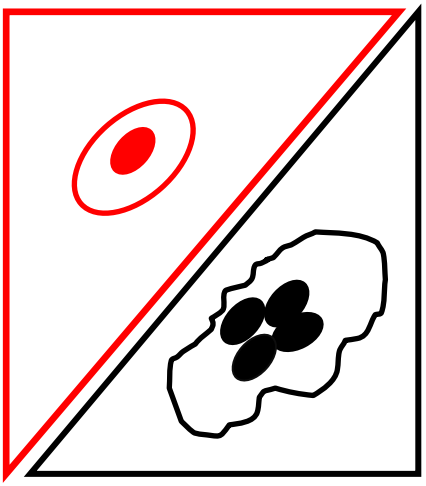
GENERAL
ONCOLOGY

Edited by
V.I.Starikov,
A.S.Khodak



Ministry of Public Health of Ukraine
Kharkov National Medical University

GENERAL ONCOLOGY

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Textbook

Kharkov 2016

UDC 616-006(035)

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General oncology: Textbook – Kharkov, 2016. –p.66

The manual sets out the general principles of diagnosis and treatment of malignant tumors
This tutorial is for English-speaking students 5 courses. Textbook meets the requirements of the Bologna system of education in oncology and is designed for medical students III - IV accreditation levels.

В.І. Старіков, А.С. Ходак
Загальна онкологія: Підручник – Харків, 2016. – 66 с.

У підручнику викладено загальні принципи діагностики та лікування злоякісних пухлин Цей підручник призначається для англомовних студентів 5 курса. Навчальний посібник відповідає вимогам Болонської системі навчання з онкології і розрахований на студентів медичних вузів III – IV рівнів акредитації.

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Approved by the Academic Council of Kharkov National Medical University and is recommended for the 5th and 6th year students of medical faculty.

Record of proceeding № 7
dated 16.06.16

Introduction

Malignant tumors are the second only to heart and vessel diseases as a cause of death in the most highly developed countries. However the existing tendency of malignant neoplasms to increase makes it possible to predict that malignant tumors will be the main cause of the population death through out the world, so we can say that the problem of malignant neoplasms is not only medical problem but is a social one.

Rapid increase of malignant tumors incidence of almost all localizations was recorded at the end of the XX th and the beginning of the XXIst centuries.

Moreover the incidence of the most frequent localizations (lung, breast, skin, prostate, and uterus corpus) of malignant tumors has been constantly increasing.

It happens because of the ruinous influence of carcinogenic factors on human body. Different pathogenic factors: chemical, physical, and biologic cause malignant cell transformation.

Cancer has been known to be widespread among multicellular plants, insects, birds. This ancient disease is much older than a man.

There is no complete knowledge about malignant process because it is a complex lengthy multistage process. However the last decade hase yielded many important achievements in molecular biology, genetics, and expiremental oncology, knowledge on the process of carcinogenes has been extended and systematized. Oncology gives the physicians an insight into the essence of malignant tumors.

Scientific and technical progress has given the explosive growth of knowledge and so possibility to study tumors on cell's genome level.

Innovations in diagnostic imaging technologies: computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound have been accompanied by enormous gains in precise evaluation and display of the sites not evaluable by palpation. New generation of fiber endoscopes has become so thin and maneuverable that there are no longer any blind areas to endoscopic evaluation. A great progress has been made in the study of morphology of malignant tumors, namely in cytology diagnosis. Surgical, radiation and chemical therapies have changed greatly.

This textbook has not been aimed at presentation of new information about carcinogenesis and treatment modalities, since this book is recommended first of all to the students of medical universities,

studying the course of oncology. This textbook can be helpful to young medical specialist: oncologysts, surgeons, therapists and students of biologic faculties.

Subject matter of "Oncology"

Oncology is the science that deals with tumors, discloses the causes and establishes general regularities of their origin (etiology) and the mechanism of their pathogenesis, preventive measures, diagnosis and treatment.

Oncology, as a general biological problem, is closely connected with different branches of natural sciences: molecular cell biology, social hygiene, and ecology.

Oncology is the branch of medical science that studies definite scientific problem. Specialization according to problem principle is very up – to – date and perspective, as it makes it possible to use different methods of research and treatment. In the last years it has begun to develop into oncogenicology, mammology, otolaryngology – oncology, toracal – oncology, abdominal oncology, oncourology, oncoproctology, oncopediatry, drug therapy and so on.

A simplified definition of malignant tumor is as follows: tumor is unlimited growth of a tissue with loss of its differentiation (pluss tissue, minus differentiation). But sometimes this definition is not true, because in some cases tumor grows and healthy tissue distruction is observed, but there is no increase in the size of tissue or organ.

More complete definition of tissue was given by a well – known scientist oncologist Blokhin N.N.. He considered tumor disease to be a particular kind of pathology widespread among animals in wild nature. It is characterized by unlimited and relatively autonomous growth and duplication of cells in the focus of disease.

A tumor grows from a primary neoplastic bud, and doesn't involve in these process the surrounding unchanged cells. Infiltrative growth and metastizing are characteristic of malignant tumors.

Tumors, especially malignant tumors, are accompanied by changes throughout the organism.

We will give a definition of malignant tumor and point out only its main biologic properties.

A **malignant tumor** is a biologic tissue with unlimited proliferation of transformed cells, losing morphologic parameters of histogenesis and capable of dissemination and implantation into other tissues and formation of new foci of tumor growth.

Benign tumor is characterized by higher cell differentiation, slow non infiltrative growth and absence of metastasizing.

The names of different tumors are usually formed from those of the tissue from which the tumors are derived (cell, tissue, organ) and the suffix "oma" which means "tumor". For example, fat tissue tumor – **lipoma**, bone tissue tumor – **osteoma**, glandular tissue tumor – **adenoma**. Cell structure may be in the name of the tumor (tumor developing from hystocytes is called **histocytoma**). The site may be given in the tumor name (for example shoulder lipoma, breast fibroadenoma). Tumor containing elements of embryonal tissue is called embryoma, or teratoma.

Tumor may be derived from epithelial, connective, nervous and muscle tissue.

There are special names for malignant tumors – carcinoma or **cancer** for tumors derived from epithelial tissue and **sarcomas** for those derived from connective tissue. About 90% of all malignant solid tumors in adults are cancers and about 10% are sarcomas. In children everything is vice versa, sarcomas account for 90% of all solid tumors, and cancers account for less than 10%.

The term "cancer" originates from similarity in appearance with Breast cancer which has the form of divergent lobster legs. The term "sarcoma" originates from the greek word "sarx" which means meat and "oma" which is tumor because some tumors in section have similarity in appearance with fish meat.

Systemic tumors of hemopoietic tissue are called **hemablastoses**. There is a small group of tumors which is called **herminogenic**, they are tumors from testicles and ovaries.

Epidemiology of malignant tumors

Epidemiology is the brach of oncology studying variations in disease frequency among population groups. It identifies cancer risk in populations, the rate of affected and dead patients from malignant tumors for a certain period of time on a specific territory and applies preventive measures.

It has been estimated by Health Department that about 90% of all malignant tumors are due to environmental factors (exogenous), the rest 10% are caused by genetic factors, hormones, and viruses (endogenous).

It is proved that malignant tumors have been registered in every nationality and ethnic group. However the geographic and ethnic differentials for most cancers appear largely determined by environmental influences. Rates for stomach cancer in different counties

varied greatly in line with socieconomic differences in the use of alcohol and tobacco and nutritional patterns. Japanese, Icelanders, Chileans experience elevated rates for stomach cancer. Americans, Indoneseans and Egyptians have low rates of this disease. These variations in cancer occurrence can be explained by genetic and dietary factors.

Correlation of microelements in the soil and drink water are of great importance.

Some regions have exceptionally high rates of certain cancers. Africans have high rates for Burkitt's lymphoma. African population experience elevated rates for primary liver cancer in comparison with American or European populations.

There are two main methods of malignant tumors epidemiologic invesigations. They are: **descriptive** and **analytic** studies.

Descriptive studies measure the number of persons affected by the disease, the length of the period covered, and the population from which they are derived. These studies can be useful in generating etiologic hypoteses. Cancer show variations according to age, sex, race, geographic location, socioeconomic class, and marital status. Descriptive studies emply mainly population based statistic on mortality, incidence, and survival to calculate rates.

Analytic studies test etiology hypotheses, involving cohort or case – control designs. These studies allow to estimate the risk of disease associated with exposure. Retrospective and prospective analyses are used in these studies.

The incidence and death rates according to sex are of great interest in the epidemiology of malignant tumors. The male malignant tumors incidence in lung cancer, stomach, larynx, oral cavity and esophagus is higher than in females. The female malignant tumors incidence in thyroid gland, liver and gall bladder is higher than in males.

Most often incidence rate or death rate is expressed in new registered cancer cases calculated per 100000 population. Incidence rates may be crude (all ages) or age – specific – standard. When summary figures are necessary to compare rates between population groups with different age distribution, they should be age – adjuted; this is done by multiplying each age – specific rate by the percent of individual in a standard population with the same ages, and then summing to produce a single value.

For several cancers with poor survival, mortality rates nearly equal incidence rates. The combined analyses of incidence, mortality, and survival statistics provide valuable data on the patterns of cancer. There are European, word and other standards.

According to registered data sicknes, rate in malignant tumors increased in Ukraine up to 325 per 100 000 population in 2003 year. It is 155265 new cases. In comparison with 1997 year the increase in incidence rates is 3.1%.

Incidence rate increase for oral cavity, lung, colon and rectum, skin, breast, corpus uteri, prostate, bladder, thyroid cancers. Incidence rates have risen most for malignant tumors of thyroid – 40%, skin – 26%, prostate – 25.4% in comparison with 1997 year. Notable declines are apparent for lip, esophagus, stomach, and larynx cancers.

The structure of male and female oncologic case rate in Europe and Ukraine is different (Figures 1,2). The sickness rate in malignant tumors of Ukrinian males is 349.1 per 100 000 population, females 304.1 per 100 000.

Among males aged 30 – 34 to 60 – 64 incidence rates of cancer increase in the following age group twice in comparison with the preceeding one. Incidence rates decrease after 80 years.

♂
lung
stomach
colon and rectum
mouth and pharynx
prostate gland

♀
breast
cervix
colon and rectum
stomach
corpus of uteri

Fig. 1. The structure of male and female oncologic case rate in Europe

♂
lung
stomach
solon and rectum
mouth and pharynx
prostate gland

♀
breast
skin
corpus of uterus
stomach
cervix

Fig. 2. The structure of male and female oncologic case rate in Ukraine

Among females aged 25 – 29 to 65 – 69 years the rate of cancer incidence has been rising rapidly (1.5 – 1.8 fold), risk decreasing steadily thereafter, becoming very small by 80 year. So, incidence rate in Ukraine has stable tendency to increase.

The highest incidence rates are for lung, breast, skin, stomach, colon, prostate, corpus uteri cancers.

Advancing age increases susceptibility to cancer. If we suppose that in case people won't die from heart disease and other diseases the leading cause of their deaths can be cancer in the result of the aging process.

The leading causes of cancer deaths are:
lung cancer – 20.1%;
stomach cancer – 13.6%;
colorectal cancer – 11.2%;
breast cancer – 7.8%;
malignant neoplasms of lympatic and hemopoietic tissue – 5.3%.

Etiology and pathogenesis of malignant tumors

Etiology of malignant tumors is the science of the causes of disease and of the conditions under which disease rises. One of the main objectives of etiology is establishment of general regulations of the cancer origin and the study of the cancer causes.

Different theories concerning the etiology of neoplastic growth have been proposed, many of them explain the origin of tumors and have been proved in practice.

The most studied theories are: chemical, viral(biologic), physical and genetic theories of carcinogenesis.

According to WHO (World HerlthOrganization) "carcinogen" (physical, chemical or biological) is the agent capable of causing or speeding the neoplastic growth, regardless of mechanism of its action or degree of effect specificity. Carcinogen is an agent which due to its physical or chemical properties can cause irreversible change or damage in those parts of genetic apparatus, which realize homeostatic control over the somatic cells. Mutation performs normall cell into malignant one, it can be proved by the fact that the change of only one nucleotide in human protooncogenes can make them function as oncogenes and in some cases can cause malignant cell transformation.

Procarcinogens are chemical substances which after series of metabolic processes are capable of causing the malignant tumors development.

Factors involved in the causation of cancer include the following:

Chemical theory of carcinogenesis

According to chemical theory, the transformation of normal cells into blastomatous ones is caused by cancerogenic substances, which have either gained entrance into the organism from without or have been possibly formed in the organism as a result of deep changes in metabolism.

Percival Pott published in 1775 year his findings that chimney sweeper work led to scrotal cancer. However only K. Yamigawa and K. Ychikawa were the first to report in 1915 that coal tar could cause skin cancer in laboratory animals. They induced skin tumors in mice by systematic rubbing into the skin of auricle the coal tar.

The number of known carcinogenic substances capable of causing neoplastic growth by action from without has now considerably increased (more than 2000 chemical substances). According to the chemical structure, the carcinogens belong to different classes of inorganic and organic compounds.

Chemical carcinogens can be divided into the following groups: organic, inorganic and endogenous substances. Organic carcinogens are polycyclic aromatic hydrocarbons (coal carbonization products and some mineral oils). They are the products of incomplete combustion contained in tobacco smoke, in the exhaust gases of motor vehicles, in the smoke of blast furnaces, in the products of smoking.

Aromatic nitrogen compounds are contained in large quantities in the nitrogen dyes used for dyeing natural and synthetic fabrics, for colour printing and graphic arts industry, in cosmetics. Aromatic amine compounds are responsible for the development of the so-called "aniline cancer" of the bladder in the workers of aniline dyeing industry.

Nitrosocompounds and nitramines are chemically stable in the body are chemically stable. Their biologic effect is due to the action of the active metabolites formed under the influence of oxides. Nitrosamines are used as intermediates in the synthesis of dyes, drugs, plastics, pesticides. Nitrosamines are used as solvent in printing inks, anticorrosion agents intermediates for herbicide synthesis. A human can be subjected to nitrosamine action not only due to occupational

exposure, but also because of the chlorinated water and foodstuff quality. Nitrites are widely used as preservatives, so one of the tasks is to reduce their content in the foodstuff.

