**MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE**

**UZHHOROD NATIONAL UNIVERSITY**

 DEPARTMENT OF GENERAL SURGERY

**Basics of oncology**

Methodological instructions for 3th year medical students’ individual training

**Uzhhorod – 2024**

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**Basics of oncology**

**I. Topic actuality:**

From the middle of the 20th century. diseases associated with neoplasms have become widespread and now occupy the second place among the causes of death (15-25%), second only to cardiovascular diseases. Reliable prevention of malignant diseases is still impossible, diagnosis in the early stages is problematic. Treatment of tumors, as a rule, begins with a delay, directed not at the pathogenetic bases, but at the manifestations of the disease. All doctors must be alert and competent in the diagnosis and treatment of neoplasms, know the examination algorithm and the principles of modern tumor treatment, which will significantly improve timely diagnosis and prognosis in the treatment of cancer patients.

**II. Teaching aim:**

**2.1. The student must know:**

* Cancer biology and natural history of cancer
* Etiopathogenesis
* Classification of tumors
* Risk factors
* Epidemiology
* Clinical workup and staging
* Basic principles of diagnosis of cancers
* Modern methods of diagnosis of cancer diseases
* Basic principles of cancer treatment
* Screening of cancer disease.

**2.2. The student should be able to:**

* List the conditions and factors contributing to the occurrence of tumors, classification, general and local clinical manifestations of cancer, specific symptoms of tumors.
* Put algorithm of diagnosis of malignancy, Assess prognosis of patient.
* Formulate the principles of complex treatment of various clinical groups of cancer patients, influence on the primary and secondary stages of the cancer process.

**III. Basic level of knowledge and skills:**

* classification and presentation of benign and malignant tumors.
* Molecular biology of neoplasm.
* Methods of radiological and laboratory investigations.
* Pharmacology of anti-cancer drugs.

IV. The program of self-preparation of the students:

|  |  |  |
| --- | --- | --- |
| **№** | **Task Maintenance** | **Task maintenance concrete definition** |
| 1.       2.      3.  | Cancer biology, natural history of cancer disease      Diagnosis      Treatment  | 1. benign and malignant tumors characteristics. 2. molecular biology of neoplasm. 3. histological classification of malignant tumors.4. pathogenesis of cancer. 5. epidemiology and risk factors.1. staging of malignant tumors.2. methods of laboratory investigations for malignant tumors, biopsy.3. modern methods of investigations in oncology4. instrumental and imaging studies in diagnosing different malignancies.1. basic principles in treatment of cancers. 2. role of locoregional therapies in treatment of cancer disease3. role of general\systemic therapies in treatment of cancer disease.4 screening.  |

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**V. Short methodical instructions for practical study work.**

* After introductory teacher's word, control of the level of knowledge and skills of the students.
* The group carried out the individual educational tasks.
* The students acquaint with work of the department in oncological clinic.

**VI. Content of the topic**

Oncology is the science that study the malignant tumors, their prevention, detection, and treatment.

The term "onco" comes from the old Greek oncoma (Greek, blastoma. neoplasma; Latin tumor) - a tumor, neoplasm.

 Malignant tumor is a pathology that arises as a result of changes in the biological, functional, metabolic and nuclear properties of cells which is characterized by unlimited progressive growth.

Natural history of cancer

 The German pathologist Virkhov R. (1821-1902) believed that chronic irritation is the trigger for the development of tumors.

There is a theory of chronic carcinogenesis. More than 1,000 chemical compounds are known to increase the risk of development of tumors. Most of them are chemically inert and are only procarcinogens. Under the action of the enzyme systems of the body, they are activated and become true carcinogens that interact with nucleic acids and the genome of cells. This serves as a trigger for the transformation of normal cells into tumor cells.

Zilber L.A. (1894-1966), the author of the virogenetic theory, believed that the transformation of normal cells into malignant ones occurs during the interaction of specific genetic viruses with the genome of cells. About 600 viruses are known, of which more than 100 have oncogenic potential. There are few highly oncogenic viruses. Transformation does not occur if the cells are resistant to viruses, and if they are sensitive, the virus is incorporated (penetrates into the genome) and multiplies. Then the cells either die or transform into malignant ones.

 Other mechanisms that can contribute to the appearance of tumors in the body is immune deficiency, immunodepression.

A tumor appears not only because carcinogens turn a normal cell into a tumor, but also because they suppress immunological reactions. As the tumor grows, its decay products support immunodepression. According to the polyetiological theory, all factors are important for the appearance of a malignant tumor.

Carcinogenesis: is a multistage process involving mutations and other genetic changes in the cells caused by repeated stimuli, leads to dysregulation of reproduction and migration of cells, reducing sensitivity of the cells to the external immune regulation signals, and invading of apoptosis.

Main theories of carcinogenesis: 1) cellular change (mutation theory).

 2) Carcinogens. 3) Proto-oncogenes and oncogenes.

Mutation theory were firstly explained by Hugo de Vries (1901), and states that evolution is jerky process where new versions and species maybe formed by mutation by sudden or spontaneous changes in heritable level of the organism.

Carcinogens are endogenous and exogenous factors that influence the cells to transformation and becoming malignant.

Endogenous factors include hormones, immune conditions, and inherited mutations.

Exogenous factors include chemical ([Aflatoxins](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/aflatoxins) , [Aristolochic Acids](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/aristolochic-acids), [Arsenic](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/arsenic) [Asbestos](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos), [Benzene](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/benzene), [Benzidine](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/benzidine), [Beryllium](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/beryllium) , [1,3-Butadiene](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/butadiene), [Cadmium](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/cadmium) , [Coal Tar and Coal-Tar Pitch](https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/coal-tar)), biological such as any infections that may lead to malignancy ( hepatitis B and C viruses, Human papilloma virus,Epstein-Barr Virus (EBV), Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1),H Pylori. Physical factors like radiation, sun exposure.

Protooncogenes are normal body genes which physiologically effect the normal cell growth and proliferation. As it comes in third theory protooncogenes turns into active cellular oncogenes as a result of the inclusion of a promoter (amplification, translocations, insertions, transduction, point mutation) lead to irreversible changes of these genes.

Stages of carcinogenesis

1. Initiation: is the stage of conversion of proto-oncogenes into active cellular oncogenes as a result of the inclusion of a promoter. Is the need for cell replication without repair of the damaged DNA. Initiation is irreversible, usually involves simple DNA mutations that are ‘fixed ’by cell division, and results in no morphological changes to the cells. Single exposure to a carcinogen may be enough for initiation.
2. Promotion: is the process whereby an initiated tissue or organ develop focal proliferations and it requires the presence of continuous stimulation for completion of this stage. The genome of the cells changed towards uncontrolled hyperplasia. This leads to the formation of the primary tumor site and then to the formation of tumors. Promotion is a reversible process requiring multiple exposures to the carcinogen, usually with a dose – response threshold.
3. Tumor progression and metastasis: described the stage whereby neoplasms acquire the ability to further grow, to invade adjacent tissues, and to establish distant metastasis. Progression is an irreversible step that results in morphologically identifiable cellular changes. Tumor progression models includes:
* Hyperplasia: proliferation increases, tissue stays organized.
* Metaplasia: cells in tissue are replaced by cells that do not belong there.
* Dysplasia: abnormal cell appearance, more cells than normally present.
* Neoplasia, invasion, malignant.

The hallmarks of cancer cells are the properties of the neoplastic cells to survive grow and spread inside a healthy tissue and these hallmarks include:

* Self-sufficiency in growth signals (independence of growth factors and growing).
* Insensitivity to anti-growth signals.
* Evading of apoptosis (don’t die).
* Angiogenesis activation (independent nutrition).
* Inflammatory microenvironment.
* Limitless replication potential.
* Tissue invasion\necrosis and metastasis.

Self-sufficiency in growth signals can be seen in growth autonomy of cancer cells. Normal cells need external signals from growth factors to divide while cancer cells are not dependent on normal growth factor signaling. Acquired mutations on normal growth factors transforming them from normal body genes into oncogenes. In such way the cancer cell become independent from body growth factor pathways which lead to unregulated growth. Cancer cells also have the ability to increase the receptors of growth factors to increase the process of growth and proliferation.

Insensitivity to antigrowth signals is another feature of cancer cell. While normal cells respond to inhibitory signals to maintain homeostasis, cancer cells do not respond to growth inhibitory signals. Acquired mutations or gene silencing interfere with the inhibitory pathways. Mostly the mutations on the antigrowth factor’s receptors make the antigrowth factors unable or hard to act on malignant cell.

Cancer cells can invade the apoptosis by acting on both extrinsic and intrinsic pathways. Malignant cells escape apoptosis by different ways, reducing levels of CD95 may render the malignant cell less susceptible to apoptosis by fas ligand, some cancer cells have high level of FLIP protein which can bind to apoptosis inducing signaling and prevent activation of caspase 8(protease which initiate proteolytic process.

Also reducing egress of chromosome c from mitochondrion, reducing the levels of proapoptotic BAX gene and losing of apoptotic protease activating factor-1 all can lead of escaping of cancer cells from immunity.

Limitless replicative potential

Normal human cells have capacity of 60-70 replication(doubling) after which the cells become senescent. This happens due to progressive shortening of telomeres at the end of chromosome. Short telomeres are normally recognized by the DNA repair leading to cycle arrest by p53 and RB genes. Cancer cells maintain the length of their telomeres, altered regulation of telomere maintenance results in unlimited replicative potential.

