles involved and the modified regional ganglion is performed).

Combined operations

1. T4N0M0 - are indicated in widespread thyroid cancers, tumors of any size, with fixation of the glandular capsule and major spread (in the trachea, larynx, esophagus). Combined thyroidectomy + resection of 1-3 tracheal rings, laryngeal cartilage and esophageal muscle layer is performed.
2. They are indicated in thyroid cancers with major spread (in the trachea, larynx, esophagus T4N0M0) and in cancers with capsule damage and metastases in the cervical, paratracheal and mediastinal ganglia - T3N2M0; T4N1M0, any T, N1-2M0. The operation is performed in the primary focus, based on the degree of local spread of the tumor + cervical or mediastinal lymph node dissection.

Patients after combined operations require postoperative radiotherapy or chemotherapy as directed for each individual case.

All patients receive L-Thyroxin in the required doses of Ca + vit after surgery for the thyroid gland. D, and are on record at the oncologist and endocrinologist at the place of residence.

Radiotherapy

In thyroid cancer, radiotherapy in the form of telegamatherapy is used in the preoperative period in case of widespread primary tumors or in recurrences after non-radical surgical treatment. Areas of regional metastasis are also included in the irradiated tissue block.

Radioactive iodine radiotherapy (I131), a method based on the ability of glandular tissue to pick up radionuclides (metabolic radiotherapy), is also used to treat thyroid cancer. This capacity is possessed by follicular adenocarcinoma and very few other forms (5-10%). The curative effect of this method is short-lived.

Drug treatment

Thyroid cancer practically does not respond to the action of cytostatics, known today, the positive reaction being recorded only in 10-15% of cases.

There was a negligible positive effect when the adriamycin was combined with cisplatin or bleomycin.

Chemotherapy is currently indicated in widespread differentiated cancers, resistant to hormone and radiotherapy, in anaplastic forms, in medullary and undifferentiated cancers inoperable.

Prognosis in thyroid cancer

The factors that influence the prognosis and survival without relapse in thyroid cancer are divided into 4 groups:

1) Biological factors - the potential for tumor invasion and metastasis;
2) Demographic factors - age and sex of patients;
3) time factor - the period from the onset of the disease to diagnosis;
4) Radical treatment - this factor is the only one that is available to the doctor. The prognosis will largely depend on the correct diagnosis and the application of the most appropriate and maximum radical method.

The prognosis also depends on the histological type of the tumor, the degree of progression, the presence of metastases, etc.

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CANCER OF THE ORAL MUCOSA

The mucosa of the oral cavity and the adjacent tissues have a complex anatomical structure, which influences the specificity of the evolution of cancers in this location and their treatment.

The vast majority of malignant tumors of the oral mucosa are squamous cell carcinomas and rank second in the structure of malignant tumors after laryngeal cancer. Men aged 60-70 are mainly affected. According to some authors, the cancer of the mucous membrane of the oral cavity is located in the following anatomical structures: - mucous membranes of the tongue - about 50%:

- oral mucosa of the mouth - about 20%
- alveolar ridge of maxilla and hard palatine ≈ 9%
- soft palatine mucosa - ≈ 6.2
- alveolar ridge of the mandible - ≈ 2%

Tumors of the oral mucosa have a different genesis, they can be both benign and malignant. The benign ones are usually of epithelial origin (papillomas), the ones of glandular origin develop from the small salivary glands.

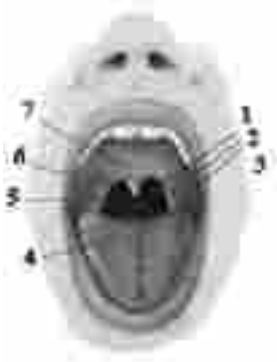
Most malignancies have an epithelial structure, and melanomas and sarcomas are less common.

Malignant tumors of epithelial origin in 90-95% of cases have epithelial structure in 90-95% of cases have the structure of keratinized squamous epithelium.

Topographic anatomy, physiology and vascularization

Primary location (s)

The oral cavity extends from the skin-vermilion junction of the lips to the junction of the hard and soft palate (upper) to the line of the circumvalled papillae (lower) and to the amygdala pillars (lateral) (see Fig. 1). In addition, it is divided into several specific locations listed below.



1. Palatopharyngeal envelope
2. Palatal tonzila
3. Palatoglossal envelope
4. The dorsal part of the tongue
5. Oropharynx
6. Uvula
7. Soft palace

Fig. 1. *The oral cavity*

Lip mucosa - The lip begins at the junction between the edge of the vermilion and the skin and includes only the surface of the vermilion or that part of the lip that comes in contact with the opposite lip. The rest of the vermilion is staged in the chapter on skin (Chapter 47). It is subdivided into the upper and lower lip, joined at the corners of the mouth.