Studies of animals show that a number of metals and metalloids have carcinogenic activity. They include nickel, chromium, arsenic, cadmium, beryllium, cobalt, lead, titanium, zinc, iron.

The study of occupational groups has indentified more carcinogens than any other branch of cancer epidemiology and has led to cancer prevention by reducing or eliminating hazardous exposures in the workplace. Most carcinogenic exposures in the workplace were noticed initially by epidemiologists as in the case of asbestos (lung cancer and pleural mesothelioma), nickel, hematite (iron dioxide), chromium and its salts, arsenic (lung cancer and stomach adenocarcinoma in experimental animals), and the leather industry (nasal cancer).

Asbestos represents the major occupational carcinogen due to its induction of lung cancer and pleural mesotheliomas. Asbestos is a naturally occurring hydrated mineral silicate. A relation of asbestos to the development of gastrointestinal tract tumors has been claimed.

Along with existence of antropogen genesis carcinogens there are more than 20 carcinogens of natural origin, the most potent hepatocarcinogens appear to be natural products that occur in the environment and are synthesized by plants, fungi, and bacteria.

Probably the best studied natural chemical carcinogen is aflotoxin, a product of the Aspergillus fungus. Aspergillus flavus mold and aflotoxin product have been found in a variety of stored grains peanuts, particularly in hot humid parts of African continent, where most village – based grains can be seen to be covered by a white layer. This layer contains high levels of aflatoxin and is consumed over the after months.

Endogenous carcinogens can also cause a number of malignant tumors. The appearance of these carcinogens is associated with genetic, hormonal, and metabolic disorders. Blastomogenic properties of endogenously produced substances such as metabolites of tryptophan and tyrosine have been proved. In particular it has been revealed that tryptophan metabolites participate in the development of bladder, lung, liver, uterus, and ovary cancer and leukemia.

Nowadays it has been proved that some hormones: estrogens, androgens, and corticosteroids are capable of causing a carcinogenic effect. It has been supposed that the excess function of pituitary gland has a direct carcinogenic effect.

Physical theory of carcinogenesis

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Malignant tumors can be induced by physical agents: ultraviolet radiation and ionizing radiation, which can be electromagnetic (photon) and corpuscular. X – rays and Y – rays are electromagnetic radiations. Elementary particles such as electrons, protons, neutrons or alpha particles are corpuscular radiation.

Life on earth has always been exposed to ionizing radiation in the form of cosmic rays or radioactivity in the earth, man – made radiations from medical radiology and nuclear power and man enhanced sources (naturally occurring radon). Radon concentrates in the houses and decays. Along with ionizing radiation cancer can be induced in humans endogenously by ingested radionuclides.

Long before the discovery and testing of nuclear weapons, two American researchers March and Ulrich had analyzed the causes of radiologists deaths and came to conclusion that they died from leukemia 9 times more often than doctors of other specializations.

The incidence of leukemia, lung cancer, breast cancer and thyroid gland cancer was multifold increased in atomic bomb survivors in Japan. Both chemical carcinogens and ionizing radiation are polytropic, i.e. can induce cancer almost in every tissue and organ (skin, lung, liver, thyroid, breast cancers, bone tumors, leukemia).

External ultraviolet radiation from sunlight includes the tendency of tumors to arise within the irradiated tissue on sun – exposed sites, but radionuclides induce tumors in the sites of deposit. There are different kinds of radionuclides. They are osteotrop radionuclides (strontium, radium), thyroid (iodine) and other radionuclides. For example, incorporated osteotropic radionuclides ^{90}Sr, ^{89}Sr, ^{140}Ba, ^{45}Ca can induce tumors of the bones and surrounding tissues. Hepatropic radionuclides ^{144}Ce, ^{140} La, ^{147}Pm, ^{232}Th, ^{198}Au are deposited in the liver and bones, and induce tumors of the liver, bones, hematopoietic tissue, stomach, and colon.

Carcinogenic effect of ionizing radiation is independent of the dose, although the probability of its occurring increases with dose. Any dose carries with it some risk of inducing cancer. Radiation has "no threshold". Radiation given gradually over time may cause less cancers overall than if the same radiation dose were given over a brief interval.

Ultraviolet (UV) radiation from sunlight has been known to be responsible for carcinogenesis. In experimental animals, repeated doses of UV radiation, particularly in the UV – B spectral range (280 to 320

nm), can induce skin cancer. It is the most biologically effective wave lengths of UV radiation. Long – term sun exposures appear closely related to the development of malignant epithelial (cancer) and connective tissue (sarcoma) tumors on sun exposed body sites.

Epidemiologists noticed that the incidence of skin cancer is higher in persons living in the southern regions of Ukraine (the Crimea, Odessa regions) and exposed to long-term insolation. There is good evidence to believe that increase in the incidence of skin melanoma occurs from repeated exposures to sunlight. It is suspected that the mechanism of action of ionizing radiation and UV rays is associated with activation of lipid peroxidation due to the formation of highly active radicals by hydrolysis of water in the cell.

There is no incontestable proof of the trauma etiology of a tumor. Some data on the origin of tumors suggest that tumors may apparently be caused by proceeding trauma: mechanical, thermal or chemical. Trauma can predispose to the development of cancer at the areas of keloid scars of burns and esophagus chemical burns. Development of osteosarcoma and Ewing's sarcoma appear to be associated with mechanical trauma. Many cases of neoplasms development at long – term stay of calculus in gall bladder, renal pelvis, urinary bladder have been described. Trauma may play a mediate role in causing cancer.

Biological (viral) theory of carcinogenesis

The biological carcinogens include a large group of viruses and some protozoa (infectious agents (Helicobacter pylori infection arises the risk of gastric cancer)).

F. Peyton Rous was the first to prove in 1911 by his experiments the etiologic role of the virus in he occurrence of malignant tumor. He showed that cell-free extracts from a sarcoma in chickens could induce tumors in injected chickens within a few weeks, even when passed through filters that retained bacteria. P. Rous pointed out that this infectious agent was not only capable of inducing tumors, but also imprinted the phenotypic characteristics of the original tumor on the recipient cell.

In the 1930s Richard Shop described cell – free transmission of tumors in rabbits. Ludvig Gross in 1950s discovered the murine leukemia viruses and described retroviruses that could cause tumors in mice. After this findings many virologists supposed that human tumors might have a viral origin. The field of viral oncology lay dormant until

the discovery of Bittner virus causing breast cancer, the murine leukemia viruses and mouse poppiloma virus. Virologists proved that oncogenic viruses can be transmitted by horizontal and vertical ways, i.e. from mother to her offspring when feeding with milk or transovarially.

Nowadays More than 150 types of RNA and DNA containing viruses have been discovered and described to have oncogenic activity. They induce tumors, generally leukemia's and sarcomas in birds, reptiles, mammals (rats, mice, hamsters, dogs, monkeys).

The discovery of oncogenic viruses in birds and mice was the basis for creation the viruso genetic theory by L.A. Zilber in 1966. According to which virally linked tumors transform normal cell into a malignant one, and this change is hereditary. The virus associated with this transformation is involved only at an early step in carcinogenesis, and plays no role in the further development of the tumor.

L.A.Zilber's theory runs that in the result of virus contact with the virus susceptible cell occurs virus deproteinization, nucleic acid release and invasion into the cell cytoplasm and then into the nucleus. The viral genome or its part is integrated into the host cellular genome as part of the life cycle of the virus. New information getting into cellular genome can cause its transformation in some cases.

The necessary condition of cell malignization under the action of oncoviruses is physical integration of viral gens following functioning of viral gens, occurrence of virus-specific oncoproteins and their influence on cellular processes, associated with proliferation and differentiation.

According to viral theory carcinogenic substances are regarded as a factor creating in the organism foci of cellular proliferation and tissue metaplasia. These foci are a necessary condition for the activation of the viruses which have gained entrance into the organism and for the manifestation of their pathogenecity.

None of the viruses is sufficient alone to induce the specific neoplasia with which it is, associated. Other Confactors are necessary for development of virally – linked tumors, including genetic, immunological, hormonal and environmental factors. Each of the viruses associated with these human cancers is thought to be involved at an early step in the multistep process of malignant progression.

Virus isn't oncogen until vital genome is incorporated by cellular genome. After integration and incorporation of viral genome in cellular genome viral genetic information is transcribed by cellular RNa

polymerases and obeys the laws of cellular DNA. Expression of viral genes turns a normal cell into a malignant one.

Almost 70 years passed between Peyton Rous's initial description of the avian sarcoma virus and the first evidence of a human retrovirus.

The first reports of a human retrovirus were published in 1980. The human T – cell leukemia virus type I (HTLV – I) is the virus etiologic agent of adult T – cell leukemia. This leukemia is endemic in the southern islands of Japan and in the Caribbean. There is evidence of vertical type transmission of retrovirus HTLV – I from mother to child.

Denis Burkitt in 1958 suggested that the lymphoma could be due to a virus because its geographic distribution was similar to that of yellow fever in a belt across equatorial Africa. In 1964 Epstein and Barr described virus particles of the herpesvirus family in lymphoblastoid lines cultured from explants of Bukitt's lymphoma (BL). Genital infection by herpes virus family is considered as an etiologic cause of cervical carcinoma.

Considerable evidence indicates an etiologic involvement of Hepatitis B Virus (HBV) with human Hepatocellular carcinoma (HCC). It is supposed that adenovirus produces carcinogenic effect and results in oropharynx tumors.

It is very difficult to study how viruses are activated, induce neoplasia, and manifest their pathogenecity, because there is a long – term period between exposure to the virus and appearance of the tumor. Further more, the virus causing the malignant tumor development is not always present in it.

VIRUS	ASSOCIATED CANCER
DNA viruses	
Epstein-Barr virus (EBV)	"B" cell Iymphoma, Burkitt's Iymphoma, nasopharyngeal carcinoma, Hodgkin's Disease
Hepatitis B virus (HBV)	hepatocellular carcinoma
Human papilloma virus (HPV) subtypes 16 and 18	cervical cancer, squamous cell carcinoma
Human papilloma virus (HY) subtypes 5 and 8	squamous cell carcinoma in association with epidermodysplasia verruciformis
RNA viruses	
Human T cell leukemia Virus - type 1 (HTL V-I)	adult T-cellleukemia / lymphoma (ATLL)
Human T cell leukemia Virus -type 2 (HTL V-II)	Chronic T-celllymphoproliferative disorders
Kaposi' s sarcoma-associated herpeslike virus (KSHV)	Kaposi' s sarcoma
Human immunodeficiency virus - type 1 (HIV-I)	Kaposi's Sarcoma, Hodgkin's Lymphoma, Non-Hodgkin's Iymphoma, anal squamous cell carcinoma

Table I: Tumor-Associated Viruses

Genetic theory of carcinogenesis

According to numerous researchers cancer is provoked by genetic cell disease, associated with mutation in DNA, which gives rise to the malignant clone. Inherited forms of cancer account for about 7% of all cancers and divided into three groups. The first group of genes inherits the gene that predisposes a person to a specific tumor type (retinoblastoma, Wilm's tumor). The second group inherits the gene increasing the risk of site specific cancer (breast cancer, xeroderma pigmentosum). It occurs due to impaired DNA repair i.e. because of decrease in the effective mutations elimination at the cellular level. The third group is polygenic inheritance: the tumor arises when the patient has several hereditary traits, associated with impaired immunity resulting in lowering the transformed cells elimination efficiency.

Childhood tumor retinoblastoma develops in early age and arises from nervous cells of the retina. This malignant eye tumor is familial

and consistent with autosomal – dominant inheritance and occurs due to the 13 chromosome long arm deletion.

Wilm's tumor accounts for 20% of all cancers in children and occurs more often in children younger than 3 years of age. More than 30% of Wilm's tumor occur in familial forms. There are two forms of inheritance: autosomal – dominant and autosomal – recessive. Structural rearrangements in some cases involve a deletion of the short arm of chromosome 11.

Down's syndrome (trisomy for chromosome 21p) predisposes persons to myeloleukemia, which occurs 20-30 times more often, than the rest population. It indirectly evidences that this cancer occurs as an inherited trait.

Thus we have presented four basic principles theories of carcinogenesis: chemical, physical, viral (biological), and genetic. These principles are the basis of modern concepts of the onset of malignant tumors.

Malignant transformation as individual change of cell heredity is a multistep process of functional change of genetic adjustment apparatus, which can be induced by different factors. This suggests that malignant tumors are multifactorial disease.

Tumor stem cells. New point of view on carcinogenesis

The discovery of cancer stem cells greately changes our concepts about the mechanisms of multi – step tumorogenesis, since these self – renewing cells (or closely related progenitor cells), rather than the bulk populations of cancer cells, may be the objects of genetic alteration and clonal selection.

Understanding of interrelationship between tumor cells and their "normal" cell analogs, determination of genetic events, succession, which results in cell transformation and appearance of tumor clon are very important in the choice of strategy and tactics of malignant tumors treatment.

Discussion about the ways of normal cell transformation into a tumor one has been going on for many decades and it is far from completion. There are a lot of tumor origin theories, many of which have been proved in practice. The more studied theories of carcinogenesis are: chemical, physical, biologic and genetic.

All theories of carcinogenesis presuppose malignant tumor development from mature differentiated somatic cell. Neoplastic cells

possess tumorotropic potential, however it has been proved that pathogenesis of hemopoietic system tumors differs greately from pathogenesis of solid neoplasms. So stem cells are considered to be true ancestral cells of hemopoiesis. They provide stable blood formation and gradually are used in the course of person's life. Stem cells pool consists of early ancestral pluripotent cells, which are able to form clones of all hemopoietic lines. Pluripotent stem cells provide two necessities of life: initial pool constancy and part of cells exit into maturating developing fraction.

Progeny (offsprigs) of ancestral cells when dividing become more and more specialized and gradually lose ability for proliferation. In the course of hemoblastosis development blocking of bone marrow cells maturation and secretion of increased proportion of blast cells is observed at any level of hemopoiesis.

It normal tissues stem cells have been found in brain, mammary and prostate glands skin, small and large intestine. It has been proved that stem cells behave our in all cases is subjected to the same laws.