Angiogenesis s (formation of new blood vessels)

Normal cells depend on blood vessels to supply oxygen and nutrients. Cancer cells induce angiogenesis, the growth of new blood vessels, needed for tumor survival and expansion.

Tumor cells cannot grow more than 1-2 mm unless they have a good vascularization. Cancer cells stimulates neo-angiogenesis during which new blood vessels sprout from the existing capillaries or stimulates the angiogenesis in which endothelial cells created from bone narrow. These new blood vessels are mostly abnormal, dilated, leaking causing bleeding, anemia and thrombosis risk for patient in addition for their function toward cancer cells of nutrition and oxygen transporting to cancer cells and helping in cancer cells transporting by vascular invasion which may lead to metastasis process initiation. Also, the newly formed endothelial cells stimulate the growth of corresponding cancer cells by secretion of growth factors such as insulin like growth factor, granulocyte macrophage colony stimulating factor and platelet-derived growth factor. The inducer of the angiogenesis process is the vascular endothelial growth factor (VEGF).

 Virtually all tumors contain inflammatory immune cells. Inflammation is an immune response that can facilitate the ability of acquiring the core hallmarks of cancer. For example, inflammatory cells can provide growth factors and enzymes that promote angiogenesis and invasion – In addition, inflammatory cells can release oxygen species that are mutagenic.

Normal cells maintain their location in the body and generally do not migrate. The cancer cells unfortunately are able to movement of cancer cells to other parts of the body and it is a major cause of cancer deaths.

Human tissues are organized into a series of compartments separated from each other by extracellular matrix which include the basement membrane and the interstitial connective tissue, each of them consists of collagens, glycoproteins and proteoglycans. In order to spread the cancer cell, need to invade the extracellular matrix, the invasion of matrix need a several processes to be done by cancer cells

* Detachment of tumor cells from each other.
* Degradation of extracellular matrix.
* Attachment to extracellular matrix components.
* Migration of tumor cells.

Epidemiology of cancer

Epidemiology of cancer diseases is the study of the distribution of the oncological diseases and their outcomes in population and specific groups of population.

The main subjects of epidemiology of oncological diseases are mainly:

Cancer incidence rate: number of new verified cases of cancer per one hundred thousand of population. Here we can see highest cancer incidence in adults is prostate cancer in men population and breast cancer in female population. While in pediatric population highest incidence oncology is the acute leukemia, and most common solid cancer is CNS tumors.

Mortality rate: is the number of deaths due to oncological diseases per one hundred thousand of population. Lung cancer has the highest mortality between oncological diseases in both males and females followed by colorectal cancer.

Prevalence of disease: is the number of people living with the oncology.

Survival rate: is the percentage of people who survive more than 5 years after the diagnosis.

Life time risk: the probability of a person over his life time to develop oncology or die due to it.

Relative risk: the study of the relationship between a specific risk factor and an oncological disease.

According WHO the most common cancer`s incidence in 2020 were:

* breast (2.26 million cases);
* lung (2.21 million cases);
* colon and rectum (1.93 million cases);
* prostate (1.41 million cases);
* skin (non-melanoma) (1.20 million cases);
* stomach (1.09 million cases).

While the most common cancer mortality in 2020 were:

* lung (1.80 million deaths);
* colon and rectum (916 000 deaths);
* liver (830 000 deaths);
* stomach (769 000 deaths); and
* breast (685 000 deaths).

Each year, approximately 400 000 children develop cancer. The most common cancers vary between countries. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020.

Risk factors of cancer

Cancer risk factors include exposure to chemicals or other substances, as well as certain behaviors. They also include things people cannot control, like age and family history and hereditary conditions.

1. Age: Advancing age is the most important risk factor for cancer overall and for many individual cancer types. As the process of aging decrease the tissue remodeling and increase risk of DNA mutations.
2. Gender: some types of cancers are gender specific such as prostate cancer in men population, ovarian, cervix and breast cancers in women population.
3. Smoking and alcohol: by causing direct and chronic damage to the tissues. Drinking alcohol can increase your risk of cancer of the mouth, throat, esophagus, larynx (voice box), liver, and breast. Tobacco use causes many types of cancer, including cancer of the lung, larynx (voice box), mouth, esophagus, throat, bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukemia.
4. Environmental factors: and includes chemical, physical and biological factors. Chemical factors include (Aflatoxins, Aristolochic Acids, Arsenic Asbestos, Benzene, Benzidine, Beryllium, 1,3-Butadiene, etc.). Physical factors include radiation (UV-radiation, ionizing radiation, overexposure to sunlight). Biological factors include several infectious agents that can increase the risk of malignancy in the affected cells (Hepatitis B Virus and Hepatitis C Virus (HBV and HCV) hepatocellular carcinoma. Epstein-Barr Virus (EBV) lymphoma. Human Papillomaviruses (HPVs) cervical cancer, colon, oropharyngeal vaginal and penile. Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1). Helicobacter pylori (H. pylori) gastric cancer.
5. Family history and hereditary germline mutations: Approximately 5% to 20% of all cancers are hereditary. (Ataxia-Telangiectasia, Beckwith-Wiedemann Syndrome, Familial Adenomatous Polyposis, Familial GIST, Familial Malignant Melanoma, Familial Pancreatic Cancer, Hereditary Breast and Ovarian Cancer, Hereditary Diffuse Gastric Cancer, Hereditary Leiomyomatosis and Renal Cell Cancer, Hereditary Mixed Polyposis Syndrome, Hereditary Pancreatitis, Hereditary Papillary Renal Carcinoma).
6. Chronic inflammations: such as Cohn's disease and ulcerative colitis in risk of colon cancer.
7. Immune systems insufficiency: congenital immunodeficiency (Wiskott-Aldrich syndrome, severe combined immunodeficiency) and acquired immunodeficiency (AIDS).
8. Hormonal imbalance.
9. Diet.

Pre-cancerous diseases: are diseases which may cause malignant tumors. These diseases may be benign conditions with highly malignization ability, or even with metaplastic changes such us Barret esophagus and Paget's disease of nipples.

Optional precancerous: diseases with low possibility of malignant transformation such as fibro adenomas of the breast, chronic gastritis.

Obligate precancerous: diseases with high incidence of malignant transformation such as chronic gastric ulcers and gastrointestinal polyposis.

Classification of tumors

Modern classification of tumors is based on clinical and morphological principles. All neoplasms are divided into benign and malignant.

Benign neoplasms (tumor benignus) are named according to the tissues where the tumor arose, and the suffix -oma is added: from adipose tissue - lipoma; from muscles - myoma; from vessels - angioma; from nerves - neuroma; from cartilage, chondroma, etc.

benign neoplasms mostly have a rounded shape, clear contours, they are painless, mobile, as they are not connected to the surrounding tissues; regional lymph nodes are not affected, there are no metastases. Benign neoplasms are almost indistinguishable in their cellular structure from the tissue from which they arose; grow, as a rule, slowly (for several years, sometimes reaching significant sizes), expansively, that is, they do not grow into adjacent tissues and organs, but only push them away. They do not affect the general condition of the body.

Clinically, they may manifest as signs of compression of nearby hollow organs, large vessels, and nerves. Sometimes benign neoplasms can disrupt the functions of organs or systems of the body, even be a threat to life (compression of mediastinal organs, brain, etc.).

"Tumor in situ" is a preinvasive tumor, that is, it is in a non-infiltrative phase of development and is localized only within the mucous membrane. It is most often diagnosed in the area of ​​the cervix due to the widespread use of colposcopy. Morphologically the tumor cell is different from the original normal tissue but without invasion of surrounding area.

Malignant tumors (tumor malignus) are divided into 3 groups: 1st - epithelial, which develop from glandular or squamous epithelium cancer (carcinoma); 2nd connective tissue, mesenchymal sarcomas (sarcoma - from the Greek sarcos meat), osteosarcoma, rhabdomyosarcoma, angiosarcoma, etc.

3rd group of mesenchymal tumors also includes hemoblastoses (mainly leukemias, non-Hodgkin lymphomas, and lymphogranulomatosis).

Malignant tumors are characterized by the following features:

a) rapid tumor growth due to uncontrolled cell proliferation;

b) Relative autonomy, that is, independence of cell reproduction;

c) anaplasia (loss of differentiation, properties characteristic of normal differentiated cells);

d) invasive or infiltrative growth- the tumor grows into adjacent tissues, destroying them, to different depths in the form of infiltrates. Clinically malignant tumors, as a rule, are lumpy, dense, immobile or immobile, fused with neighboring tissues, and do not have a capsule. There are 3 types tumor growth: endophytic (similar to infiltrative, ulcerative infiltrative, characterized by lack of clear margins), exophytic, when the tumor grows into the lumen of the organ with relatively clear edges, and mesophytic (a transitional form, combination of both types above).

Therefore, for the intervention to be radical, a tumor, especially an endophytic one, must be removed with a part of the surrounding tissues.

e) tendency to relapse: Relapses most often occur precisely because of infiltrating growth and the presence of tumor cell complexes in healthy tissues;

f) the ability to metastasize. Initially, the tumor is localized. Over time (after several weeks, months), as a result of infiltrative growth, the basal membranes of the tissue are destroyed, the process begins to spread.