Oral Mucosa - The oral mucosa includes the entire membrane of the mucosa lining the inner surface of the cheeks and lips, from the line of contact of the opposite lips to the line of attachment of the mucous membranes of the alveolar ridge (upper and lower) and the pterygomandibular ligament.

Inferior alveolar ridge - Inferior alveolar ridge refers to the mucosa that covers the alveolar process of the mandible, which extends from the line of attachment of the mucosa in the lower gingival-buccal groove to the line of attachment of the free mucosa of the buccal floor. Later, it extends to the ascending branch of the mandible.

Upper alveolar ridge - The upper alveolar ridge refers to the mucosa that covers the alveolar process of the jaw, which extends from the line of attachment of the mucosa to the upper gingival-buccal groove to the junction of the hard palate. Its posterior margin is the upper end of the pterygopalatine fossa. Retromolar gingiva (retromolar trigone) The retromolar gingiva, or retromolar trigone, is the attached mucosa that covers the ascending branch of the mandible, from the posterior surface of the last lower molar to the upper apex, adjacent to the tuberosity of the jaw.

Buccal floor - The buccal floor is a semicircular surface that covers the mylohyoid and hypoglossal muscles, which extends from the inner surface of the lower alveolar ridge to the lower surface of the tongue.

Its posterior limit is the base of the anterior pillar of the amygdala. It is divided into two parts by the frenulum of the tongue and includes the ostia of the submanidibular and sublingual salivary glands.

Hard palate - The hard palate is the crescent-shaped area between the upper alveolar ridge and the mucous membrane that lines the palatine process of the palatine maxillary bones. It extends from the inner surface of the upper alveolar ridge to the posterior edge of the palatine bone.

Considered a separate category from the World Health Organization (WHO).

Two previous thirds of language (oral language)

The anterior two thirds of the tongue represent the free mobile portion of the tongue, which extends anteriorly from the line of the circumvalled papillae to the lower surface of the tongue, at the junction with the buccal floor. It consists of four areas: the apex, the lateral margins, the dorsum and the lower surface (the non-villous ventral surface of the tongue). The lower surface of the tongue is considered a separate category from the World Health Organization (WHO).

Diagnosis of oral mucosal cancer

Clinical and laboratory

There are 3 periods in the clinical course of cancer of the oral mucosa:

1. early period - is characterized by unclear sensations, in the oral cavity, on the mucosa appears an induration, may appear a whitish spot or papillomatous growths, or an ulceration; Pain is rare during this period, if present it is associated with angina or toothache.
2. onset period - is characterized by a lot of symptoms. Pain of varying intensity (mutilating), local or irradiated in the temporal, auricular region, or at the base of the skull. Hypersalivation occurs as a result of superinfection tumor decomposition (fetid odor).
3. advanced period - the tumor spreads to adjacent tissues, affecting all nearby organs, swallowing disorders (mechanical dysphagia), hemorrhagic phenomena, phonation disorders.

There are 2 clinical forms of cancer of the oral mucosa.

Exophytes:

- papillary
- Ulcerative

Endophyte:

- infiltrative-ulcerative form (small ulcer, extensive infiltration, the limits of which are difficult to establish;
- infiltrative form, extensive infiltrate without ulcerative manifestations.

For cancer of the oral mucosa, it is characterized by rapid spread on adjacent anatomical structures and a relatively rapid metastasis (40-76%) depending on the location of the tumor, the clinical form and the degree of spread.

Classification of tumors of the oral mucosa according to the TNM system – AJCC, 8th edition, 2017

Tx - the primary tumor cannot be detected
T0 - the primary tumor is not detected
Tis - carcinoma in situ
T1 - tumor less than 2 cm
T2 - tumor up to 4 cm
T3 - tumor larger than 4 cm
T4 - tumor invades neighboring anatomical structures - bone, deep muscles of tongue, maxillary sinus, dermis

N - regional lymph nodes

N / pNx - not enough data to assess regional lymph nodes;
N / pN0 - metastases in regional lymph nodes are not detected
N / pN1 - solitary metastasis less than 3 cm in diameter on the affected side
N / pN2 - a) Mt ganglion up to 6 cm in diameter on the affected side;
b) Mt multiple lymph nodes on the affected side, of which at least one is 6 cm in diameter;
c) Mt bilateral or contralateral ganglia up to 6 cm in diameter
N / pN3 - Mt ganglion greater than 6 cm.

M - hematogenous metastases at a distance of Mx, M0, M1

Clinical stage 0 - Tis - N0 - M0
Clinical stage I - T1 - N0 - M0
Clinical stage II - T2 - N0 - M0
Clinical stage III - T3 - N0 - M0
Clinical stage III - T1-3 - N1 - M0
Clinical stage IV - T4 - N0, N1 - M0
- any T - N2, N3 - M0
- any T - any N - M1

Histopathological classification

1. Intraepithelial carcinoma (in situ) - the epithelium has signs of malignancy, the basement membrane is intact;
2. Squamous cell carcinoma - invades the connective tissue;
3. Variants of squamous cell carcinoma:
   - wart carcinoma
   - fusiform carcinoma
   - lymphoepithelioma.