It was the group of researchers from Michigan University laboratory in Ann-Arbor who were the first to publish in 2003 the information about cancer stem cells presence in solid tumors. It has been also found out that epithelial stem cells have proteins CD 44, Sca-1 on their surfaces. Stem cells stain in the process of interaction of these proteins with monoclonal antibodies.

Recently reliable data has been obtained which evidences that stem cells can undergo malignant transformation and only small part of tumor cells has properties similar to the properties of stem cells. This data has convinced the researchers that subpopulation of cancer cells similar to stem ones initiate carcinogenesis.

Flow cytometry and use of specific antigen markers made it possible to reveal cancer stem cells at multiple myeloma, brain tumors, mammary gland cancer, pancreas cancer prostate cancer, large intestine cancer, and melanoma.

The researchers showed that in all cases tumor stem cells behave our is subjected to the same rules. In particular, there are systems regulating the number of their pool and mechanisms taking decisions concerning individual cells. It occurred that asymmetric division happens in tumor cell of any type. This fact is also one more evidence that cancer cell is an offspring of the stem cell.

Stem cell division in host tissues is an intricate process, which is regulated by genes. Normal stem cells ability to self maintenance also

gives them some kind of freedom, not characteristic for the majority of other cells. They can originate tissues of any type, and tumor is heterogenous: it seems that it represents the whole organ, but only non – structural at all. It has been proved that in response to the damage signal hemopoietic stem cells are directed to the most remote parts of the body. In the same way tumor cells can spread about the whole any part of the body.

Stem cells are arranged in the tissues not chaotically, but are in specific microsurrounding or stem niche formed by regulatory connective tissue cells and fixed in it by adhesion molecules. Niche is necessary for stem cells for survival and keeping stem status. Signals from stromal cells, forming niche, are delivered to stem cells with the help of molecules. These signals block definite genes activity in stem cells and activate them in daughter cells, leaving the niche. Stem cells leave their niche very seldom, as they are connected with it by adhesion molecules. Ancestor tissue cells, on the contrary leave the niche.

Proceeding from aforementioned it can be supposed that local external signals influence the behaviour of cancer stem cells, disposed in niche. Experiments prove it. In case stem cells, predisposed to malignant degeneration due to oncogenic mutations, are placed in new niche, they don't initiate tumor formation. And on the contrary, tumor will develop if normal stem cells are transplanted into preliminary irradiated tissue. Besides it has been established that if malignant stem cells are kept by forming the niche, surrounding in the state of quiescence and then this niche changes by one or other way or grow in size, the malignant cells grow in number.

Under the influence of mutations cancer stem cells may stop respond to external signals and they become completely uncontrolled.

So cancer stem cells with oncogenic mutations are under strict control implemented by their surrounding (niche), till the further changes in cancer stem cells occur or niche will widen. In the latter case the population of cancer stem cells and the number of their abnormal offsprings may increase.

Normal stem cells have much in common with malignant ones: they are clonogenous, minimum differentiated, immortal, have autonomous division (autocryne mitoze stimulation), and activated oncogenes. If stem cells are identical with tumor cells according to their properties, then they don't need any genetic damages to trigger tumor transformation. The latter can happen not because of mutation, but

exclusively due to disorders of tissue control of stem cells and their derivatives proliferation.

Mutations can happen in stem cells predisposed to malignant degeneration. Mutations cause loss of control over stem cells. Ancestor cells declined to malignant transformations due to mutations, which they inherited from paternal stem cells undergo further transformations, leading to restoration their ability for self revitalization.

Such ancestor cells live infinitely long, they are oncogenous and become cancer stem cells. Different states of local immunity are possible during stem cells malignant transformation.

New data contributes dramatically to our understanding of tumor. Some time ago it was thought that malignant tumors are relatively homogenous structures, consisting of homogenous cells, in case of cell heterogeneity it was considered to be the consequence of cancer genome instability.

Spontaneous malignization of cells, cultivated in vitro confirms the important role of tissue influence in mechanism of transformation. From the point of view of oncogene conception this phenomenon hasn't got rational explanation, because such transformation can happen without any external carcenogenous influence. On the contrary from the point of view of decisive role of tissue homeostasis this phenomenon is understandable and logical: without tissue system control clonogenous cells practically inevitably undergo malignant changes.

Nowadays conception about carcinogenesis makes it necessary to elaborate the strategy of malignant tumors treatment. Before complete destruction of tumor tissue and separate cells in the organism, irrespective of their location was the main strategy of tumor treatment. However only small quantity of stem cells take part in the tumor development, and if that cell population is not removed completely, the recurrence is inevitable. And conversely in case of only stem cells destruction, the rest tumor cells will be ruined in themselves.

The period from the beginning of the carcinogens influence on the cell to the presence of diagnosed tumor is called latent period. Carcinogenesis initiation and promotion, tumor progression happens within this period.

Both carcinogenecic latent period and life duration are species signs and they amount to about 5-6% of life duration. It is very difficult to define exactly difficult to define exactly duration of peoples carcinogenesis latent period, though hypothetically it is 10 to 20 years.

Tumor progression is a quantative and qualitative process. 20 redoublings are necessary to develop lung cancer from some cells to 1mm tumor.

Exfoliation of tumor elements and hematogenous metastasizing are possible. During this early biologic phase. There are about 10^6 cells in 1 to 2 mm tumor.

Clinical effects of defective DNA repair indicate that much of the normal aging process will one day be traced to genetic damage that we accumulate in our stem cells throughout life; their progressive attrition seems to lead to the inability of tissues to renew themselves, yielding precisely the changes observed in the aged. Consequently, cancer and aging may be found to share a common root – the progressive deterioration of our genomes as we get older. And both cancer development and aging may one day be forestalled by treatments and lifestyles that protect our genomes from the ongoing attacks that they suffer, decade after decade, deep within our cells.

Phases of carcinogenesis

It was I. Foulds who proposed a multistage hypothesis of carcinogenesis (1976) according to which three stages of carcinogenesis are identified: initiation, promotion, and progression, they pass successively into each other (Fig. 3.)

Initiation is the first stage of carcinogenesis. During this stage the cells with hereditarily fixed properties i.e. immortality, blocked terminal differentiation, and ability to promotion are transformed. The DNA configuration of the cells undergoes some basic changes.

As it has been mentioned above all cancers arise as a result of changes in genes that regulate cell growth behavior. Any carcinogenic factor affects the genetic apparatus of the cell responsible for the propagation, differentiation, and heredity.

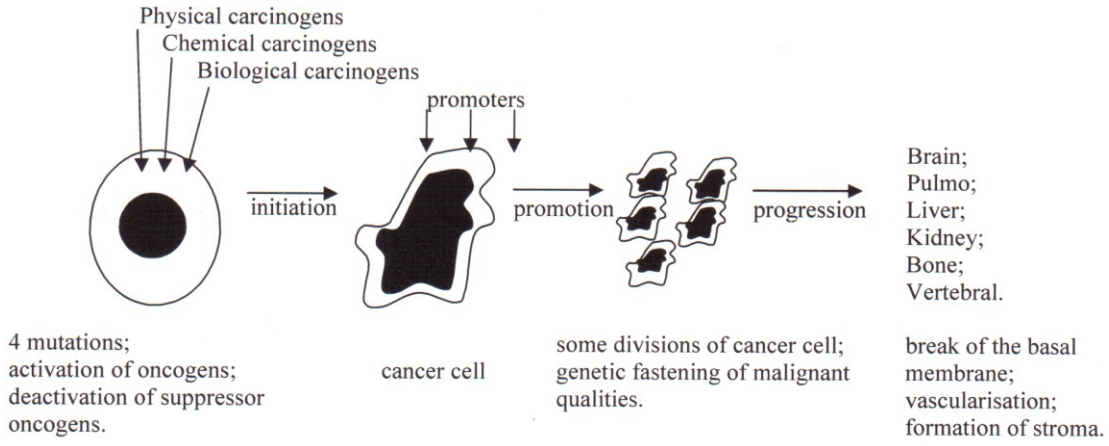

Fig.3. Phases of carcinogenesis

Each cell in the nucleus has regulatory proteins that can inhibit the uncontrolled growth. They are so-called tumor suppressor genes (e.g. p53 tumor suppressor gene). In case of their mutation and loss of ability to produce the cell corresponding inhibition proteins the cell begins to divide uncontrollably. Mutation or even a slight change in molecule shape results in the loss of normal suppressive function, leading to uncontrolled cancer growth. Mutations of $_{p}53$ have been identified in many solid tumors. Besides, there are well-known mutations of the so-called heritable breast cancer "predisposing" gene (BRCA- 1) which has been found in families with high incidence of this disease.

Nowadays it is known that during the initiation phase many intricate damages and changes of cell's gene (mutations) take place, and they are not to be eliminated by restoration cell mechanisms Fig.4. Probability of a successful initiation is low.

A lot of cells are exposed to carcinogen influence and the following neoplastic transformation. However, the majority of neoplastic or preneoplastic tissue cells, subjected to carcinogenic exposure will never proliferate or they can be destroyed before the stage of proliferation. Cells acquire a number of traits which were not specific to them before, e.g. loss of contact inhibition of growth, simplification of cytoskelet structure, changes in the necessity of humoral factors that control cell proliferation, increased secretion of proteolytic enzymes involved in subsequent degradation of extracellular matrix. Transformation differentiation traits include changes of protein, phospholipid, glycoprotein spectra of cell structures antigenic properties, synthesis of proteins characteristic of embryogenesis.

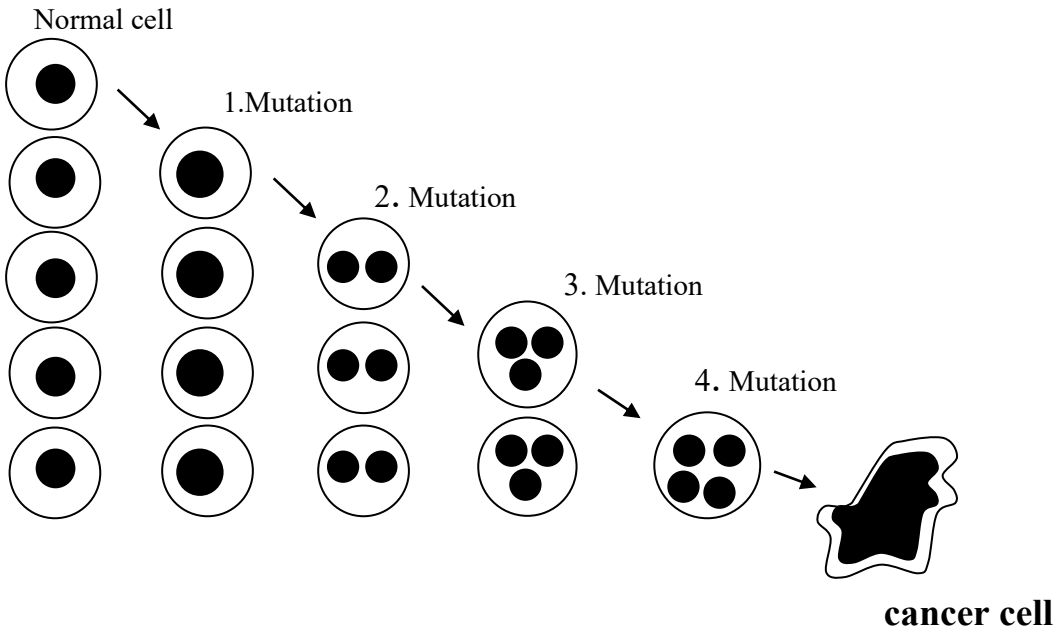

Fig.4. Change of genetic apparatus in the process of carcinogenesi

Most of the cells exposed to carcinogens undergo mutations and die. Initiated cell divides several times, fixes its genotype, and passes it on to daughter cells and only then becomes tumor. It is believed that in case the carcinogen exposure of the initiated cell ceases the futher cell development and division stops as well.

Promotion follows the initiation phase of carcinogenesis. For genetic consolidation of qualities in the initiation phase replication of damaged cells must occur before these lesions are restored. Specific factors – promoters continue their action on the cell and in the result it is divided for several times and acquires the property of immortality. It is the basic property of the transformed cell and is the ability of the cell to unlimited duplication with block of terminal differentiation. Both exogenous chemical compounds and endogenous compounds (hormones, bile acides etc.) can be promoters. The process of carcinogenesis becomes reversible after promoters action termination. Action of promoters is to be long – term.

As it was already mentioned, the main feature of the transformed cell is its immortality. In the presence of nutrient medium, cancerous cells can divide infinite number of times. Tumor cell division in humans continues until their death.

The British L. Hayflick and P.S. Moorhead made a very important discovery in 1961. They determined that normal somatic cells have a limited replicative potential. In particular, human skin fibroblasts in a nutrient medium are divided about 50 times, after that the division rate

decreases, and morphological changes, characteristic of old cells, take place. Then follows apoptosis i.e. biologic cell death.

Later it was established that the terminal fragments of chromosomes, called telomeres are shortened with each cell division. It is known that telomerase fragment of DNA consists of more than 1000 nucleotide TTAGGG repeats. In the result of each cell division chromosome length is shortened by about 10-20 telomerase fragments as during DNA replication DNA enzyme of DNA polymerase can not provide replication of the terminal nucleotides in the DNA strand. And when telomerase DNA fragments are reduced by 1000 nucleotide repeats (about 50 divisions), violations incompatible with the existence of normal cells take place, which results in apoptosis, so we can say that normal cell has so called "biological clock". This phenomenon has been called the **Hayflick limit.**

Active telomerase enzyme in cancer cells constantly increases chromosome fragments decreasing in the process of division, therefore in spite of its "old age", the life duration of cancer cells is not in fact limited. Tumor cells overcome the Hayflick limit, they are devided infinite number of times, exceeding, to a considerable extent the regulated number of normal cells divisions. Moreover, cancer cells are divided more frequently than healthy ones, and live longer.

Progression is the third phase of carcinogenesis during which the tumor acquisits in the process of its growth more malignant properties and the cells structure and functions become more simplified. Tumor progression happens due to the tumor cell population heterogeneity and their genetic instability, which results in additional mutations and in this way cells loss their ability to differentiate and to fulfill their normal function and so the tumor looses organotypic and gistotypic structure. At the time of clinical onset a tumor is a population of phenotypically and genetically heterogenous cells, due to their genetic instability and is a manifestation of progression, and is evolution "from bad to worse" (Tubiana M., 1991).