Metastasis occurs in several stages:

1- Separation of cells from the tumor;

2- penetration of cells into the lymphatic and (or) vascular blood stream;

3- migration, circulation of cells in lymph and blood throughout the body. During this period, many cells are lysed and die due to immunity.

4- stage of sticking to the vessel wall or in the lymph node;

5- tumor embolus;

6- exit of the cell from the vessel to the outside;

7- development of a metastatic node.

Routes of metastasis:

1. Lymphatic.
2. Hematogenous.
3. Body fluids (peritoneal, CSF).
4. Local invasion.

 The main periods of tumor development are:

1. Preclinical period - the time from asymptomatic tumor development of malignant cells before the first symptoms.
2. 2- Clinical period - the disease within 2-4 years after the first symptoms of the disease and the patient's recovery or death.

TUMOR STAGES

The stage of the disease is the anatomical spread of the process, which we objectively assess during clinical presentation, instrumental and laboratory methods of investigation.The objective data of the stage never change. It is determined on the basis of the following signs: a) the size of the tumor; b) growing into adjacent organs; c) absence or presence of metastases (regional and distant).

There are 4 stages of tumors.

Stage 1 - a tumor, as a rule, no larger than 3 cm. Not invading surrounding tissues. There are no metastases.

Stage 2 - the tumor is not larger than 5 cm, grows into the deep layers of the organ wall. There may be isolated mobile regional metastases.

Stage 3 - a) the tumor is larger than 5 cm; spreads beyond the organ from which it grows, but does not sprout adjacent organs; there may be isolated regional metastases; b) the presence of multiple regional metastases regardless of tumor size, even minimal ones.

Stage 4 - tumor growth in neighboring organs or the presence of distant lymphogenic and hematogenous metastases, regardless of the size of the primary tumor and even if it is not found (tumors of unknown primary origin).

The size of the tumor may not always be the main criterion when determining the stage. For some tumors, the most important feature is the degree of narrowing of the hollow organ and penetration of tumor inside the layers of the hollow organ (colon tumor and gastric tumors), spread along it (esophageal cancer) and the depth of invasion and infiltration (skin melanoma).

CLINICAL CLASSIFICATION OF MALIGNANT TUMORS ACCORDING TO THE TNM SYSTEM

The international TNM classification (lat. T - tumor; N nodus; M - metastasis) was first developed in 1953 and continues to be improved. Clinical classification is based on clinical, endoscopic, radiological, laboratory examination carried out before treatment. Moreover, histological verification of the diagnosis is mandatory.

The symbol "T" means local spread of the tumor. It has certain differences for tumors of different organs.

Tx-primary tumor can't be assessed.

To, no primary tumor detected.

Tis - cancer in situ ("cancer in place").

T1-T4 dimensions, distribution of the primary tumor. The size criteria of tumors of different localizations are different, in parenchymal organs tumors size play the rule while in hollow organs growing in the layers of the organ have the criteria for primary tumor staging.

The general thing is that in the case of T1-T2 radical surgery is possible. With T3, a combined intervention is often possible (with resection of adjacent organs and structures and using additional therapy).

With T4, such an intervention is mostly impossible. According to indications, palliative and symptomatic operations are performed.

The symbol "N" means the state of regional, juxta-regional and more distant lymph nodes (juxta-regional are adjacent, closest to the regional group of lymph nodes, that is, the next collector of metastasis).

No- absence of signs of metastases in the lymph nodes.

Nx- it is impossible to assess the state of the lymph nodes.

N1-N3 - different degree of lymph node metastases - metastases in regional (I stage, collector) lymph nodes. 2- metastases in juxta regional (II stage, collector) lymph nodes, 3-metastases in more distant (stage III, collector) lymph nodes.

The symbol "M" means distant metastases.

Mo - no distant metastases were detected.

Mx - insufficient data on the presence of distant metastases.

M1. - distant metastases were detected.

Patho-histological(postoperative) classification pTNM:

pTX - microscopic evaluation of the prevalence of primary tumor is not possible.

pT0 - initial microscopic tumor not confirmed.

 pTis - preinvasive carcinoma (carcinoma in situ).

 pT1, T2, T3, T4 - microscopic evaluation of the prevalence of primary tumor.

 pNX - microscopic assessment of regional lymph nodes is not possible.

 pN0 - microscopic metastases in regional lymph nodes are not found

 pN1, N2, N3 - microscopically confirmed metastatic lesions in regional, juxtraregional lymph nodes.

 pMX - microscopic evaluation of the presence of distance metastases impossible.

 pM0 - microscopic distance metastases not confirmed.

pM1 - microscopically confirmed distance metastases.

Tumor grading: is the degree of severity in differentiation of tumor cells histologically.

Gx Grade cannot be assessed.

G1 Well-differentiated (low grade).

G2 Moderately differentiated (intermediate grade).

G3 poorly differentiated (high grade).

G4 Undifferentiated (high grade).

DIAGNOSTICS

 In oncology, early diagnosis occupies a leading place, because the earlier a tumor is detected, the better the results of treatment. About 1/3 of newly diagnosed cancer patients are subject to radical treatment, and 2/3 to palliative or symptomatic therapies.

Diagnosis of tumors is divided into 2 stages:

Stage 1 - primary diagnosis, stage of detection of primary tumors, in this stage primary methods of investigations mostly used.

Stage 2- staging diagnostics (staging workup). the degree of spread of the tumor is determined, morphological verification, differential diagnosis is carried out, and the functional state of the body is studied. Advanced and specific methods of investigations are used in this stage.

Therefore, the tumor can be detected:

a) during preventive examinations;

b) in persons who independently applied to the polyclinic;

c) in dispensary population groups;

d) in a hospital;

e) during the operation;

f) during autopsy.

GENERAL PRINCIPLES IN DIAGNOSTICS OF CANCER DISEASES.

* 1. Collection of complains. Usually the patients will mention the main complains that because the real discomfort to them, doctors should try to ask about the presence of any other symptoms or signs that may be associated with the main complains.
	2. Collection of patient's histories and clarifying presence any risk factors such as past medical or family history of tumor or a specific hazard such as exposure to chemicals or radiation or a history of some infections or chronic inflammatory conditions.
	3. Physical examination, primary methods of investigations that can be performed in polyclinics (CBC, urine analysis, blood biochemistry)
	4. Special methods of investigations which include both primary diagnostics methods of investigation such us x-ray, endoscopy and ultrasonography and specialized methods of oncological investigations such as tissue biopsy and Pet-scan.

Main complains of patients mostly associated to the affected area or organ which are called the local disease symptoms. Other symptoms are systemic symptoms which are mostly associated with the systemic spreading of disease.

Local symptoms can vary from presence of a lump, chronic skin ulcer, functional changes or chronic illness which do don’t responds to the typical treatments specific for a specific organ pathology.

General symptoms may include unexplained weight loss, bleeding, chronic anemia, sub febrile fever, night sweating, other organs failure due to metastatic process.

Collection of patient’s histories should be wide and informative, past medical history of the patient should be taken carefully, notifying presence of any chronic diseases, hereditary conditions, chronic infections, previous surgical intervention or any occupational hazards or radiation\chemical exposures.

Then the family history of the patient should be taken, any history of cancer diseases especially in first line relatives should be concerned.

Personal and behavioral habits, past or current using of any drugs or treatments of any chronic conditions.

In physical examination all the three classical methods will be used in primary investigations as well as in workup, monitoring of patient and follow up after the treatment.

Inspection for asymmetry, color changes or other skin changes, ulceration and other general body changes.

During palpation a mass or lamp can be palpated, lymph nodes enlargement, pain and tenderness during palpation.

Auscultation and percussion also used specially in the evaluation of abdominal and thoracic cavities.

Laboratory studies includes:

Complete blood count: anemia, leukocytosis, lymphocytosis, increases monocytes count, thrombocytosis or thrombocytopenia, elevated ESR may be seen.

Clinical, biochemical, immunological, hematological blood tests.

Clinical analyzes of urine, sputum, feces, gastric content, cerebrospinal fluid; study of tumor markers, enzyme studies.

Tumor markers are biological substances (hormones, enzymes, antigens, immunoglobulins, glycoproteins) that can be detected in the blood, urine, or body tissue of some tumor patients. Although some tumor markers may aid in the diagnosis of cancer, they are primarily used for monitoring treatment response and detecting cancer recurrence. Tumor markers are not reliable screening or diagnostic markers due to their low sensitivity (i.e., not elevated in all cancer patients) and low specificity (i.e., also elevated in benign, noncancerous conditions or otherwise healthy patients).

* Peripheral blood tumor markers:

Alpha fetoprotein (AFP): hepatocellular carcinoma, Hepatoblastoma, yolk sac tumor, mixed germ cell tumor, ataxia-telangiectasia.

Carcinoembryonic antigen (CEA): elevated in most adenocarcinomas,

сolorectal cancer, pancreatic cancer, breast cancer, lung cancer (especially in non-small cell cancers), gastric cancer, endometrial cancer, medullary thyroid cancer.

Prostate-specific antigen (PSA): prostate cancer, benign prostate hyperplasia, prostatitis.

[Human chorionic gonadotropin(β-HCG):](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin)

testicular germ cell tumors (choriocarcinoma, embryonal cell carcinoma, mixed germ cell tumor, seminoma), ovarian cancer: choriocarcinoma.