Metastatic pathways

Regional lymph nodes

The risk of regional metastases is usually related to category T. In general, cervical lymph node involvement at a primary location in the oral cavity is predictable, spreading first to the upper cervical lymph nodes, then to the middle and later the lower ones. Any previous treatment of the neck, surgery or radiation therapy, can alter the normal patterns of lymphatic drainage and can lead to the unusual spread of the disease in the cervical lymph nodes. Lip cancer, with a low metastatic risk, initially affects the adjacent submental and submandibular lymph nodes, then the jugular lymph nodes. Hard palate cancers also have a low metastatic potential and affect the buccal ganglia, facial and submandibular, vascular, and occasionally retropharyngeal lymph nodes. Other oral cancers spread mainly to the submandibular and jugular lymph nodes and less frequently to the lymph nodes of the posterior / supraclavicular triangle. Cancer of the anterior oral language can occasionally spread directly to the lower jugular ganglia. The closer the primary location to the midline, the greater the tendency to spread to the bilateral cervical ganglia.

Benign tumors

From benign tumors of the oral floor we distinguish: obligatory processes with a high potential for malignancy - Bowen's disease (dyskeratosis); doctors with a low potential for malignancy - warty leukoplakia, papillomatosis, postactin stomatitis, lupus erythematosus, etc.

BUCCAL FLOOR MUCOSA CANCER

A fairly high incidence in the structure of cancers of the oral cavity is cancer of the oral mucosa (20% of all locations of the oral cavity).

It is characterized by rapid spread of the tumor process in the adjacent tissues (tongue, alveolar process of the mandible, on the contralateral side of the floor, which greatly aggravates the prognosis. The tumor spreads in all directions, including the lower hyoid bone.

Oral cancer often develops asymptomatically in the form of a small ulcerous fissure, but with hard infiltration over a large area. The association of the common infection causes an inflammatory process, which results in pain, hypersalivation and difficulty swallowing.

For this form of cancer, lymph node metastasis is characteristic, often the metastatic lymph node being the first clinical sign. Occult lymph node metastases increase as the cancer progresses. Thus, at st. They are found in about 40% of patients, and in st. III - 70%. Remote metastases occur in 10-15% of patients.

Cancer of the mucous membrane of the cheeks, gums, alveolar ridges in most cases is asymptomatic in the early stages. Only painless leukoplakia can be observed, only in locations on the alveolar ridges pain appears in the region of the teeth, which leads to diagnostic errors.

The adenocarcinomas of the hard palatine are particularly aggressive, which are painless and soon invade the bone tissue, then spread to the nasal cavity and paranasal sinuses.

Diagnostic methods

The diagnosis of tumors of the oral mucosa includes: visual and palpable examination, orthopantography may show a thickening of the bone tissue but does not reveal in the early stages the damage to the cortical layer. Oral and nasopharyngeal fibroscopy, X-ray and computed tomography of the facial skeleton is the most optimal diagnostic method that shows the spread of the process in the soft tissues, the identification of vessels and bone tissue. MRI provides better visualization for soft tissues and the

base of the skull, as well as CNS visualization. Biopsy with cytological and morphological examination of the material collected from the primary tumor and the modified regional ganglia.

Treatment of cancer of the oral mucosa

In st. I-II (T1-2-N0-M0) applies to:

- Telegamatherapy or associated radiotherapy in the primary focus (60-70 Gy) and metastatic areas. The remaining tumors undergo surgical treatment.
- Surgical removal of a primary tumor - fascicolo-fascial lymph node dissection or Crile-type surgery. In infiltrative tumors or neuro-vascular invasion, postoperative radiotherapy is recommended in the removed tumor lodge. Chemotherapy is applied only in cases where previous methods have failed.

The st. III (T3-NO-M0) is applied combined treatment: surgical removal of the tumor with plastic recovery, highlighting of uni- or bilateral regional lymph nodes + radiotherapy in the tumor lodge (60-70 Gy).

In st. III-IV (T1-3N1-3M) surgery is used in case the tumor is operable + lymph node discharge in adequate volume. Chemotherapy is applied in cases where other methods have been ineffective.

Rehabilitation of patients after extended interventions includes soft tissue defect plasty and / or bone defect closure, immediate endoprosthesis or post-operative wound healing. Patients with defects of the hard palate, in particular, need immediate prosthetic rehabilitation in order to improve their quality of life (isolation of the oral cavity from the nasal cavity).

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