At the time of diagnosis, most neoplasms consist of different populations of cells with diverse biologic characteristics. Subpopulations differ in immunogenicity, growth rates, radioresistance, susceptibility to anticancer drugs. Rise of tumor cells genetic instability, increase in the number of chromosomal disturbances are associated with reduction of their differentiation. Malignant cell genomic instability is the leading trait according to which the selection is carried out at carcinogenesis.

Tumor differentiation is reduced, in the process of progression so it is sometimes impossible to identify an organ only on the basis of microscopic investigation Tumor becomes undiffrerentiated. at further increase of anaplasia, and it is often impossible to determine its histogenesis.

Malignant tumors metastasizing

Metastasizing is one of the main biologic traits of malignant tumors. More than 80% of cancer patients have clinically detectable metastases, which are the major cause of treatment failure and mortality.

It is supposed that the formation of metastases is a continuous process commencing early in the growth of primary tumor and increasing in time. A group of coordinated cellular processes, not just one gene product, is responsible for metastasis. It has been calculated that most metastases are initiated when number of tumor cells exceeds 1000(10^3), and the tumor diameter is 0.5 mm.. After that cancer cells can gain access to blood vessels for further dissemination. Lymphogenous metastasis is characteristic of epithelial genesis (cancer). Hematogenous metastasis is characteristic of sarcoma.

Regional lymph nodes don't function as mechanical barrier to tumor dissemination, so lymphatic and hematogenous dissemination occur in parallel.

The process of metastasis involves multiple tumor – host interactions. To be successful, a metastatic tumor cell must leave the primary tumor, invade blood and lymph vessels (intravasation), enter the circulation, arrest in blood vessels (sedimentation), extravasate, implant cells and multiply to initiate a metastatic colony (Fig. 5.).

Heightened hydrostatic pressure in the tumor as well as ameba – like motility (series of adhesion and detachment steps) of cancer cells are of great importance in the first phase (stage). Most (99%) of the tumor cells circulating in blood vessels don't survive and only small quantity of them initiate metastatic colonies. The distribution of metastases depends on the histologic type and anatomic location of the primary tumor. Tumors can metastasize to various organs and tissues. The most common sites of spread of distant metastasis are "target organs", which include **brain, lungs, liver, kidneys,** and **bones**. Tumor cells can embolize in the capillars. Selective hematogenous metastasis is due to capillary endothelium which shows organ specificity of metastasis. It has been proved in the experiments that tumor cells can

adhere preferentially to the endothelial cells only in the target organ for metastasis, so it is supposed that many sites can be considered as examples of organ tropism.

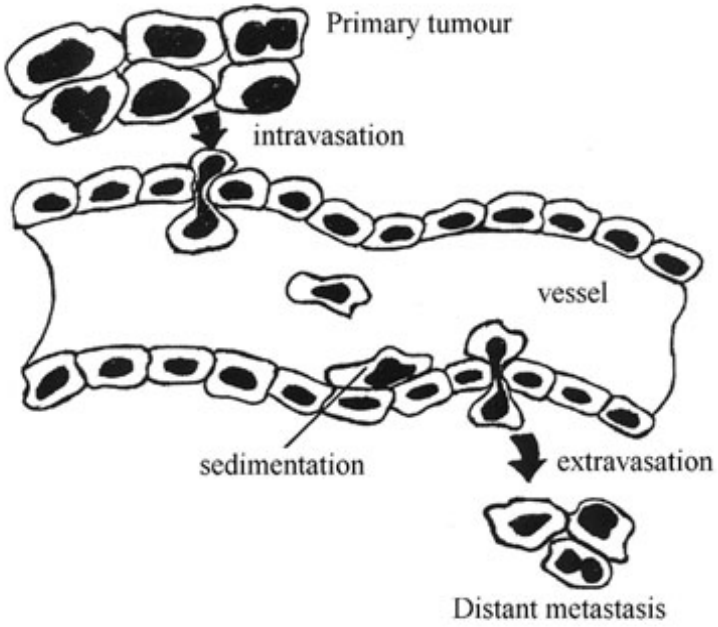

Fig. 5. The process of an initiation
(Malignant cells stages of metastasis)

Metastasis development includes triad of factors: traits of tumor cells, immunologic host organism reactivity and functional state of the organ, which was invaded by tumor cells. It is considered that metastatic tumor cells preexist at a very early stage far before clinical tumor onset within first 20 duplications (Furnier D. et al., 1985). The time of clinical presentation of metastasis depends on the tumor growth rate. Numerous clinical reports provide evidence for the existence of "dormant" metastases which can occur 10-20 years after surgical removal of the primary tumor.

Experimental and clinical studies have proved that microscopic tumors can have multiple metastases, which grow faster than primary focus. It explains the cases when at first metastases are revealed and some time later the primary tumor. So it is considered that the tumor is in actually a systemic disease in the period of its clinical manifestation. Recent studies have demonstrated a close correlation between the size and tumor stage differentiation, initial tissue and organ are significant as well. The higher cancer organ (lung, kidney, tongue) vascularization, the higher probability of metastasis.

Tumor growth rate

The duration of tumor growth is not clear. Preclinical tumor stage is essential. Since the initial stage of carcinogenesis in humans remains beyond the reach of modern diagnostic methods, it can be calculated only theoretically.

In accordance with C.Henderson et al. (1989) calculations, 1cm in diameter tumor can be palpated. One cubic centimeter of tumor tissue contains 10^9 neoplastic cells. Their production from an initial transformed cell requires around 30 duplications of volume (divisions) in case of its development from a single cell. Having supposed that breast cancer cell duplication time in average takes 100 days, the authors calculated that tumor had been developing until clinical manifestation for 10 years. According to Moiseenko et al. (1997) the doubling time of human tumors ranges from 1.75 year in rapidly growing tumors with doubling time less than 35 days to 18 years in case of slow growing ones with doubling time more than 110 days. Average doubling time of preclinical period is 8 years. There are slow growing tumors with doubling time 400 days, which can't be clinically manifested during a person's life. Anderson et al. (1985) prove this data. They found out that 25% of women, who had died from different reasons, had cancer. It was proved by hystologic examination of breast tissue layered slices. Clinically manifested tumor is developing for 3 years, so in total the tumor can develop from initiation to the patient's death 12 to 15 years (Fig. 6).

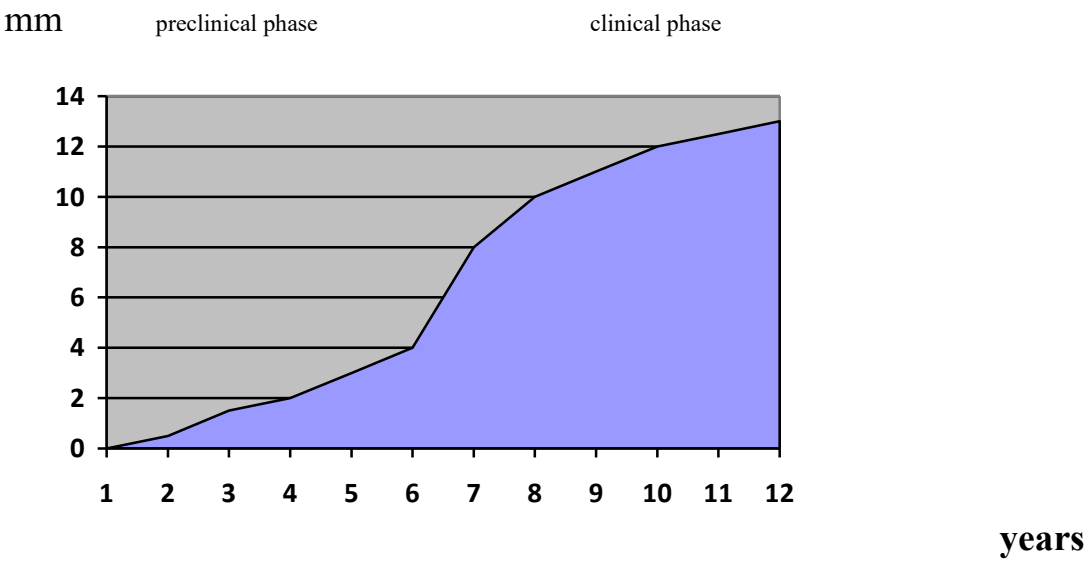

Fig. 6. Malignant breast tumors growth rates

Preinvasive and invasive cancer

Malignant cells develop both along and in the depth of the epithelial layer. The basement membrane separates the epithelial layer from the connecting tissue, including lymphatic and blood vessels. For some time it works as a barrier, which prevents the contact of cancer cells with lymphatic and blood vessels. Existence of this barrier even in theory makes it impossible to discharge tumor cells into lymph or blood drainage, so having the traits of malignant tumor, the latter can't metastasize.

Such kind of tumor, in which cancer cells haven't disrupted the basement membrane, is called intraepithelial preinvasive cancer or carcinoma in situ. This term was introduced in 1932 by A.Brothersome. Microscopically at carcinoma in situ, the whole epithelial layer consists of atypical cells, vertical anisomorphology (layer differentiation) is violated though basement membrane is preserved (Fig.7).

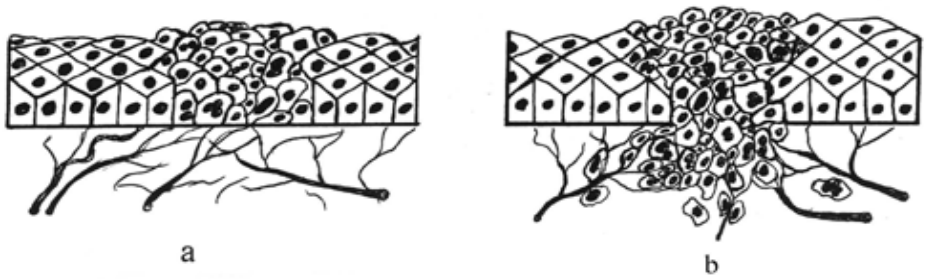

Fig.7. Overview of a) preinvasive (carcinoma in situ) and b) invasive cancer

Nowadays at some cancer localizations (oral cavity, stomach, cervix etc) it is possible to diagnose tumor in Ca in situ phase. It would be ideal in clinical practice to diagnose all kinds of cancer in preinvasive phase, that allows to cure all the patients. Volume of intervention is minimal in patients with carcinoma in situ and it is possible to save the organ.

The next step in tumor development is disruption by its cells of the basement membrane and initiation a metastatic colony. After that carcinoma in situ is transformed into invasive cancer. Now the tumor cells are able to gain access to blood and lymph vessels and to invade. At this stage cancer development the possibility of lymphatic and hematogenous metastasizing is little. Microinvasive cancer doesn't clinically manifest itself and so it can be diagnosed only microscopically.

Tumor cells secrete angiogenic factor, which diffuses into the tissue. This factor stimulates endothelium cells division and causes capillar proliferation. Tumor vascularization abruptly speeds progession and increases the probability of metastases. Malignant growth occurs in the first instance along lymphatic and blood vessels.

Malignant tumor cells also produce lytic substances (invasion factor), which action is similar to the effect of hyaluronidase and proteolytic enzymes. Tumor can sprout into normal tissues.

Many oncologists suppose that only when the tumor weight is 1g it can be defined visually, by palpation, by X – raying and endoscopically. 1g tumor has diameter about 1cm and it can have lymphatic and hematogenous metastases. Metastasizing depends not only from tumor size, but in more degree from the tumor cell division speed, its differentiation, localization, hystologic type, and form of tumor growth (exophyt, endophyt).

Tumor impact on the host

Common symptoms develop as the result of tumor impact on the body. The most common symptoms include weakness, fatigue, decreased ability to work, loss of weight. Sometimes patients have an avertion to meat diet. These syndromes develop in some cases long before the clinical manifestation of the underlying disease. Non – cancer diseases are developing under the influence of malignancy and are called paraneoplastic syndromes. They develop due to metabolic and immunity disorders, disturbances in functional activity of host regulatory system but not in the result of tumor direct action on tissues and organs.

Paroneoplastic syndromes are nonspecific. They can be present before the clinical manifestation of the tumor.

Paraplazia can arise due to tumor production of biologically active substances. Ectopic hormone secretion is especially characteristic in small cell lung cancer, in particular adrenocorticotropic, antidiuretic, melanocyte stimulating and also seratonin, calcitonin, reninlike substances, insulin, prolactin and oxytocin.

According to Yu.I. Lorie., A.E. Vermel and I.V.Poddubnaya (1972), secondary non – specific syndromes in malignant tumors are classified as follows:

1. **Metabolic – endocrine disorders:** systemic hypertrophic osteoarthropathy, hypercalcemia, hyperurectomy, acantosis nigricans, carcinoid syndrome, hyperfibrinogenemia, Itsenko - Cushing's

syndrome, gynecomastia, hypoglycemic coma, increased secretion of antidiuretic hormone.

2. **Vascular (endothelial) disorders:** trombophlebitis migrans, paraneoplastic tromboendocardit.

3. **Secondary autoimmune and allergic syndromes:** dermatomyositis, scleroderma, systemic lupus erythematosus, rheumatoid arthritis and rheumatoid syndrome, Hoshimoto thyroiditis, hemolytic anemia, thrombocytopenic purpura, hemorrhagic vasculitis; nephrotic syndrome (amyloidosis, glomerulonephritis); allergic syndromes (urticaria, anaphylactic shock).

4. **Lesions of central nervous system and neuromuscular disorders:** psychosis and dementia, cerebellum cortex degeneration (Lambert – Eaton syndrome), acute demyelination of the brain or spinal cord substance peripheral sensory or sensory – motor neuropathy.

5. **Other syndromes:** exudative pericarditis, steatorrhea. Hemocoagulation failure syndrome is characteristic of many localizations of malignant tumors. Excessive consumption of fibrogen by the tumor through vessels chemoreceptors stimulates its synthesis in the liver resulting in high blood levels of fibrogen. Besides the tumor itself produces protein, which precipitates fibrogen, thereby contributing to the induction of intravascular thrombus formation. Initiated intravascular coagulation in its turn leads to the activation of physiological anticoagulation system and release into the blood stream of heparin and activators of fibrinolysis. In the result functional physiological anticoagulation system reserves are depleted and there may come a time when it will not be fully able to level hypercoagulation which inevitably results in thrombosis formation.