Calcitonin: Medullary thyroid cancer (both sporadic and associated with MEN 1 and MEN 2).

Alkaline phosphatase: liver and bones metastasis, Paget disease of the bones.

CA 19–9: Pancreatic adenocarcinoma, gastric cancer.

CA 15–3 and CA 27–29: breast cancer.

CA 125: ovarian cancer.

β2 microglobulin (β2M): multiple myeloma, сhronic lymphocytic leukemia, renal disease.

[Thyroglobulin](https://next.amboss.com/us/article/Vg0G82#Zaf3a71807289f3807bf5ddfce26b1226): papillary thyroid carcinoma, follicular thyroid carcinoma.

Monoclonal immunoglobulins: multiple myeloma, waldenstroms macroglobulinemia.

* Some genetic mutations also considered to be tumor markers taken from tissue samples.

EGFR (epidermal growth factor receptor) gene mutation: non-small cell lung cancer and certain head and neck cancers.

HER2neu (human epidermal growth factor receptor-2): breast cancer.

ALK gene rearrangement: non-small cell lung cancer and neoplastic large cell lymphoma.

* There are Antigens on the surface of cells that can be detected via tissue histopathological evaluation called immunohistochemical markers.

Desmin: rhabdomyosarcoma and leiomyosarcoma.

Mesothelin: mesothelioma and pancreatic, esophageal, and gastric carcinoma.

Vimentin: Sarcomas (Ewing sarcoma, osteosarcoma, chondrosarcoma, soft tissue sarcomas). Endometrial carcinoma, renal cell carcinoma, meningioma, mesothelioma.

Cytokeratin: Squamous cell carcinoma, basal cell carcinoma.

Chromogranin A: Neuroendocrine tumors (carcinoid tumor), small cell lung cancer (SCLC), medullary thyroid cancer.

Neurofilaments: Neuroendocrine tumors (carcinoid tumor), neuroblastoma, medulloblastoma, small cell lung cancer (SCLC).

PSA: prostate cancer.

S-100: Schwannoma, melanoma, Langerhans cell histiocytosis.

CD20: [B cell](https://next.amboss.com/us/article/ln0vtg#Z3cedd6934a8fe093751c71b9a536d993) lymphoma.

CD3, CD8, CD4: T cell lymphoma.

Morphological diagnosis (cytological and pathohistological studies)

Cytology: is a nonsurgical procedure, which aims to take a scrap or swab from the tissue need to be investigated.

Cytology report result can be: Class I – normal cells. Class II- minor atypia, no malignancy. Class III- wide atypia, precancerous\ carcinoma in situ, biopsy needed. Class IV- few cells with malignant characters or cells with borderline changes, biopsy is mandatory. Class V- obviously malignant, biopsy is mandatory.

Histology (biopsy): is a surgical intervention aims to take a sample of a tissue for microscopic examination.

Aspiration biopsy: using a needle a syringe to penetrate a lesion and aspirate its content.

Core needle biopsy: a hollow needle use to withdraw cylinders of tissue.

Incisional biopsy: removal of small part or multiple small parts of a large tumor.

Excisional biopsy: surgical removal of all the tumor or affected organ. Widely use in lymphoma, skin lesions and breast tumors.

Other types of biopsy such as: punch biopsy, brush biopsy, endoscopic guided biopsy, and curettage.

Endoscopic studies: bronchoscopy, thoracoscopy, esophagogastroduodenoscopy, laparoscopy, colonoscopy, rectoscopy, cystoscopy, hysteroscopy, endoscopic retrograde cholangiopancreatography (ERCP) all may be done with biopsy for both primary diagnosis or staging workup.

Thermography: Based on the detection of asymmetric hyperthermal areas. The method used for the differential diagnosis of malignant and benign tumors.

Ultrasound examination: Ultrasound informative when examining soft tissue and parenchymal organs. But should take in concern that it is a specialist dependent investigation. Can be beneficial in guiding biopsy.

 X-ray diagnostics (with or without contrast): include X-ray, tomography, X-ray, pneumography, mammography, digital tomosynthesis, lymphography, urography, cholecystography, arterio-, phlebography.

Computer tomography or magnetic resonance imaging (MRI)?

Computer tomography is highly sensitive method that enables differentiate tissue and lesions, also allows obtaining accurate quantitative information about the size and integrity of organs and lesion, relationship of the detected tumor to the surrounding tissues and organs and lymph nodes. But in many cases need to be used with contrast to get informative view about the pathology.

MRI has the ability to image without the use of ionizing radiation. MRI images demonstrate superior soft tissue contrast than CT scans and plain films making it the ideal examination of the brain, spine, joints and other soft tissue body parts , some angiographic images can be obtained without the use of contrast material, unlike CT or conventional angiography, functional MRI allows visualization of both active parts of the brain during certain activities.

Radionuclide diagnostics.

This method uses high energy gamma rays or positrons molecules which are injected to the body and accumulates in some areas showing a difference in metabolic aspect. PET scan, SPECT, radioisotope-scanning, bone scintigraphy.

* Bone diseases and tumors —Sodium Fluoride F 18, Technetium Tc 99m Medronate, Technetium Tc 99m Oxidronate, Technetium Tc 99m Pyrophosphate, Technetium Tc 99m (Pyro- and trimeta-) Phosphates.
* Brain diseases and tumors—Fludeoxyglucose F 18, Indium In 111 Pentetreotide, Iofetamine I 123, Sodium Pertechnetate Tc 99m, Technetium Tc 99m Exametazime, Technetium Tc 99m Pentetate.
* Cancer(tumors)—Fludeoxyglucose F 18, Gallium Citrate Ga 67, Indium In 111 Pentetreotide, Methionine C 11, Radioiodinated Iobenguane, Sodium Fluoride F 18, Technetium Tc 99m Arcitumomab, Technetium Tc 99m.
* Lung diseases—Krypton Kr 81m, Technetium Tc 99m Albumin Aggregated, Technetium Tc 99m Pentetate, Xenon Xe 127, Xenon Xe 133.
* Thyroid diseases and thyroid cancer—Fludeoxyglucose F 18, Indium In 111 Pentetreotide, Radioiodinated Iobenguane, Sodium Iodide I 123, Sodium Iodide I 131, Sodium Pertechnetate Tc 99m.

GENERAL PRINCIPLES OF TREATMENT IN ONCOLOGY.

Treatment of patients with benign neoplasms is usually surgical. Tumor removal is necessary:

1. suspicion of malignancy;
2. mechanical compression of organs or tissue structures;
3. prevention malignant transformation.

Neoplasms are removed within healthy tissues to prevent recurrences that may occur. If there is a suspicion that the tumor is malignant, an urgent histological examination is carried out.

In cases of malignant tumors, the treatment is more complex and varies according to several factors. Some of these factors are disease related; others are related to the patient health and social conditions.

* biological properties of the tumor and the stage of development (size, location, shape and growth rate, histological and molecular type and structure, locoregional and systemic spread, pathogenic type, degree of differentiation of tumor).
* characteristics of the patient (gender, age, physiological and physical condition of patient, the state of endocrine metabolic processes, comorbidities and other illnesses, immune system condition).

 There are 3 groups of anticancer measures:

1 - local-regional (surgery, local perfusion of chemotherapy drugs, radiation therapy);

2 - general (systemic chemotherapy, biological therapy (target therapy), hormone therapy);

3 - auxiliary (immunotherapy, hyperthermia, oxygenation).

According to the way of administered treatment in the classification above and the usual need for using more than one treatment we will have 3 types of combination treatments.

Combined treatment: is using of more than one treatment method from the same group orientation, e.g. combination of surgery and radiation therapy (both loco-regional type), or combination of chemotherapy and hormonal therapy (both general type).

Complex treatment: is the treatment that use therapies from both loco-regional and general (systemic) treatments, e.g. combination of surgery and chemotherapy.

Associated treatment: using one type of treatment in multiple administrations, e.g. polychemotherapy, external beam radiotherapy and brachytherapy.

According to treatment influence, the treatment of oncological patient can be radical, palliative and symptomatic.

 Radical treatment is treatment aim to radically (completely elimination of disease), such type of treatment mostly can be given for patients with localized tumor growth.

Palliative treatment, due to the large spread of the tumor, recovery is impossible. Its purpose is to reduce the tumor, delay its growth, reduce intoxication, and prolong the patient's life.

Symptomatic treatment is not expected to achieve antitumor effect Its aim is to eliminate or reduce the manifestations of the tumor or side effects of anticancer treatment (pain syndrome, gastrointestinal organs perforation, obstruction, compression of tissues and organs, bleeding from tumor site or site of metastasis, paraneoplastic syndromes , cancer emergencies, complications and side effects of systemic therapies, mainly chemotherapy and target therapy, radiotherapy side effects).

Surgical method of treatment

The role of surgery in oncology includes:

The cancer prevention (preventive surgery and removal of precancerous lesions or lesions or high affinity for malignization such as fast-growing benign masses, familial medullary thyroid cancer (MEN 2 and 3) -thyroidectomy, polyposis coli/chronic ulcerative colitis- colectomy.

Cancer staging and diagnosis: such as biopsy of primary lesion of secondary metastatic lesion, diagnostic laparoscopy, laparotomy, hysteroscopy, etc.