The cause of migratory thrombophlebitis in cancer patients is hemostatic potential change. The process is localized predominantly in low extremities superficial veins, but can also be located in other parts of the body. Paraneoplastic thrombophlebitis defies anticoagulation treatment.

Anemia is one of the gematopaties accompanying malignant process, it is observed quite often. The cause of anemia development may be the violantion of erythropoiesis due to primary or metastatic lesion of bone marrow. Autoimune hemolytic anemia development is often a symptom of the tumor distribution process so the life expectance at developing paraneoplastic anemia is often unfavourable.

Most cancer patients have increased erythrocyte sedimentation rate, more than 30 mm/h. This parameter change is caused apparently by rise

of erythrocyte aggregation capacity and the change in blood protein composition.

Syndromes of central nervous system include carcinomatous neuropathy, manifested in the development of psychosis, encephalopathy, myelopathy. Mental and nervous system functions disorders due to sensory and sensorimotor neuropathy can be in patients long before the clinic of lung cancer.

Predominant destruction of white matter of the brain occurs with focal symptoms – hemiparesis, aphasia, while destruction of grey matter is accompanied with dementia, depression.

Harrison et al. in 1957, were the first to describe carcinoid syndrome in small cell lung cancer. Clinical features of this syndrome are: quickened pulse, sudden hyperemia of face and body, profuse diarrhea, abdominal and muscle pain.

It should be noted that paraneoplastic syndromes very often improve with removal of malignant tumor and may reappear when the tumor relapses or metastases.

We should keep in mind that paraneoplastic syndromes can occur sometimes at a very early stage of malignancy development, when it is very difficult or impossible to diagnose the tumor.

Primary multiple tumors

Malignant tumors can develop simultaneously from several buds in one host. Such tumors are of multicentric growth. Typical sites of multicentric cancer are breast, stomach, colon, lungs (not so often), kidneys, liver.

Malignant tumors localizing in several organs are called primary – multiple. Tumors detected simultaneously or with an interval less than 6 months are called synchronous. Those that develop successively over definite time (more than 6 months) in different organs are called metachronous.

Primary – multiple tumors developing in paired organs of one system (lungs, kidneys, tests and others) are called corresponding, and those developing in organs of different systems (lungs and stomach, cervix and lungs, breast and colon) are called.

Clinical and morphological criteria of primary – multiplicity of malignant tumors are:

a) Differences in histological structure of tumors;
b) Presence of regional metastases in each tumor;

c) Presence of precancerous changes or cancer in situ near the tumor;
d) More than 5 years between the detection of metachronous tumors.

Presence of neoplastic lesions in two organs excludes metastatic involvement of one of them.

Precancerlesion and cancer prevention

The term precancer embracers all the morphologically recognizable disorders thought to predispose a person to the development of malignancy. Many oncologists believe that pathogenesis of malignant tumors is indissolubly linked with precancerous condition and that precancer obligatory preceeds cancer.

Under the term "precancer" we mean long – existing chronic diseases, which always or often give rise to malignant neoplasms. Diseases which always develop into malignant tumors are called **obligate** precancers, they include hyperkeratosis, xeroderma pigmentosum, systemic lupus erythematosus, Bowen's disease, family stomach and colon polyposis.

Diseases which are not always but often transformed into cancer are called **optional** precancers. **Optional** precancers prevail in number over obligate ones and include leukoplakia, trophic ulcers of limbs, chronic gastric ulcer, gastritis with decreased secretion, breast fibroadenomatosis, after burn scars and others.

Evidence gathered from precancer patients makes necessary careful monitoring of them and makes possible radical treatment of all patients with precancer pathology and in this way we can prevent malignant tumors.

Cancer prophylaxis it is the system of measures aimed at prevention of cancer development in the population.

Preventive measures are divided into **primary** and **secondary**.

Primary prevention involves the system of social and hygienic measures aimed at elimination of risk factors and increase of nonspecific antitumor resistance of humans (hosts). Primary prevention of cancer includes:

a) environmental protection from carcinogenic pollution;
b) maintenance of safety devices at hazardous works;
c) use of healthy foodstuff and drugs without carcinogenic effect;

d) refuse from most important lifestyle risk factors in carcinogenesis, such as tobacco smoking, alcohol abuse);
e) rational diet (food rich in vitamins A, C, E, and fiber).

Secondary prevention is the eradication of premalignant diseases before their transformation into cancer (xeroderma pigmentosum, lupus, interstine polyposis), as well as some chronic diseases (atrophic gastritis, peptic ulcer, trophic ulcers of limbs, etc). It is possible to indentify examine and treat some patients at high risk for developing cancer. Secondary prevention strategies in these patients may include determination of the contingent, who are at high risk for main localizations.

It is obvious that primary prevention of malignant tumors is the most promising and essential.

Classiffication of tumors

Tumors are classified according to histological structure, localization, clinical groups, extent of proliferation, dissemination, spreading and differentiation. There is no uniform classification, which includes all of above mentioned symptoms. Current classification of human neoplasms reflects, in an imperfect and sometimes imprecise manner, the attempt to name and arrange tumors according to a combination of histogenetic and behavioral (benign and malignant types) traits. So, nowadays several classifications characterizing neoplastic process are usually used.

Histogenetic classification of tumors

Histogenetic classification takes into consideration the tissue from which it develops and is very important for practical work. According to histogenetic scheme it is possible to identify the main types of tumors.

Tumors may be derived from epithelial, connective, nervous, and muscle tissue, there are also mixed tumors. The names of the different tumors are usually formed from those of the tissue from which the tumors are derived and the suffix "oma", as fibroma, epithelioma, neuroma, myoma. There are special names for malignant tumors: carcinoma and cancer for tumors derived from epithelial tissue and sarcomas for those derived from connective tissue.

Common tumors

1. Epithelial tumors (cancers).
2. Connective tissue tumors (sarcomas).
3. Nervous tissue neoplasms.

Rare tumors

1. Tumors of the mesothelium and endothelium (blood and lymph vessels).
2. Tumors of the hematopoietic tissue (hemablastoses, hematologic malignancies).
3. Tumors of APUD – system cells.
4. Tumors from embryonic remmants.
5. Trophoblastic tumors.
6. Mixed tumors.
7. Hamaromas.

Cancer is epithelial tumor developing from the multilayer squamous epithelium of the skin and mucous membranes, as well as from the glandular epithelium of internal organs parenchima, including endocrine glands.

Papillomas and adenomas refer to benign tumors, squamous cell carcinoma (epidermoid), glandular (adenocarcinoma), undifferentiated carcinoma.

Connective tissue tumors are named according to the source elements. The most common are fibrosdrcoma (fibroma), liposarcoma (lipoma), osteosarcoma (osteoma), chondrosarcoma (chondroma), leiomyosarcoma (leiomyoma), rhabdomyosarcoma (rhabdomyoma), myxosarcoma (myxoma).

Tumors of the **nervous tissue**, which are the most common, include neurofibrosarcoma (neurofibroma), neurilemmoma (neurinoma), ganglioneuroblastoma (ganglioneuroma), astoblastoma (astrocytoma), medulloblastoma (meningioma).

Tumors of **blood and lymphatic** vessels include hemangiosarcomas (hemangiomas), lympangiosarcomas (lymphangiomas), synovial sarcomas (binign synovioma), mesothelioma.

Tumors of the **hematopoietic tissue** (hematologic malignancies): leukemias and hematosarcomas.

APUD – system (diffuse endocrine system) is presented by scattered throughout the body functionally active cells of neuroectodermal origin. APUD is abbreviation from English Amin Precursore Urtake and Decorboxylation. APUD – system cells have the capacity to produce biologically active substances (adrenalin, serotonin, melotonin, kinins), it is often accompanied by development of carcinoid syndrome. Tumors from the APUD system are called apudomas, they include endocrine glands adenomas (pituitary, pineal gland, pancreas), and carcinoids.

Tumors from embryonic remnants include teratoma, malignant teratoma (teratoblastoma), dermoid cyst, nephroblastoma (Wilm's tumor).

Trophoblast tumors are malignant tumors of the female genital organs originating from the trophoblast cells. They include hydatid mole and uterus choriocarcinoma (chorionepithelioma). These tumors are characterized by production of chorionic gonadotropin.

The systemic tumors include neoplasms arising from several types of tissue or resembling multitissue structures.

Hamartoma is regarded viewed as a tumor conventionally (it is not in fact a tumor). It consists of the same tissue as the organ in which it has developed, but differs in its incorrect location and the degree of differentiation. Hamartomas include congenital hemangiomas of liver, spleen, pigmented nevi, lungs chondroma. This pathology can transform into a malignant tumor.

Malignant tumors clinical staging

The predictable mode of metastases has improved the accuracy of initial clinical evaluations, although they remain far from perfect. Clinical staging system takes into account the size and the character of primary tumor growth, spread on the adjacent organs and tissues, and also existence or absence of regional or distant metastases. The investigators separated the extent of disease into the following four groups by decisions for therapy to predict prognosis and assess response to treatment.

Stage I is defined as limited neoplastic process with no invasion into adjacent tissues and absence of metastases in regional lymph nodes. For instance, at stomach cancer it is defined as the lesion of the mucous layer without metastases; or at breast cancer it is defined as a tumor up to 2cm in diameter without metastases.

Stage II is defined as a small tumor greater than 2cm in diameter with single metastases to regional lymph nodes.
Stage III is defined as a tumor of greater dimension than 5 cm in diameter with multiple metastases to regional lymph nodes.
Stage IV is defined as a tumor of any size with distant metastases.

This clinical classification of malignant tumors in stages is not perfect. It lacks exact definition of primary tumor, regional and distant metastases, there is no accuracy in evaluation of the definite stage of malignancy.

TNM International classification for tumors

The TNM classification was developed by P.Denoix (France) in 1943 – 1952. In 1950, the Internetional Union Against Cancer (UICC) established a commettee on Nomenclature and Statistics of tumors, which is constantly working on TNM classification improvement. **Now we use the 7th edition (TNM – 7) which was published in 2010.**

The introduction of the TNM tumors classification worldwide can be very useful in: 1) treatment planning for individual patients; 2) prognosis estimation; 3) assessment of treatment results; 4) the exchange of information between health care centres; 5) the uniform presentation of clinical data; 6) further study of cancer. This classification makes possible the computer processing.

TNM stands for tumor, nodes, metastasis. TNM classification describes:
T (tumor) – spead of primary tumor;
N (nodes) – the number and location of any regional lymph nodes;
M (metastasis) – distant lymphogenous and hematogenous metastases.

Digits and letters are used for detailed designation of the extent of the tumor spread in the TNM system. Classification can be adjusted after surgical research and histopatological examination. Therefore, for any localization of the tumor, there is a clinical (with TNM) classification based on clinical, radiologic, and endoscopic methods of investigation and pathohistological (with TNM), based on the data of surgical research and histological examination of tumors.

Symbol T (tumor) has the following designations:
T0 – no evidence of primary tumor.
Tis – carcinoma in situ (preinvasive intraepithelial carcinoma).
Tx – primary tumor cannot be assessed.

T1, T2, T3, T4 – show the increase in size and/or local spread of the primary tumor.

Symbol N (nodes) describes regional lymph nodes involvement:

N0 – no regional lymph node metastasis.
Nx – regional lymph nodes cannot be assessed.
N1, N2, N3 describe different degree of regional lymph node metastasis.

Symbol M describes distant metastatic involvement:

M0 – No distant metastasis.
Mx – Presence of distant metastasis cannot be assessed.
M1 – Distant metastasis.

Depending on the metastasis location M1 category may be supplemented by the following symbols:

PUL – metastases to the lungs;
MAR – bone marrow;
OSS – bone;
PLE – pleura;
HEP – liver;
PER – peritoneum;
BRA – brain;
SKI – skin;
LYM – lymph node;
OTH – others.

In some cases, information relating to the primary tumor can be supplemented with the symbol G (Gradus), determining the degree of tumor cell differentiation. Possible values of G are as follows:

Gx – degree of differentiation cannot be assessed;
G1 – high degree of differentiation;
G2 – the average degree of differentiation;
G3 – low degree of differentiation;
G4 – undifferentiated tumors.

Undifferentiated tumors are those that have lost morphological traits of histogenesiss.

$_{p}$TNM determined in an individual patient doesn't change throughout his life.

Clinical groupings

clearly define the tactic of oncologic patients therapy. All the patients are divided into the following groups:

Ia group includes patients with suspected malignant tumors. They are to be carefully examined within 10 days from the time of their registration. After the final diagnosis patients are transferred to other groups or taken off the books.
Ib group includes patients with precancerous diseases which are to be observed in dispensary and followed – up.
II group includes patients, who can be cured due to appropriate treatment or may have long – term remission.
IIa group includes patients to be radically (surgically) treated.
III group includes patients, who after radical treatment (surgery, radiotherapy, combined or complex) have no recurrence and metastasis curd so can be considered relatiwely hellhy. In case of relapse, patients are to be radically treated so they are transferred to II clinical group. In case special radical treatment cannot be indicated, patients are transferred to the IVth clinical group.
IV group includes patients with disseminated malignant process who are indicated palliative or symptomatic treatment.

It is evident that the clinical group and the stage of disease are not just the same.

Diagnosis of malignant tumors

Survival in patients is usually related to the stage at presentation. The earlier a malignant tumor is diagnosed the more successfully it can be cured. It is known that at the stage carcinoma in situ patients can be cured in 100% of cases. At the 1st stage full recovery occurs in 80-90% of patients, at the 3rd stage only 30% of patients can be cured. Delay in diagnosis is very dangerous, because oncologic diseases are very common and there is a great variety of their clinical presentation.

Physician factors such as adequate diagnosis or misdiagnosis are very important. Health care professionals of any specialization should keep in mind oncologic factors, that is:

1) know symptoms of malignant tumors in the onset (at early stage);
2) know precancer diseases;
3) know the structure of oncology service to recommend the patient the oncologist of proper specialization;
4) thorough examination of patients to exclude oncologic disease;
5) overdiagnose malignant tumors in doubtful cases.

No single clinician has all the skills needed to treat all cancers.

Clinician isn't to diagnose oncologic disease in details. He is to conduct clinical, radiological, endoscopic, and other researchers to suspect the tumor and arrange consultation with oncologist as soon as possible.

At early stages oncologic patient almost never feels pain, considers himself healthy and continues his usual style of life. It should be noted that there are no pathognomonic signs and symptoms for cancer.

When taking the history one is to pay attention on the following data:

1) unexplained change in general state, increased fatigability, loss of appetite and weight;
2) habits change, aversion to some kinds of food or smell of food;
3) abnormal discharge (bloody sputum, blood or mucus in the stool);
4) violation of hollow organs patency (dysphagia, vomiting, persistent constipation, bloating);
5) presence of previously unexisting visible or palpable entities or ulcerations on skin, lips and mouth mucous membrane.

The most important symptom in patients with visual forms of cancer (skin, lip, oral cavity, breast, rectum, vulva) is the presence of the visible or palpable tumor. If the patient has long – term chronic disease the physician can notice changes in previously existing symptoms and should pay attention at them and suspect the danger of oncologic diseases. Besides the clinician should notice that chronic disease treatment is ineffective, though previously it was. The doctor should ask the patient about his bad habits (smoking, chewing tobacco, consumption of hot drinks and food). It is very important for the specialist to know the oncologic patient history, in particular, it he had cured before tumors of other localizations and if he had close relatives with tunors.

If certain oncologic pathology is suspected in patient, for instance lungs pathology, it is necessary to ask questions, which can help to find out symptoms and signs about disease, because very often the patient complains of things, which don't concern the disease and make it difficult to diagnose the exact pathology.

Clinical examination of the patient is very important, especially if the patient has visual forms of cancer.

Physical examination and palpation remain the most important tool in diagnosis. Regional lymph nodes and abdomen are to be thoroughly palpated.

Digital examination of the rectum gives the physician very important information about tumor presence and its spread. Some metastases can be detected by palpation through the rectum. Auscultation and percussion can also give information about tumors, especially in the presence of free fluid in the pleural and abdominal cavities.

Imaging modalities and specialized techniques of cancer diagnosis

Diagnostic imaging studies are used in suspected cancer pathology most often. X – rays are the radiation energy used to produce medical images including plain film radiography, fluoroscopy, and X-ray CT. In X- ray imaging, the photons transmitted through a patient are recorded by some type of detector. Other imaging modalities record radiant energy emitted from within the patient by detecting the reflected sound waves in ultrasound the radiofrequency waves in MRI, and Y rays (photons) in nuclear medicine. X – ray method is widely used in screening of the population at prophylactic examinations for lung and breast cancer pathology detection. X – ray method allows to detect pathologic changes in different organs. Oncologist can order additional CT, ultrasound, or MRI study that can be used to make more just diagnose. X – ray method allows to assess response to special treatment. Lungs tomography, angiography, pielography and other, are widely used.

X-ray CT studies are frequently employed for cancer patients and allow to conduct cross – sectional "scanning" and get differentiated images of tissues and organs, radio contrast of which is 0.5%. Computed tomography (CT) makes it possible to detect small – size tumors even in the brain, kidneys, pancreas, and in the pelvic organs.

Magnetic Resonance imaging (MRI)

is increasingly used for diagnostic studies.

MRI radiation energy is 9 times lower than in X – ray imaging and radionuclide techniques.

MRI is a cross – sectional and three – dimentional imaging technique employing the principles of nuclear magnetic resonance (NMR).

Magnetic Resonance images are formed by transmitting a radiofrequency wave at frequency of the targeted hydrogen nuclei and registration of the energy emitted by hydrogen nuclei.

Hydrogen is the nucleus used in most clinical MRI because it has the greatest sensitivity, i.e. highest gyromagnetic ratio. Hydrogen nuclei are found mainly in fluids (water-density tissues) and fat containing tissue. Response signal is amplified and used for image formation by computer. The advantages of MRI include possibility to work without contrast agents, to get images in any plane (including three orthogonal anatomic projections), high resolution of contrasting soft tissues.

MRI can be used for diagnosis of virtually all kinds of human tumors. MRI is very useful in studying the tumors of brain and spinal cord, mediastinum, retroperitoneum, pelvic, bones and soft tissues.

The signal strength, the relaxation time and the proton density are so-called tissue characteristics which allow to understand the biologic nature of the tumor.

Ultrasound (US) uses waves for image formation.

US has become one of the most common radiologic methods in recent years. The advantage of this method is high resolution, and safety, allowing repeated study. Almost all organs and tissues can be studied by ultrasound. Tumors of the lungs, stomach, intestine, bones, brain and spinal cord are inaccessible to ultrasound.

Radionuclide diagnosis is employed in case when above mentioned imaging modalities can't diagnose disease and determine the stage of desease. Nuclear medicine uses radioisotopes as tracers to access normal and abnormal physiology of living tissues. Nuclear medicine studies use and rays which are recorded with scintillation counters.

Scintigraphy allows to detect not less than 2 cm tumors or metastasis in the sites inaccessible to X – ray studies long before their X – ray imaging (sometimes prior to 6 month) as "Cold" or "Hot spots". "Cold spots" occur when tumors displace normal structures and tissues, pathologically changed tissue doesn't concentrate the radioactivity, "Hot spots" are detected when tumors concentrate the radioactivity, isotope is fixed in the tumor selectively.

The following tumor tropic radiotracers are used for direct tumor visualization:

- in primary bone tumors and metastases in them – $^{99m}T_c$, ^{85}Sr, ^{131}I;
- in liver ^{198}Au sulphate colloid solution, $^{99m}T_c$, ^{113}In;
- in kidneys – ^{203}Hg and ^{197}Hg Neogidrin, $^{99m}T_c$ glycoheptonate;

tyroid – ^{113}L – sodium iodide;
pancreas – ^{75}Se – methionine;
brain – ^{99m}Tc – pertechneted α^{113} In

Emission computed Tomography

significantly extended the possibilities of radionuclide diagnosis. This method demonstrates precise evaluation of lesion focus and visualization of poorly contrast structures, that cannot be detected at scintigraphy.

Radionuclide immunescintegraphy with the use of monoclonal antibodies is the method which has prospects for long – term success in tumor and metastasis detection.

Mammography is the only diagnostic imaging modality currently used to detect cancer in an asymptomatic population. Substantial advances in technology resulted in improved diagnostic images with lower radiation doses. Increasing expertise in interpreting the resultant images should be noted.

Endoscopy is the rapidly advancing and leading method. With endoscopy the anatomy is directly imaged with visible light and video or electronic instruments. Internal organs can be examined by endoscopy with video documentation, biopsy, cytology, and sonographic evaluation to determine diagnosis, operability and staging. This method allows to determine tumor localization size, growth boundaries and to obtain material for morphologic verification of diagnose. Endoscopic method enables determination of early – stage cancer, when tumor size is some millimeters. In diagnosis of such small tumors performance of biopsy and cytology during endoscopy is more effective than roentgenography.

Cytologic specimens can be obtained by brushing, washing off, and puncture. The most meaningful information is achieved with biopsy forceps and the following microscopic examination. Histopathologic conformation determines accuracy.

Endoscopic evaluation is now virtually compulsory for patients with pathology of many internal organs: bronchoscopy, esophagoscopy, gastroscopy, colonoscopy, rectoromanoscopy, laparoscopy, colposcopy, thoracoscopy. Modern vide endoscopic systems have solved the problem of high – quality images of brain ventricles.

Malignant tumors immunodiagnosis

Immunodiagnosis method is based on differences of tumor – associated and normal tissue antigens. This differences can be of qualitative and quantitative nature. Cancer – specific or cancer – associated substances are called malignant tumor markers. Markers can be detected in blood and other body fluids. Alpha – fetoprotein (AFP) is Abelev – Tatarinov test and it is the most studied serum tumor marker. AFP peak values between 40 mkg/l and 3 mg/l highly diagnostic for primary malignant liver tumor, testis and ovarian terablastoma. Heightened AFP concentration in blood can precede clinical symptoms of cancerous liver by 3 to 10 months. AFP specificity is 80% in adults and 90% in children.

Carcinoembryonic antigen (CEA)

is elevated in patients with adenocarcinoma of the colon and pancreas. CEA elevations in blood are related to the stage and extent of disease CEA titers decrease and normalize some days after successful surgery. CEA marker has 70-80% specificity in patients with colon cancer.

Chronic gonadotropin (CG) is a marker in choriocarcinoma, it exists in the serum of all patients (100%) with this disease. Presence of chronic gonadotropin in urine and blood is characteristic for nonseminatous testicular cancer. Levels of CG reflect the course (size) of the tumor.

Tumor – associated antigen CA – 125 is non – invasive technique increasingly used nowadays. Elevated values of this marker are highly diagnostic for serous ovarian cancer. Rising levels indicate recurrence in 100% of patients and may precede clinical symptoms by 6 months.

Acid Phosphotase and Prostate-specific antigen (PSA) have been used in evaluating prostate cancer and are specific markers of prostate cancer.

The use of monoclonal labeled antibodies to identify with high selectivity tissues sharing common antigens is the most promising non – toxic imaging method in radioimmunodiagnosis. This method is the most sensitive (i.e. having ability to detect disease) nowadays.

Morphological method of tumor diagnosis

Cytology and histology are morphological methods of examination. Diagnostic cytology deals with the morphologic examination of individual cells, histology (histopathology) examines tissues.

Morphological verification of the diagnosis is to precede any special treatment modality (surgery, radiation therapy, chemotherapy).

Only after suspected sites are subjected to biopsy and microscopic examination it is possible to determine the accuracy of the examination. Data on accuracy are essential for planning patient management and favourably affect patient outcome. Without morphological verification we can't speak about data accuracy and so it can lead to misdiagnosing and wrong patient management (undergo unnecessary operations, radiation therapy with hard radiation effects on the patient, and chemotherapy, producing teratogenic and carcinogenic effect). Exclusion of malignancy without morphological examination may be erroneous and can result in delays in diagnosis and treatment and so worsens its long – term results.

Cytologic method of research has achieved popularity on a worldwide basis.

Cytology deals with the morphologic examination of individual cells (as opposed to tissues in histopathology). Specimens used for this purpose are obtained in the following ways: by exfoliation or desquamation from an epithelial surface; by fluid from a body cavity, whether obtained spontaneously (i.e. urine) or by aspiration; and by fine – needle aspiration of solid lesions (aspiration biopsy cytology).

Specimens used in the first case are: sputum, urine, prostate secretion, discharge from the nipple of the breast, cervix and vagina, rectum. Material from body cavity hollow organs can be obtained by lavage with isotonic sodium chloride solution, by imprints or scrapping the tissue surface with a cotton swab or special brushes. Material for exfoliative cytology can be smear – imprint from the surface of pieces, obtained by biopsy. Non exfoliative (aspiration) cytology involves the

aspiration of cells and tissue fragments through a needle that has been guided into suspected tissue of thyroid, breast, salivary and prostate glands, lymph nodes, lung and mediastinal tumors, tumors of soft tissues and bone marrow.

Puncture provides a cytologic material from the pleural and peritoneal cavities of the spinal canal, the pericardium and synovial sheaths. Bone marrow tissue is also obtained for cytologic analysis with the help of sternal puncture.

The set of features characteristic of the neoplasm cells and their interaction with other cells show mean malignant cell transformation.

The basis criteria for the evaluation of cytologic specimens relate to specific features of the nucleus and cytoplasm. The main features of malignant tumors are abnormalities compared with the corresponding normal cells, which include polymorphizm of size and shape of the cells, increased nuclear size compared with cell size, formation of the giant nuclei, eccentric location of the nucleus presence of some nucleus in a single cell (Fig.8). Abnormal mitoses, nuclei hyperchromasia, cytoplasm vacuolization and great number of "bare" nuclei are characteristic of malignant tumors.

Tumor cell size varies from 4 to 60m. In most – cases they are bigger than original tissue cells and may have a variety of shapes: oval, round, spindle shaped, cylindrical, triangular, star – shaped, polygonal, etc. Irregular shape cells having cytoplasmic spikes, inclusions and vacuoles resemble amoeba.

Nucleus forms of malignant cells are also diverse (various) and can be oval, bean - shaped, spindle – shaped, crescent – shaped and irregular.

Tumor cells nuclei are stained with basic dyes more intensely than normal ones. Chromatin is disposed in them unevenly as large grains and thick filaments. The nuclear – cytoplasmic ratio generally increases, largely because of the increased nuclear size but also because of the smaller amount of cytoplasm compared with the corresponding normal cells.

In tumor cells **there** are 4 to 6 nucleoli and so the nucleus – nucleoli ratio is 1:25 and even 1:15, whereas in normal cells this ratio is 1:50. Malignant cells boundaries are often blurred and uneven.

One of the basic morphological features of malignant tumors is formation of multinuclear giant cells as a consequence of unseparated cytoplasm in the cell, where mitoses has occurred. One of the nucleus of

multinuclei cell can devide mitotically, while the other nuclei do not have signs of division.

A large number of mitoses are characteristic of malignant tumors. There are less than 4 mitoses in 1000 cells in healthy tissue. Ratio of deviding cells to the total number of cellular elements is set according to kariokinetic activity index. 1:200 index indicates a low degree of malignancy, 1:100 index indicates average degree of malignancy, and 1:50 index is the highest degree.

Tumor cells activity is often manifested in the form of pinocytosis and phagocytosis. Consequently, there are a lot of vacuoles, various inclusions, fragments of erythrocytes and other cells in the tumor cells cytoplasm.

Autophagy ("cannibalism", "selfdevour"), which is absorption of a small cell by a large tumor cell is often observed in malignant cancer tumors. Absorbed cell then is almost completely destroyed ("digested").

Nowadays, there are about 200 different cytomorphological signs of tumor. The combination of these signs indicates the nature of cell changes relative to their histogenetic prototype under physiological conditions.

The greatest success is achieved in the cytologic diagnosis of cervical cancer and stomach. Very often cervical cancer can be diagnosed in the stage of development of Ca in situ, when the patients can be cured in 100% of cases. The simplicity, availabity and safety of cytologic studies makes it suitable for use in polyclinics for surveying large number of population.

Cytologic study, in the case of necessity can be followed by cytochemical analysis, allowing to determine the metabolic processes in cells. Methods of genetic research may be also used.