Cancer treatment surgery, usually points to those operative interventions that aims to completely eliminate the disease from the body (radical surgeries) also called curative surgery, such surgery done usually as a role either to small early tumors or to more advanced cases such as locally advanced tumors after getting additional suitable neoadjuvant therapy prior to surgery. Also, the skill of the surgeon plays an important role in maintaining the radical state, by successes excision borders and lymph nodes excision (regional lymphadenectomy). Examples, radical mastectomy, radical prostatectomy, whipple’s procedure, total gastrectomy, esophagogastrectomy, radical hysterectomy.

Debulking surgery that aim to remove only a part of the tumor when other part of tissue where tumor is growing can’t be removed, such us tumors growing to main vessels and other vital sites. The remaining cancer tissue treated usually with additional systemic or radiotherapy (adjuvant therapy).

Oncological emergencies also can be indication for surgery in a lot of cases. Abdominal cavity organs perforation, internal bleedings that don’t respond to hemostatic therapy, bowl obstructions, organ rapture such us spleen rupture mostly in hematological malignancies urgent thoracentesis, paracentesis, lumbar puncture, pericardiocentesis, etc.

Palliative surgeries, the main aim of such surgeries is palliation of cancer symptoms, no curable aim is goaled. This may include, surgeries for obstruction complications, such us nerves blockage due to tumor growth, or vascular compression. Surgeries for formation of stomas (nephrostomy, cystostomy, tracheostomy, colostomy, relieve gastric out-flow obstruction, Biliary stents or choledochojejunostomy to relieve obstructive jaundice. Other palliative surgical interventions can include endoscopic bowl stenting, pathological fractures reduction and fixation.

Reconstructive surgeries aims to reduce defects caused by primary tumor resection and, in combination with plastic surgeons, the discipline of surgical oncology has developed reconstructive surgery to reduce some of the effects of tums major residual defects and, in combination with plastic surgeons, the discipline of surgical oncology has developed reconstructive surgery to reduce some of the effects of tumor resections. Examples, limbs reconstruction surgeries following sarcoma treatment using bone grafts and prostheses, silicon injection to overcome the hoarse voice associated with recurrent laryngeal nerve palsy caused by mediastinal tumors, breast reconstruction following mastectomy.

Surgeries can be done classically (open surgeries) or minimally invasive surgeries. [Laparoscopy](https://www.cancercenter.com/diagnosing-cancer/diagnostic-imaging/laparoscopy), laser surgery, cryosurgery use of liquid nitrogen to freeze and kill cancer cells, [robotic surgery](https://www.cancercenter.com/treatment-options/surgery/surgical-oncology/robotic-surgery) and microscopically controlled surgery.

Surgery in oncology can be performed directly or sometimes after a course of radiotherapy or chemotherapy aim to freeze and decrease spreading of tumor called neoadjuvant therapy.

Unresectable cancer is defined as a cancer or tumor that cannot be removed completely through surgery.

A tumor may be unresectable due to its size so it can be too large to safely be removed, also location of the tumor which can be invading to blood vessels and other vital structures in the body the removal unsafe, metastasis of the tumor to distant sites (metastases): Since metastatic cancer (stage 4 cancer) has spread to regions beyond the tumor, removal of the tumor will not control all of the cancer, and other factors related to the health conditions of the patient: Such as heart disease, lung disease, or severe diabetes that would raise the risk of surgery complications which can be fatal.

Main side effects and complications of surgery include:

* Damage to organs in the body.
* Hemorrhages.
* Adverse reactions to medication\anesthesia.
* Pain or discomfort.
* Infections.
* Swelling.
* Lymphedema.
* Thromboembolism.

Radiation therapy

Is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors.
Treatment malignant tumors can includes radiotherapy and surgical treatment under which preoperative, sub operative and postoperative irradiation can be applied.

Preoperative radiation is aimed at:

* the prophylaxis of relapses and metastases of tumors;
* the decrease of perifocal inflammation;
* stimulation of connective tissues development and encapsulation of tumor cells complexes;
* the decrease of the tumor volume, which gives the opportunity to perform cells complexes;
* the decrease of the tumor volume, which gives the opportunity to perform surgical intervention.

Sub-operative(intraoperative) radiation is performed during operative intervention with the aim of:

* irradiation of the removed tumor bed;
* prevention of implantation metastases

Postoperative irradiation is performed after surgical intervention with the aim of:

* the devitalization of residual tumor cells:
* the prophylaxis of relapses and metastases of tumors:
* the destruction of regional metastases;
* stimulation of connective tissues development and encapsulation of residual cancer cells.

Radiotherapy cab also be a part of complex treatment with hormone therapy or chemotherapy.

Types of radiation used in therapy of cancer treatment includes:

X-ray therapy
X-ray therapy is a type of radiotherapy in which X-radiation is used for medical purposes. X-ray therapy is performed in a roentgenotherapeutic room of a radiotherapeutic department of a medical-prophylactic institution (oncological dispensary, oncological center), clinics, research institute and others

Methods of X-ray therapy.
1. Long-focus X-ray therapy-is performed with the help of the RUM-17 X-ray apparatus.
Superficial-used for irradiating the damaged area at the depth of up to 1 cm from the skin surface.
Half-deep - used for irradiating the damaged area at the depth of up to 3 cm from the skin surface.
Deep used for irradiating the damaged area at the depth of up to 5 cm from the skin surface.
2. Close-focus X-ray therapy- is used in the localization of the pathology at the depth of up to 1 cm from the skin surface. In close-focus X-ray therapy mostly aluminum filters of 0,1-3 mm and cones of various shapes and sizes are used.

Long-focus gamma therapy.
Long-focus gamma therapy is performed with the help of gamma-therapeutic apparatuses, generators of decelerating high energy radiation and generators of high energy corpuscular radiations.

Radiotherapy with high energy sources.

1. Electron-photon therapy - is performed distantly with the use of linear electrons accelerators, betatrons generating electrons and decelerating radiation with the energy within the range of I to 45 MeV.
2. Neutron therapy-is a type of corpuscular radiotherapy which is performed with help of neutron radiation. In the interaction of neutron radiation with a substance there prevail the processes that lead to ionization with a high linear energy transmission, therefore it is also called densely-ionizing. For neutron therapy they use neutron generators for irradiation and neutron generating RP. In neutron therapy they use long-focus, intracavitary and interstitial irradiation.
3. Proton therapy is a type of corpuscular radiation energy based on the application of high-energy protons accelerated on synchrophasotrons and synchrocyclotrons.
Proton therapy is used for irradiating distantly delimited pathological foci as well as for irradiating deeply located tumors when the irradiation zone is entered by a large volume of healthy tissues.
Proton therapy is applied for irradiating intracranial tumors of small volume (for example, hypophysis adenoma, eye tumors and others).
4. Stereotaxic radiosurgery - is the destruction of the arc as of neoplasm (tumor) due to the highly accurate delivery of a high single irradiation dose. In radiosurgery there are used some types of apparatuses: modified linear accelerators, Leksell gamma-knife, photon cyberknife.

Brachytherapy

1. Intracavitary method of radiotherapy-is applied in malignant tumors of the oral cavity (alveolar cancer, tongue cancer, labial cancer and others) as well as that of the esophagus, rectum, vagina, uterus and cervix uteri. The radiation source is placed maximally close to the tumor. The immediate contact of the radiation source enables to obtain a high absorbed dose in endostates the pathological area.
2. The interstitial method of radiotherapy:
3. interstitial gamma-therapy: radioactive gamma preparations (closed and open radiation sources) are introduced immediately into the tissue of a tumor.
4. interstitial beta-therapy. interstitial beta-therapy is performed with the use of open RP (colloid solutions and suspension of radionuclides 198 Au, silicate 90Y). Using special tools, they introduce syringe needles into a tumor in parallel rows at the distance of 0,6-1,2 cm from each other; the needles being removed after RP has been introduced into tissues.
5. The application method is the method of contact radiotherapy in which radioactive preparations are deployed on the damaged area of the patient's body surface. It is used in superficially located malignant tumors at early stages of their development (cancer of skin, oral mucous membrane, lower lip). Radioactive or gamma radiation sources are located in the thickness of the previously manufactured plastic applicator which corresponds to the shape of irradiation area. Radiation is performed daily during 4-6 hours depending on the dose power of the radiation source.

Programs of radiotherapy.
The radical program of radiotherapy supposes the complete destruction of tumorous elements in the zone of the primary focus and is aimed at the full recovery of the patient. They irradiate the primary focus and zones of regional metastasizing. The total dose per part of the primary tumor is, as a rule, 60-75 Gy, on the zones of metastazing-45-50 Gy.
The palliative program of radiotherapy is performed for patients with the advanced tumorous process under which it is impossible to achieve a complete and stable recovery. As a result of radiotherapy there comes just tumors' partial regression, intoxication decreases, the pain syndrome disappears and the function of the organ damaged by a tumor is partially restored, which provides the patient's lifetime prolongation. Under palliative radiotherapy they use the total doses of 40-55 Gy.
The symptomatic program of radiotherapy is applied for removing the severest symptoms of tumor disease (the pain syndrome, compression of the ureters, bile ducts, obturation of the esophagus lumen).

For more accurate treatment effect, we should notify radiotherapeutic interval - is the difference between the degree of damage and the degree of recovery of tumor and healthy tissues under equal doses absorbed by them.

To increase the effectiveness of radiotherapy and decrease of the negative impact of ionizing radiation on surrounding healthy tissues, radio-modifiers applied for increasing tumor cell radio-sensitivity are called radio-sensibilizers (for example, saturating tumors with oxygen, hyperthermia, magnetotherapy, pharmatheutical preparations and hem-preparations fluorouracil, ftoraful, methotrexate).
Radio-modifiers decreasing the radio-sensitivity of normal tissues are called radioprotectors (for example, pharmatheutical preparations (cystamine, serotonin); a decrease of the oxygen partial pressure, hypothermia).

Main side effects of radiotherapy include:

* Early side effects: They develop during treatment usually in the second to third week of radiotherapy course and they can be non-specific effects (tiredness and lack energy during treatment. There may be many factors in addition to radiation exposure to account for this, including depression, anxiety, travelling daily to treatment and concomitant medication.

And specific local effects related to the area being treated. The acute symptoms mostly self-limited and includes: erythema, diarrhea, constipation, urine urgency or dysuria, hair loss and mucositis.

* The late side effects are potentially the most serious effects of treatment since, unlike the acute effects, they are not self-limiting and indeed tend to be progressive and irreversible.

They arise owing to loss of stem cell recovery potential and progressive damage to small blood vessels resulting in their occlusion (endarteritis obliterans). These effects include: Fibrosis of skin; telangiectasia; skin necrosis, bowls Stricture; internal organ perforation; bleeding and fistulae, lung fibrosis, bladder Fibrosis which causing frequency; hematuria; fistulae, Myelitis causing paraplegia; cerebral necrosis. Risk of skin cancer and lymphomas are the most dangerous late complications of radiation therapy.

Chemotherapy

 Chemotherapy drugs have a direct cytostatic (loss of the cell's ability to reproduce) and cytotoxic (damage to cells) effect on cellular tumors. The object of action of chemotherapy drugs are proliferating cells.

Types of chemotherapy

1. Systemic chemotherapy of administration of chemo-preparations using different methods (oral, intramuscular, intravenous.

 2. Regional chemotherapy with the introduction of chemo-preparations in rather large concentrations: a) endolymphatic; b) into a relatively isolated blood stream (in liver artery, kidney, carotid artery) intra-arterial infusion; c) in a completely temporarily isolated arteriovenous system of a part of the body (extremity)

3. Local chemotherapy by injecting chemo-preparations into serous cavities (abdominal, pleural); intrathecally (into the cerebrospinal fluid during spinal puncture); intravesical (into the bladder); intratumorally.

Chemotherapy can be neoadjuvant used before surgery and adjuvant, introduced after surgery, also, can be for palliative aim such as, in cases of metastatic cancers, or radical aim such as in treatment of lymphoma and leukemia.

Chemotherapeutic agents.

Drugs acting on the structure of DNA

* Antimetabolites: 5-Fluorouracil (5FU), gemcitabine, methotrexate, cytosine, arabinoside.
* Taxanes: paclitaxel, docetaxel and Cabazitaxel.
* Alkylating agents: cyclophosphamide, chlorambucil, melphalan, busulfan, and mitomycin C.
* Intercalating agents: cisplatin, oxaliplatin, carboplatin, adriamycin, epirubicin and idarubicin.
* Topoisomerase inhibitors: Camptothecin Topotecan Irinotecan
* Anthracycline drugs such as doxorubicin, epirubicin, daunorubicin.

Drugs acting on mitosis: vincristine, vinblastine, vindesine, paclitaxel and docetaxel.

Drugs starting apoptosis: bortezomib.

Signal transduction inhibitors: tyrosine kinases inhibitors include imatinib, gefitinib, sorafenib and sunitinib.

Antitumor antibiotics: bleomycin, doxorubicin and mitoxantrone.

Hormones glucocorticoids: prednisolone, dexamethasone.

For treatment of breast cancer mostly we see combinations of Taxanes and Anthracyclines, while the addition of taxanes, docetaxel and paclitaxel, to adjuvant regimens resulted in reduced risk of distant recurrence. Also, antimetabolites such as 5-Fluorouracil (5FU) and methotrexate and alkylating agent such as cyclophosphamide. The anthracyclines such as doxorubicin, epirubicin, or daunorubicin induce damage to cellular DNA and RNA and taxanes are antimicrotubular agents interfering with cell division. Regimes such as FAC (Fluorouracil 500 mg\m2 iv day 1 and day 4, doxorubicin 50 mg\m2 iv infusion over 72 hours, cyclophosphamide 500 mg\m2 iv on day1) this cycle repeated every 21-28 days. Another regime includes AC (doxorubicin and cyclophosphamide)

 For Hodgkin’s lymphoma treatment ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine] followed by involved-field radiotherapy. Favorable disease is treated with 2 cycles of ABVD followed by 20 Gy radiation while unfavorable disease is typically treated with 4 cycles of ABVD followed by 30 Gy radiation. Intensive chemotherapy with 2 cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) followed by 2 cycles of ABVD and radiotherapy improves tumor control in high-risk patients at the cost of higher toxicity.

For treatment of non-Hodgkin’s lymphoma usually, combination chemotherapy is given of which the most widely used is RCHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisolone). The first four drugs are given intravenously on day 1 of a 21-day cycle with oral steroids on the first 5 days. A total of six to eight courses is usually given, the standard dictum being to deliver two courses of chemotherapy beyond complete clinical remission. Also, recently a CVP regime (cyclophosphamide, vincristine and prednisolone) is been used.

For treatment of soft tissue sarcomas several regimes are available and most commonly used in adult patients is IVAD regime ( vincristine 1.4 mg\m2 day 1, doxorubicin 30 mg\m2 day 1and 2, Mensa 1.2 g\m2 before Ifosfamide day 1and 2, Ifosfamide 3g\m2 day 1 and 2, Mensa 2.4g\m2 after Ifosfamide for day 1 and 2. This cycle repeated after 21 days for 6 cycles. Other regimes include VAC (vincristine, dactinomycin, Mensa, and cyclophosphamide).

For the carcinomas of hear and neck mostly XRT+ cisplatin and 5FU regime is used (cisplatin 80 mg\m3 day 1, fluorouracil 1g\m2 day 1-4, this cycle is repeated in 21 day and for 2-4 cycles

Chemotherapy effects include: Early side effects and late side effects\complications.

Early side effects:

* + nausea and vomiting
	+ anaphylaxis (can happen after introduction of chemotherapeutic agents and mostly with taxanes and asparaginase, the incidence of anaphylaxis with paclitaxel is so high so that a routine prophylaxis with steroids and antihistamines (H1 and H2) is administered to all patients receiving paclitaxel regimes).
	+ Extravasation (happens after administration of chemotherapy into subcutaneous tissue. This leads to local pain, erythema, swelling and discomfort, which if unrecognized and untreated can lead to tissue necrosis with the possibility of serious complications).
	+ Tumor l lysis syndrome (happens due to rapid cytolysis of a large volume of cancer cells, and mostly occurs in aggressive chemotherapy as in polychemotherapy or using target therapy in addition to chemotherapy. This can lead to tumor lysis syndrome or metabolic chaos. The destruction of tumor cells DNA leads to hyperuricemia as a result of breaking down of nucleotide bases. The cytolysis also causes hyperkalemia by releasing of intracellular potassium and the breakdown of proteins and DNA in cancer cells lead to hyperphosphatemia and secondary hypocalcemia. Acute renal failure may be a consequence of the high levels of urate and phosphate while cardiac arrhythmias may occur due to hyperkalemia. Paresthesia, muscular spasm, tetany, and seizures can happen due to hypocalcemia.
	+ Suppressed immunity.

Late side effects include:

* + Alopecia and o onychodystrophy (Long - term therapy may result in loss of pubic, axillary and facial hair in addition to scalp hair. The loss of scalp hair often occurs in an acute episode while washing, usually two to six weeks after starting chemotherapy).
	+ Myelotoxicity of chemotherapy (bone narrow suppression is a serious condition that may occurs later after chemotherapy. Pancytopenia may be seen, erythrocytopenia will cause anemia and tissue hypoxia, leukocytopenia which suppress immunity and case frequent infections, and thrombocytopenia which will increase the risk of bleeding.
	+ Gastrointestinal tract mucositis (chemotherapy and radiotherapy damage basal epithelial cells in the intestinal mucosa leading to apoptosis, atrophy and ulceration. Once ulceration occurs, bacterial and fungal infection and activation of macrophages leads to further inflammation. Mucositis is associated with significant morbidity and mortality risk.
	+ Other organs and system complications such as cardiotoxicity (anthracyclines like doxorubicin, epirubicin also cisplatin and carboplatin have cardiotoxic effect), nephrotoxicity (cisplatin, methotrexate, pemetrexed, Ifosfamide, cyclophosphamide), neurotoxicity (cisplatin, oxaliplatin, paclitaxel, vincristine and cyclophosphamide).

Target therapy

Target agents act mainly against pathways that lead to uncontrolled cell proliferation, loss of cycle inhibitors and loss of death regulation.

Monoclonal antibodies are specific antigens that induce a toxic effect by a specific surface antigen to a target cancer cell.