The reliability of cytologic method is usually measured in terms of false – negative and false – positive results. False – negative diagnosis is characteristic of those cases when there is tumor but no tumor cells. Such result is possible in case of taking the material from necrotic part of the tumor or healthy tissue. False – positive diagnosis is possible in cases when a pronounced proliferative process is thought to be a tumor.

Histologic evaluation of tissue is necessary if cytologic method does not allow an accurate diagnosis. A tissue is acquired for exact histologic diagnosis. Various techniques exist for obtaining tissues suspected of malignancy, including needle (punch) biopsy, forcept bioposy, aspiration biopsy incisional biopsy, and excisional biopsy. The least traumatic is punch (needle) biopsy which refers to obtaining a core

of tissue through a specially designed needle introduced into the suspect tissue. Forcept biopsy is performed in the process of endoscopic research. In excisional biopsy, an excision of the entire suspected tumor tissue (more often the tumors of external localization) with little or no margin of surrounding normal tissue is done (sector of mammary gland, pigmented skin formation, part of a lung). Incisional biopsy refers to removal of a small wedge of tissue from a larger tumor mass.

Tissue for histologic study from hollow organs can be obtained by forcept biopsy or curettage (scrapping).

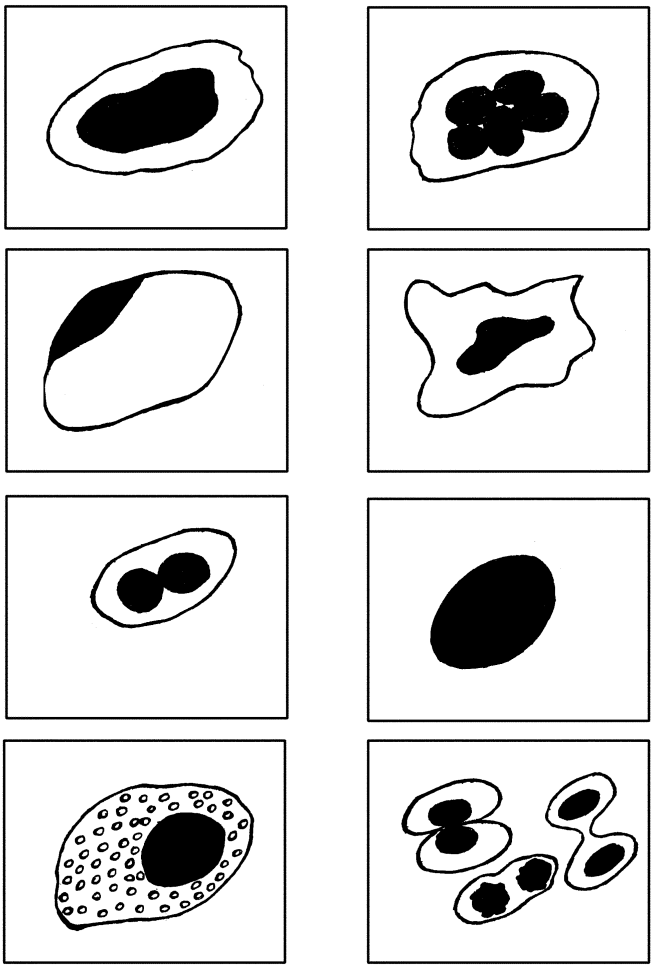

Fig. 8 Tumor cells morphologic features

1. large nucleus, 2. giant multinucleated cell, 3. "signet ring cell", 4. ugly cell with irregular shape, 5. dual – nucleus cell (amitosis). 6. kernel "bare" nuclei. 7. foamy cytoplasm. 8. large number of mitoses.

Biopsy material obtained in vivo is subjected to histological examination, and reveals tumor histogenesis, growth patterns, the degree of its anaplasia and invasion into th surrounding tissues.

In the practice of oncology centres urgent suboperation biopsies are performed. The standard technique involves sampling of the tissue received, freesing, cutting of sections in a cryostat, staining of those sections and examination under the microscope. This procedure takes about 5 minutes per specimen and is often called frozen section.

Cytology supplement and sometimes replace the frozen section procedure as a way to provide an intraoperative diagnosis. Cytology saves time (it takes 1 minute or less per slide and 5 to 10 minutes for a frozen section. The result of this procedures influences the course of operation, the magnitude of surgical resection (e.g. radical mastectomy or sectoral resection).

The less tumor resembles the original tissue the more malignant its clinical features. Tumors can undergo such profound changes that it becomes very difficult to determine their histogenesis, due to this fact they are called undifferentiated (anaplastic).

Tumor histogenesis determination is an important criterion in the choice of treatment.

Malignant tumors are characterized by invasive growth, so there is no clear – cut boundary between the tumor and the surrounding tissues. Tumor cells invade the normal tissue structures. Basal membrane germination and sprouting into blood vessels and lymphatics indicates the infiltrative growth. Tumor cells spread along loose connective strata, serous cover, through the lumen of glands excretory ducts.

Histological diagnosis is mainly based on the data from the study of the tumor parenchyma state and the peculiarities (atypia) of its cells. Irregular parenchyma structure, wrong correlation with stroma and remote resemblance to normal tissue are signs of organ and tissue atipia.

It is proved experimentally that malignant properties of cancer has only tumor parenchyma. Stroma plays the role of mediator between the neoplasia and the organism. In most of malignant tumors it is built out of normal structures. Data about its structure is of secondary importance in the diagnosing of tumors, so histo and cytochemical examination studies and electron microscopy are performed for accurate morphological diagnosis.

Malignant tumors can develop from the coating and glandular epithelium. Covering epithelium cancer can be intraepithelial

(carcinoma in situ) and squamous cell (epidermoid) keratinizing and nonkeratinizing carcinoma.

Squamous cell keratinizing carcinoma is characterized by the ability of some cancer cells to keratinization. The latter form rounded clusters in the centre of which they merge into homogenous oxyphilous mass with basophilic granules, which are called horn pearls.

Squamous cell nonkeratinizing carcinoma differs from keratinizing one by the less cell differentiation, absence of epithelium keratization and greater mitotic activity.

Cancer of the glandular epithelium is called adenocarcinoma. Microscopycally the tumor is formed by tubular glands, it has uneven lumen and thick multi – layered walls, consisting of markedly atypical columnar epithelium.

A malignant tumor in which stroma considerably predominates over parenchyma is called a scirrhous (fibrous) cancer. Tumor in which parenchyma (cancer cells) predominates over stroma, is called medullary (soft) cancer. Scirrhus is referred to infiltrative forms of cancer, causing wrinkling and induration of organ walls, the cut resembles a whitish scar tissue. Medullary cancer macroscopically is grey - yellow crumbling tissue with abundant scraping.

Colloid or mucous (slimy) cancer is adenocarcinoma, producing a lot of mucous that is accumulated in the irrequlars shape cells ("lakes" or"tanks"), separated by connective tissue layers. Colloid (mucous) cancer is qreyish – pink on the cut and looks like jelly.

Most diverse combinations of adduced forms occur in cancers. Each of these forms can arise and develop on its own without going through the previous steps and without transition to subsequent transfer.

General principles and methods of malignant tumors treatment

Approaches to the treatment of malignant tumors differ fundamentally from the approaches to the treatment of therapeutic, surgical or infectious diseases. This is due to the unusual properties of malignant tumor, namely its ability to uncontrolled growth and metastasizing. So the main direction of strategy in tumors treatment is complete destruction of tumor tissues and individual cells, wherever they are in the body.

In most cases, at the time of diagnosis of malignant tumor we have a systemic body damage, but not a local pathologic process. In this regard there is a term cancer disease in oncology and the treatment is to

include not only methods of local tumor treatment but systemic one in order to eradicate all tumor cells from the body. The second task is the most difficult as it requires a selective affect on tumor cells with minimal damage to healthy ones.

In oncology there are several types of treatment depending on the task : radical, palliative and symptomatic.

Radical treatment is aimed at the total elimination of all foci of tumor growth. However radicalism is relative to some extent as there are no research methods which allow to prove show the complete eradication of tumor cells from the body, so after radical treatment we can speak only about clinical cure. Complete biological recovery occurs after a certain period of time. Biological criterion of recovery in adults is a 5 – year period, in children a 2 – year period. There temporal criteria are relative, since recurrences and metastases of resected tumors may develop 10 or more years later.

Palliative treatment is aimed at tumor mass reduction in patients with incurable cancer. Gastrectomy leaving schnitzler metastasis can be used as example. Palliative treatment often prolongs the life of the patient and improves its quality.

Symptomatic treatment is aimed at elimination of painful symptoms and complications. Symptomatic treatment is often tracheostomy, gastrostomy, cystostomy, the imposition of bypass anastomosis, ets.

Surgical, radiation and drug therapies are used in the treatment of malignant tumors. The combination of two kinds of therapy is called combined therapy.

Complex treatment means use of all three methods in a different sequence or simultaneously.

Immunotherapy, hyperthermia, hyperglycemia and other methods don't have independent value and are used as additional ones.

Surgical treatment

Surgery is the oldest treatment for cancer. The surgeon has a central role in the prevention, diagnosis, definitive treatment, palliation, and rehabilitation of the cancer patient. Surgery may be radical,

palliative, and symptomatic in dependence of tumor spread and the objectives pursued.

Radical standard operations include en block removal of the entire organ or its part with tumor and zones of possible regional metastisising.

Radical operations can be expended and combined ones. Expended radical operations remove additionally more distant lymph collectors. Combined operation involves radical removal of the tumor with one or some adjacent affected organs. Fore example, gastrectomy with resection of pancreas tail and splenectomy is often performed at gastric cancer.

Radicalizm of surgical intervention in tumors is achieved by adhering to the principle of ablation (ablastics) and antiblastics.

Ablation is a surgical principle of malignant tumors recurrence and metastasis prevention which is implemented by prevention of tumor cells dissimination in the process of operation. Tumor cells can discharge into the wound from traversed lymphatic ducts and venules when tumor cut in the process of tumor removal by parts and alike procedures. Mechanical manipulations with tumor during the operation dislodges tumor cells into lymphatic and blood vessels.

Ablation is also achieved by tumor removal within the healthy tissue en block with the regional lymph nodes and lymph outflow paths taking into account fascial sheaths and metastasizing zones.

Antiblastics is a set of measures aimed at the removal of tumor cells from the surgical wound. Physical, chemical and biological methods can be used for this purpose. The physical methods include irradiation of the operative field, electrocoagulation, cryodistruction and laser application. Chemical methods are selected for alcohol or acetone (for breast cancer) treatment of the wound surface after tumor removal, preoperative radiotherapy and chemotherapy. Immunotherapy methods have a bearing to biological antiblastics.

Surgical operations in the cure of patients with malignant tumors are traumatic because of the removal of the most part or the whole organ, so morphological verification of the diagnosis of a malignant tumor prior to of great importence.

Radiation therapy

Radiation therapy is one of the leading methods of treatment in oncology. Over 70% of oncologic patients need this treatment. Ionizing radiation can be electromagnetic or particulate. Electromagnetic

radiation can be considered as a wave and as a packet of eneregy (a photon). Electromagnetic radiation consists of roentgen Breaking (Breasstrahlung) and radiation. Examples of particulate radiation are the subatomic particles: alpha – particles and β – particles, neutrons, protons pimesons and heavy ions.

Radiation therapy can be used as an independent method or in combination with surgical or drug therapy. Radiation therapy can be radical, palliative, and symptomatic. Two general types of radiation techniques are used clinically – remote and contact ones, which can be used simultaneously. This treatment is called combined.

Gamma radiator therapeutic apparatus "Rokus", "Agat - B", "Agat - S", generators of electron and breaking (bremsstrahlung) radiation having different levels of energy (2-30 MeV) are used for remote use. High – energy radiation souces (betatron, cyclotron, linear accellerator) allow to create big depth dose with less side scatter, which makes possible the radiation of internal organs. Lowvoltage close focuse roentgenotherapeutic devices are only used for irradiation of the superficial tumors.

Contact radiotherapy can be applicative, intracavitory and interstitial

Sealed sources of radionuclides, beta – applicators (^{32}P, ^{90}Sr, ^{204}T) and gammaapplicators (^{60}Co, ^{137}Cs, ^{192}Ir) in the form of needles, beads, and tubes are used for intracavitary and interstitial radiation therapy. Open emitters are available in the form of colloidal solutions ^{198}Au, ^{32}P, ^{131}I.

Ionizing radiation, irrespective of the radiation nature is absorbed by tissues in a very shot time period and causes atoms and molecules ionization and excitement which leads to direct damage of DNA cells genetic material.

The second mechanizm, having a large share of the damaging effect of radiation is water radiolysis. Free radicals H^+ and OH^- are produced as the result of chemical bonds rapture. Oxydation or molecules renewal and formation of peroxide compounds is the result of free radicals action. Nucleic acids and proteins undergo various physical and chemical changes. Free radicals cause complex chain reactions in nucleoproteins, lipids, carbohydrates leading to functional and morhological changes of cell and tissue structures.

Free radicals cause chemical damage to DNA, DNA – membrane complex and other vital cell components and in the result one strand and two stand DNA breaks and formed, nitrogen DNA bases are damaged, DNA complex with nuclear membrane if spoiled, membrane permeability changes, enzymes are inhibited, energy cell metabolism is disrupted.

Mitotic activity inhibition occuring immediately after exposure is the first manifestation of radiation damage to cells. A small portion of cells die prior to mitosis in the period between divisions (in interkinesis), so this form of cells inactivation is called interphase or interkinetic.

Most of the tumor cells after the end of mitotic block begin to devide and die after a few divisions. This form of irradiated cells death is called mitotic or reproductive one. The main reason for the inactivation of mitotic cells is chromosome damage, occuring due to radiation, which is easily detected in various stages of mitosis in the form of so – called chromosome aberrations.

Most proliferating cells are maximally sensitive to ionizing radiation in the postsynthetic (G2) and mitosis (M) phases and to a lesser extent in the late stage of DNA synthesis (S). The cells in the rest phase (Go) generally have low radiation sensitivity (Fig.9). Less differentiated cells are more sensitive to ionizing radiation.