Human epidermal growth factor receptor 2 inhibitors (HER-2): HER-2 gene overexpression can be seen in about more than 20% of invasive breast cancers so HER-2 inhibitors such as Trastuzumab ( Herceptin) shows a high clinical effect in treatment of patients with HER-2 neo positive receptor breast cancer as well as decrease the recurrence and metastasis in early discovered and locally advanced cancers of mammary gland. Other drugs include Lapatinib, Pertuzumab, and Adotrastuzumab emtansine.

Immune checkpoint inhibitors have the potential to produce durable tumor remission and induce long standing anti-tumor immunity in a subgroup of breast cancer patients. Pembrolizumab is a highly selective, humanized immunoglobulin (Ig), currently FDA-approved for use in advanced melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, and classical Hodgkin lymphoma. Pembrolizumab has been recommended in breast cancer both as monotherapy and in combination with chemotherapy, for both advanced and early stage breast cancer as well as in triple negative breast cancer.

Rituximab, ibritumomab are drugs targeting CD20 antigen for treatment of B cell lymphomas.

Alemtuzumab is an CD52 antibody used for treatment of CLL.

thalidomide and lenalidomide. Inhibitors of Epidermal Growth Factor Receptors: monoclonal antibodies cetuximab, panitumumab, erlotinib and gefitinib.

Molecular target drugs are small molecules inhibitors of specific signaling pathway. Angiogenesis inhibitors (vascular endothelial growth factor VEGF inhibitors) suppress angiogenesis ability in cancer cells; these drugs include bevacizumab which is considered as monoclonal antibodies, others are ranibizumab, dasatinib, sorafenib, sunitinib.

The mammalian or mechanistic target of rapamycin (mTOR) pathway plays a crucial role in regulation of cell survival, metabolism, growth and protein synthesis in response to upstream signals in both normal physiological and pathological conditions, especially in cancer. There is an unmet therapeutic need in endocrine-resistant, hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (BC). Imatinib mesylate is a small molecule inhibitor of signaling kinase pathway.

Hormone therapy

 Hormone-active tumors are more often benign neoplasms that grow from internal secretion organs, secrete hormones and affect the body (insulinomas lead to hypoglycemia). Also, hormonal therapy can be used as a replacement therapy in many cases such as in prescription of L-thyroxine after thyroidectomy.

But using hormones and hormone inhibitors add a big advantage for treatment of several hormonal sensitive tumors (which is known to have a high rate of recurrence) and decrease their recurrence as well as decreasing the metastatic risk. Mainly such therapy seen in cases of treatment of hormonal positive breast and prostate cancers.

Tamoxifen, toremifene, luteinizing hormone– releasing hormone (LHRH) agonists, and aromatase inhibitors (AI) are hormonal therapies used in the treatment of hormonal positive breast cancer. Tamoxifen was the gold standard adjuvant hormonal therapy for three decades and is generally considered the adjuvant hormonal therapy of choice for premenopausal women. Premenopausal women benefit from ovarian ablation with LHRH agonists (eg, goserelin) in the adjuvant setting, either with or without concurrent tamoxifen. Aromatase inhibitors (anastrozole, letrozole, and exemestane) are recommended to be added into adjuvant hormonal therapy for postmenopausal, hormone-sensitive breast cancer.

Approximately majority of the patients with metastatic prostate cancer respond to androgen withdrawal therapy. The main aim of this therapy is to activate apoptosis and block cell proliferation. Drugs include Flutamide, Enzalutamide, Bicalutamide. Other strategies can be used as alternatives are using of ketoconazole to inhibit steroid synthesis, using of glucocorticoids such as prednisone which then will cause inhibition of (ACTH) which lead to decrease production of androgens by adrenal gland.

Immunotherapy

 Modern immunotherapy (more precisely, immunostimulant) plays an auxiliary role in treatment; it is used to activate the patient's body's immune defenses (before and after surgery, after chemotherapy, in case of recurrence or metastases). It must be carried out because a malignant tumor in the body causes immunodepression.

Interferon Alfa-2b which increase activity of cellular & innate immune responses, Interleukin-2 (Aldesleukin, Proleukin) which increase lymphocyte mitogenesis & cytotoxicity.

Lenalidomide (Revlimid) displays immunomodulatory, antiangiogenic, and antineoplastic effect by decreasing the proinflammatory cytokines and signals to angiogenic factors, also, increase the cell-mediated immunity and induces cell cycle arrest.

Pomalidomide which shows in addition to immunomodulatory effect an antineoplastic effect by decreasing proliferation and angiogenesis. And increases apoptosis, increases NK cells/T-cell-mediated immunity. Romidepsin and Vorinostat which inhabits histone deacetylase enzymes causing termination of cell growth and enhancing apoptosis.

Chemo radio-Modifiers have been used in recent years for more effective treatment of patients with locally advanced tumors. Artificial hyperglycemia and local hyperthermia, which increase chemosensitivity and radio sensitivity of tumors, are considered the most effective. Due to artificial hyperglycemia in the tumor, pH is selectively reduced, blood flow slows down, cell hypoxia increases.

Thermo-sensitivity increases, the number of cells in the S- and M-phases of the mitotic cycle increases (almost twice), in which they are more sensitive to chemotherapy and radiation therapy. The effect of hyperthermia on the tumor is cytotoxic and radio sensitizing.

Photodynamic therapy

In 1924, light-induced red luminescence of malignant neoplasms in the human body was discovered. This phenomenon was explained by the presence of endogenous porphyrins in tumors. In 1948, it was shown that rapidly growing cells actively absorb porphyrins, and in 1955, the selective absorption of hematoporphyrin by tumor cells was discovered. Thus, living tissue cells that accumulate hematoporphyrins are photosensitized, i.e., their subsequent exposure to light with a selected wavelength has a cytotoxic effect.

Photodynamic therapy (PDT) of tumors is a method based on the catalyzed destruction of tumors sensitized by hematoporphyrin. Its essence is as follows. Hematoporphyrin dye is injected into the body (as a rule, intravenously). After 24-26 hours, it spreads in tissues, selectively accumulating in tumor cells. Then the tumor is irradiated with a red laser with a power of up to 1.5-2 W. At the same time, as a result of photochemical reactions in cells, a singlet form of molecular oxygen (a strong oxidant) is formed, which has a cytotoxic effect. The difference in dye concentrations in cancerous and healthy cells leads to a predominant damage to malignant cells with minor damage to perifocal healthy tissues. Thus, PDT is a palliative agent in the late stages of the disease, when other types of treatment are no longer effective, and in the early stages, PDT provides effective treatment and long-term control of the disease.

Symptomatic treatment

 Symptomatic treatment is required for patients with malignant tumors of the IV clinical group. It is necessary to show humanity and patience towards such patients. They are prescribed sedatives, hypnotics, analgesics, and drugs for pain. They conduct psychotherapy, strengthening therapy, perform manipulations aimed at alleviating the general condition (for ascites, exudative pleurisy - puncture, paracenteses with fluid evacuation). Most importantly, the patient should not suffer.

Also, treatment of symptoms related to cancer treatment mostly those of chemotherapy and radiotherapy should be considered in symptomatic treatment.

Cancer screening

Cancer screening due to national cancer institute is looking for cancer before a person has any symptoms. Screening tests can help to find the cancer tissue at early stages before the appearance of symptoms. When the abnormal tissue found early it may be easier to treat.

Screening tests can include physical examination, laboratory tests such as tissue samples, blood, urine. Imaging tests and genetic tests also widely used in early cancer discovery and specially for high risk patients.

Screening mostly performed to patients with high risk of having malignancy.

In general, the advantage of cancer screening derives from detecting cancer in earlier and more treatable stages, thereby, reducing mortality.

Generally, cancer risk increases with aging, but there some individuals have higher risk for malignancy which are:

* Patients with family history of cancer of past personal history of cancer, or patients with inherited genetic mutations which can be associated with cancer.
* Patients who suffered from exposure to environmental or occupational carcinogens (asbestos, uranium miners)
* Patients with behavior relater cancer risk (smoking, alcohol, sun and solary exposure.
* Patients whose been exposed to radiation even the therapeutic radiation (mostly those who had radiotherapy in childhood, adolescence.
* Patients with known medical chronic condition that can turn to malignant such as untreated peptic ulcer disease, ulcerative colitis and crohn’s disease, erosions of cervix…. etc.

 Wilson criteria of screening:

• the condition should be an important health problem

• the natural history of the condition should be understood

• there should be a recognizable latent or early symptomatic stage

• there should be a test that is easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific

• there should be an accepted treatment recognized for the disease

• treatment should be more effective if started early

• there should be a policy on who should be treated

• diagnosis and treatment should be cost-effective

 •case-finding should be a continuous process.

**VII. Questions for self-control:**

1. Classification of tumours. Pathological features of cancer tissues.
2. Concept of carcinogenesis.
3. Role of protooncogenes; tumor suppressor genes, controls of apoptosis and angiogenesis.
4. Hallmarks of cancer.
5. Groups of carcinogens. Risk factors for various malignancies – genetic and non-genetic
6. Natural history of most common cancers. Preclinical, clinical periods.
7. Primary, secondary, tertiary prevention of malignant tumours.
8. Clinical epidemiology, epidemiological concepts of morbidity (incidence and prevalence), mortality, relative risk and survival in relation to common cancers.
9. Staging of cancers. International TNM classification.
10. Clinical diagnostic methods (symptomology of cancer, physical examination, assessment of performance status).
11. Instrumental, biochemical methods of diagnosis.
12. Immunological, genetic, hormonal methods of diagnosis.
13. Modern methods of medical imaging in oncology.
14. Types and principles of biopsy.
15. Principles of treatment of malignant tumours. Special (combined and complex) treatment.
16. Radical treatment. Basic concepts of supportive and palliative care.
17. Types of surgeries, general principles of common procedures, pre-operative assessment, post-operative management.
18. Radiobiology, radio sensitivity, radio curability. Radiation principles and techniques used in oncology.
19. External RT. Brachytherapy. Advances in radiotherapy.
20. Principles of systemic therapy chemotherapy.
21. Principles of hormone therapy.
22. Principles of immunotherapy and biological therapies (including immunomodulators, signal transduction inhibitors and monoclonal antibodies).

VIII. Tasks for verification of concrete teaching aims achievement:

1. Genes that normally prevent cell division are:
2. Tumor suppressors.
3. Proto oncogenes.
4. Oncogenes.
5. Transcription factors.
6. A proto-oncogene can become an oncogene when:
7. it is translocated next to a gene that is not being expressed.
8. it is translocated next to a highly expressed gene.
9. checkpoints are added to the cell cycle.
10. the cell cycle temporarily runs backwards.
11. Cancer cells:
12. divide uncontrollably and then die.
13. are particularly sensitive to extracellular signals.
14. divide uncontrollably and are immortal.
15. are impossible to grow in culture.
16. A Malignant neoplasia is characterized by all of the following EXCEPT:
17. Hypo chromatic nuclei.
18. Anaplasia.
19. Rapid growth.
20. Local nodal enlargement.
21. Which of the following statements about carcinogenesis is false?
22. Asbestos exposure increases the incidence of lung cancer.
23. Papilloma viruses produce tumors in animals but not in humans.
24. Exposure to aniline dyes predisposes to cancer of the urinary bladder.
25. Hepatitis B virus has been implicated in hepatocellular carcinoma.
26. A Surgery is an effective method of treating cancer when:
27. a primary tumor is yet to invade healthy tissue.
28. a primary tumor has spread through the blood stream.
29. all rapidly dividing cells are targeted by the surgery.
30. a patient has multiple tumors spread across body.
31. Traditional cancer treatments include:
	1. nutritional therapy and physical therapy.
	2. monoclonal antibodies and cytokines.
	3. gene therapy.
	4. surgery, chemotherapy, and radiation
32. Which three of the following statements are FALSE about diagnostic imaging?
	1. Radionuclide imaging allows function to be studied.
	2. Magnetic resonance imaging (MRI) scans give excellent contrast resolution.
	3. Computed tomography (CT) scan has a higher resolution than plain radiographs.
	4. MRI scan has no disadvantages.
33. Which three of the following are indications for the surgical treatment of cancer?
	1. Long waiting time for radiotherapy.
	2. Fracture of a weight-bearing bone.
	3. Acute intestinal obstruction.
	4. Hypercalcaemia.
	5. Anaemia.
	6. Intestinal perforation.
34. A combination of the long-focus and close-focus methods of irradiation is named:
35. The independent method of radiotherapy.
36. The associated method of radiotherapy.
37. The combined method of radiotherapy.
38. The complex method of radiotherapy.
39. A source of ionizing radiation whose application makes getting of the radioactive substance to the environment possible is named:
40. Radionuclide source of ionizing radiation.
41. Non-radionuclide source of ionizing radiation.
42. A closed source of ionizing radiation.
43. An open source of ionizing radiation.
44. Early findings of carcinoma of breast include:
45. Skin ulceration
46. Skin retraction
47. Single non-tender, firm to hard mass with ill-defined margins
48. All of the above
49. Treatment of cancer T1N0M1 is considered as:
50. Radical
51. Palliative
52. Chemotherapeutic
53. Surgical
54. Target
55. Insertion of the radioactive source in the organ cavity is called:
56. Superficial method.
57. The intracavitary method.
58. The intratissue method.
59. The application method.
60. Radiation is most often used to treat:
61. Slow growing tumors.
62. Metastasized tumors.
63. Fast-growing tumors.
64. Localized tumors.
65. The postradiation period includes:
66. Evaluating the treatment effectiveness.
67. The choice of the optimal regime of irradiation.
68. Performing irradiation.
69. A detailed examination of a patient.
70. Which three of the following statements apply to cytology as a diagnostic tool?
71. Can distinguish in situ disease from invasive.
72. Allows precise characterization of the tumor.
73. A negative result makes cancer very unlikely.
74. Can provide a rapid diagnosis.
75. Which one of the following is the most important feature of preoperative radiotherapy?
76. Allows treatment of regional lymph nodes.
77. Downstages disease by neoadjuvant therapies to facilitate surgical resection.
78. Removes need for radiotherapy after surgery.
79. Lessens morbidity from radiotherapy.
80. Which two of the following chemotherapeutic drugs are neurotoxic?
81. Irinotecan
82. Cisplatin
83. Cyclophosphamide
84. Doxorubicin
85. Which two of the following chemotherapeutic drugs are cardiotoxic?
86. Carboplatin
87. Methotrexate
88. Ifosfamide
89. Doxorubicin
90. Which two of the following chemotherapeutic drugs need renal function measuring before administration?
91. Vincristine
92. Methotrexate
93. Cisplatin
94. Doxorubicin
95. A 46-year-old female patient diagnosed with Her2 neo receptor + local breast cancer, which biological drug should be chosen in her treatment regime?
96. Gemcitabine
97. Tamoxifen
98. Trastuzumab
99. Nilotinib
100. Which drug of the following is the treatment of choice for female patient with estrogen + breast cancer?
101. Gemcitabine
102. Tamoxifen
103. Trastuzumab
104. Nilotinib
105. Which drug of the following drugs is an Aromatase inhibitor:
106. Tamoxifen
107. Trastuzumab
108. Anastrozole
109. Nilotinib
110. Exemestane
111. Which of the following statements regarding cancer diagnosis is true?
112. Tumor markers are golden standard for diagnosing malignancy.
113. MRI is not useful in metastatic workup.
114. Tissue biopsy is the only golden standard in diagnosis of malignant tumors.
115. PET-CT scan is not useful in diagnosis of bone tissue metastasis.
116. Lenalidomide is considered to be:
117. Chemotherapeutic drug
118. Hormonal drug
119. Immune modulator
120. Biological drug
121. Patient with local breast cancer treated with surgical excision followed by radiation therapy, what type of treatment offered to the patient?
122. Complex oncological treatment.
123. Associated oncological treatment.
124. Combined oncological treatment
125. Palliative treatment.
126. A patient with bowel obstruction goes throw a surgical excision(lobectomy) due to sigmoid colon cancer, the histology and further investigations confirmed the patient to have metastatic cancer of colon, the patients prescribed chemotherapy, what type of treatment offered to the patient?
127. Complex oncological treatment.
128. Associated oncological treatment.
129. Combined oncological treatment
130. Radical treatment
131. Which of the following statements regarding cancer epidemiology are true?
132. Lung cancer have the highest mortality rate between all oncological diseases.
133. Prostate cancer is the most common cause of death in men population and effecting mostly men younger than 65
134. Breast cancer is the most common malignancy in female’s population
135. Melanoma is the most common type of skin cancer.
136. Pancreatic cancer has a good prognosis and treatment outcome.
137. Patient underwent an endoscopic submucosal dissection due to carcinoma in situ of colon, the histological margins came free of cancer cells a well differentiated carcinoma, further investigations shows no lymphatic of metastatic lesions. Which treatment been offered to the patient?
138. Complex treatment
139. Palliative treatment
140. Radical treatment
141. Supportive therapy

Correct answers: 1-A ,2-B ,3-C ,4-A, 5-B ,6-A, 7-D, 8-D, 9-B,C,F, 10-B ,11-D, 12-D, 13-B, 14-B, 15-C, 16-A , 17-D , 18-B , 19-B,C , 20-A,D , 21-B,C , 22-C , 23-B , 24-C,E , 25-C , 26-C , 27-C , 28-A , 29-A,C , 30- C .

**ІX. Suggested Literature:**

**ІX 1. Basic:**

1. Cancer principles and practice of oncology – Vincent T. DeVita Theodore S. Lawrence, Steven A. Rosenberg,12th edition,2023 . Surgical oncology, theory and multidisciplinary practice 2nd edition,2020.

2. Practical radiation oncology, 1st edition,2020.

3. Textbook of complex general surgical oncology -Shyne Y. Morita, Charles M. Balch, V. Suzanne Klimberg, Timothy M. Pawlik, Mitchell C. Posner, Kenneth K. Tanabe, 2018.

4. The Basic Science of Oncology, Lea A. Harrington, Ian F. Tannock, Richard P. Hill, David W. Cescon, sixth edition 2021.

5. Cancer principles and practice of oncology – Vincent T. DeVita Theodore S. Lawrence, Steven A. Rosenberg,12th edition,2023.

**ІX 2. Additional:**

1. . Oncology, lecture Notes: Mark Bower, Jonathan Waxman, third edition 2015.

2. Basic principles of radiotherapy methodological instruction, Rusin A.V., Bedey N.V., Kutsenko A.Y.,Odoshevska O.M., Khoma E.S., department of oncology, medical faculty, uzhhorod national university,2016.

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