These radiosensitivity features prove Bergonie and Tribondeau rule, according to which the higher the frequency of cell division and the lower their differentiaton the higher cell sensitivity to radiation therapy. Bergonie and Tribondeau first established an association between the rate of proliferation and the response of normal tissues. A similar relation was pressumed to apply to tumors that devide more frequently than healthy ones, have low differentiation and are more prone to damage by ionizing radiation. Damaged cells of healthy tissues recover faster than the tumor ones.

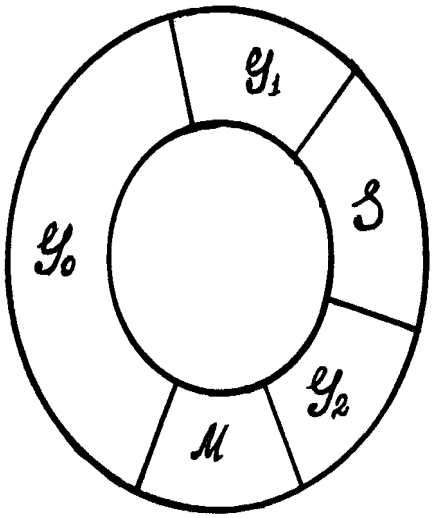

Fig.9 Cell cycle phases:
G1 – presynthetic;
S – synthetic;
G2 – postsynthetic;
M – mitosis;
Go – proliferative rest.

The difference in radiosensitivity of the tumor and healthy tissue surrouding it is called radiotherapy interval. Radiosenssitivity distinction makes it possible to use ionizing radiation for medical purporses. Tumor radiosensitivity is one of the important factors determining the effectiviness of radiation therapy. Tumor tissue radiosensitifity varies widely. Lymphosarcoma, testicular seminoma, dysgerminoma are considered to be highly radiosensituve.

Relatively high radiosensitivily tumors include breast cancer, larynx, bladder, small cell lung cancer, skin cancer; low radiosensitive tumors are: cancer of the liver, kidney, pancreas, chondrosarcoma and osteosarcoma; radioresistant tumors are: rhabdomyosarcoma, leiomyosarcoma, glioblastoma, neuroblastoma.

Radiation therapy can be carried out with different doses (fractions): fractional (2Gr), moderate (3-5Gr) and large (6-10Gr) ones.. The total focus dose ranges from 20 to 80Gr, depending on the purpose of radiation.

The maximum safe dose of radiation of the part or the whole of the tissue is called tolerant.

Radical radiotherapy provides complete devitalysation of the primary malignant tumor and also possible metastases in the areas of

regional metastases. This type of radiation therapy provides in some cases a complete cure.

Palliative radiotherapy is aimed at removal of masses that are causing severe pain or disfigurement, improvement of the quality of life for cancer patients and prolongation of their lise.

Symptomatic radiation therapy is performed to relieve the symptoms of complicated tumors, such as compression of the superior vena cava stenosis of the larynx, pain.

Radiation therapy can be performed only after morphological verification of the diagnosis.

Radiation and surgery can be combined in many different ways. The general rationale for combining surgery and radiation is that the mechanizm of failure for the two techniques is different. Radiation rarely fails at the periphery of tumors, where cells are small in number and well vascularized. Surgery, in contrast, is limited by the required preservation of vital normal tissues adjacent to the tumor. In particular, preoperative radiation has the advantages of sterilizing cells at the edges of the resection, sterilizing cells that perhaps would be dislodged and seeded at the time of surgery, reducing the tumor volume sufficiently to allow resection. In this case radiation is given in conventional 2Gr fractions 4 days a week (total focus dose – 40Gr) and delay between radiation and surgery 3-4 weeks.

Preoperative radiation of resectable tumors is directed at devitalization of tumor cells, seeding of which is possible at the time of surgery. The radiation dose is moderate and given in 4-56 Gr large fractions 4-5 days a week (total focus dose 20-30 Gr), a patient is operated in first three days after radiation therapy.

Postoperative radiation therapy is given to devitalize the remaining in the wound tumor cells, and as well as for the destruction of subclinical non resectable metastases in the areas of regional metastasis.

Irradiation of parasternal or supraclavicular areas in breast cancer may serve as an example of the latter. The indication for postoperative radiotherapy may be an incomplete removal of the tumor and the violation of ablation rules. Both preoperative and postoperative radiation appear to be valuable and the choice of the method, the dose of radiation, and the time between radiation and surgery should be considered in terms of the goals planned.

Radiation therapy complications can be radiation reactions and radiation damage.

Their frequency and severity increases proportionally with irradiation dose and volume. Changes in organs, tissues and in the whole-body during the radiotherapy or immediately after it are called radiation reactions.

Radiobiologic studies evidence that early reaction of the organism to the exposure is associated with transient metablism shifts and dominant role of the nervous system in this process, in particular with dysfunction of subcortical – diencephalic parts of the brain. Thus, the neuro – reflex symptoms are vasomotors overirrigation and paretic condition of the vascular walls, low venous and gradually lowering blood pressure, hyperemia, stasis in the capillaries of the irradiated tissues, transient decrease in alkaline reserve of blood.

Common radiation reactions are characterized by reversibility and are manifested by weakness, dizziness, loss of appetite, nausea and vomiting. Hematopoiesis is marked by leucopenia, lymphocytopenia, thrombocytopenia.

Local radiation reactions occur at the site of radiation exposure. Most often they are observed in the irradiated area of the skin and are manifested by erythema, dry or exudative radioepidermit. Esophagitis, cystitis, enterocolitis, colpitis or rectitis.

Radiation damage (lesion) is organic change in healthy organs and tissues due to radiation. Therapy these lesions require special treatment. Radiation damage can be early or late. Early radiation damage develop within the first 3 month after radiation. Late lesions develop 3 month or more later, after radiation completion.

Changes of endothelium, small blood and lympvessels are common in the pathogenesions. They cause disturbance of microcirculation and transcapillary metabolism accompanied by the releaze of protein into the interstitial space.

Collagen is not fully resorbed, subjected to aging and forms dense layers of connective tissue due to fibroblast number and functional activity reduction after radiation.

Tissue fluid exudation, combined with collagen fibers swelling and pulping results in their hyalinization, considerable swelling, of blood vessel walls swelling, vacuolization of muscle cells and their nuclei, endothelium swelling and sloughing and sharp decrease in the vascular lumen at radiation exposure. Necrosis, fibrosis and tissues hardening also develop.

Radiation treatment of tumors of any localization has an inhibitory effect on T – immunity system, the state of the organism natural reactivity and hormonal homeostasis. Early radiation damage is manifested by acute radiation necrosis and the development of radiation skin ulcers. Necrotic lesions may develop on the oral mucosa, interstine, bladder, etc. Radiation pneumonitis, esophagitis, enterocolitis, cystitis and other complications may develop.

The most serious complications of radiation therapy include cancer, which develops at the site of radiation damage, or induced tumor of the organ exposed to radiation. Bone marrow, thyroid gland, lymph nodes, mammary gland and tissues of the pharynx have high sensitivity to the induction of malignant tumors after irradiation. Clinical observations evidence that the local radiation injuries of various severity preced the development of radiation skin cancer. Latent period of radiation carcinogenesis is 10 to 50 years.

Drug therapy of malignant tumors

Drug therapy has become one of the most common treatments for cancer in recent years. This is due to the changes in the understanding of the neoplastic process, which is in the most cases systemic, so both systemic method along with local method of exposure treatment are necessary for complete destruction of tumor cells in the body.

The concept of "drug therapy of tumors" include chemotherapy, hormone therapy and immunetherapy.

Drug therapy can lead only in some cases to a complete cure of, for example uterus horionepithelioma, Burkitt's lymphosarcoma, testicular seminoma, lymphogranulamatosis. In the other cases, it is carried out as an independent method of treatment in order to achieve remission and prolong life in patients with Ewing's sarcoma, metastatic breast cancer, nephroblastoma, prostate cancer and ovarian cancer, lymphosarcoma, etc.

Medication is performed most commonly as an adjuvant treatment in combination with surgical and radiotherapeutic methods of local treatment.

Chemotherapy

Chemotherapy involves predominantly cytotoxic chemical agents which inhibit cell proliferation or make damage of tumor cells irreversible.

Alkylating agents, the first modern chemotherapeutic agents were a product of the secret war gas program in both world wars. An explosion in Bari Harbor during World War II and the exposure of seamen to mustard gas led to the observation that alkylating agents caused marrow and lymphoid hypoplasia, which led to their use in humans with hematopoetic neoplasms such as Hodgkin's disease and lymphocytic lymphomas, first attempted at Yale – New Have Medical Center in 1943. Because of the secret nature of the gas warfare program, this work was not published until 1946. After the development of folic acid antagonists as cancer drugs, the chemotherapy of cancer began. The cure of child hood leukemias and Hodgkin's disease with combination chemotherapy in the 1960s proved that human cancers, even in their advanced stages could be cured by drugs, and the application to the chemotherapy of solid tumors began. Nowadays more than 50 cancer drugs are used in clinical practice.

According to the method of drug application one can distinguish systemic, regional and local chemotherapy.

Systemic administration denotes the use of chemotherapy drugs inside, subcutaneously, intravenously, intramuscularly or rectally, and is aimed at the overall anti-tumor effect.

Regional chemotherapy of tumors denotes injection of high concentrated cytostatic into the vessels feeding the neoplasm. Regional chemotherapy is carried out when tumors are localized on the upper or low extremities.

Local chemotherapy denotes the application of cytostatic in appropriate form (ointments and solutions) on the surface tumor foci, into the serous cavities with effusion (cancerous ascites, pleurisy), into spinal canal (intrathecally) in patients with neuroleukemia or intravesically in patients with bladder cancer.

Single-agent and combination chemotherapy can be used.

2 or 3 cytostatic drugs are used in combination simultaneously or in a different sequence to produce durable clinical responses. Drugs to be used in combination should have the same antitumor activity, but different mechanism of action, and they should effect in the different phases of the cell cycle. *Such* kind of drugs are called phasespecific.

Vincristine, for example, acts on cells in mitosis, cytarabine kills the cells in phases. The drugs, which are derivateves of nitrosomethylurea affect cells in the phase (Go) rest. Fast – growing low – grade tumors are more sensitive to chemotherapy than slow-grading. There are differences in the sensitivity of primary tumor and metastases to chemotherapy. The efficacy of chemotherapy is inversely proportional to tumor mass at the time of starting treatment. Several types of chemotherapy can be distinguished in dependence of the purpose.

Neoadjuvant chemotherapy precedes radical surgery and is aimed at devitalization of the most invasive tumor cells and reduction of tumor mass.

Adjuvant chemotherapy is subsidiary (prophylactic) and denotes the use of cytostatic drugs after radical surgery to destroy cancer micrometastases that may remain after surgery.

Induction chemotherapy is the most common form of treatment, aimed at complete or partial tumor regression and achievement of the patients remission.

Consolidating chemotherapy is carried out at complete regression for prophylactic, for maintenace of achieved effect and prevention of relapse. Consolidating chemotherapy has been used for patients with leukemia and gematosarcoma.

Antineoplastic agents are devided by origin on synthetic and natural. Alhylating and antimetabolites are synthetic drugs; antitumor antibiotics, alkaloids, and enzymes are natural ones.

Alkylating antineoplastic agents are capable of reacting with the nucleophilic centers, disrupting the DNA structure and to a lesser extent – RNA, which results in the formation of discontintinuities and crosslinks in DNA molecules, impaired replication, protein synthesis, cell membrane damage. Consequently tumor cell lose their ability to division. This group includes the following drugs: novembihin, dopan, cyclophosphamide, sarkolizine, mielosan etc.

Antimetabolites are similar to the coenzymes or normal metabolic intermediates in their chemical structure, but at the same time they are so different from them, that when included in the process of metabolism act as competitive inhibitors of important metabolic processes. Antimetabolites take part in the formation of abnormal nucleotide in tumor cells and thus block the synthesis of DNA, and they are included in RNA, disrupting protein synthesis leading to tumor cell death. Methotrexate, 5 – fluorouracil, fluorafur, 6 – mercaptopurine and others are drugs of this group.

A new group of anticancer compounds: complex salts of cys – dihloridaminoplatinum, which are similar in their action to alkylating drugs were discovered in late 60s. Carboplatin an analog of cysplatin was obtained later.

Natural origin drugs are antineoplastic antibiotics, the vast majority of which inhibit nucleic acid synthesis. Actinomycins, antracycline and aureol group antibiotics form complexes with DNA, impede enzymes advancement along a DNA – matrix, selectivery blocking DNA, RNA and protein synthesis. Currently, the most widely used drugs are: anthracycline, adriamycin, pharmozubicin, and carminomycin. The anthracyclines have been associated with cardiomyopathy since their introduction in the late 1960s.

Pleomycin is another kind of antitumor antibiotics causing DNA damage. This group includes bleomycin and bleomitsetin.

The group of aurel acid antibiotics include olivomycin, mithramycin, and bruneomitsin.

Vincristine and vinblastine are herbal drugs which are mitotic poisons, blocking cell mitoses. These drugs are alkaloids and are derived from the pink perwinkle plant.

The drug Taxol (taklitaksol) is produced from the bark of Pacific yew tree, and its close structural analog taxotere is synthesized on the basis of the substance extracted from the needles of the European yew.

L – asparaginase enzyme is used as antitumor drug and destroys asparagine amino acid. Temporary disruption takes place when L - asparagnase is injected into the organism, and thus cells that need it die.

All drugs should be given with reference to body surface area. Calculations based on body surface area allow doses to be determined for adults and children without further adjustment and are determined according to nomogramm.

Side effects and complications of chemotherapy

Cancer chemotherapy is characterized by low selectivity of action and narrow therapeutic range of cytostatic drugs. Antitumor drugs have therapeutic effect but at the same time they are toxic. Chemical agents damage not only tumor cells but also cells of actively proliferating tissues (hematopoietic and lymphoid on alimentary tube epithelium, reproductive organs, hair follicles) and are substantially toxic.

Complications include pathologic reactions of the organs and tissues arising after chemotherapy and require prevention and correction.

The severity of toxic effects depends on the dose and mode of drugs administration, general state of the patient, presence of concomitant disease, and functional status of main organs and systems.

Chemotherapy side effects can be direct, immediate and delayed.

Direct side effects are seen immediately after drug administration or during the first day (nausea, vomiting, fiver, diarrhea, allergic reactions).

Immediate complications occur during the first week after chemotherapy (bone marrow depression, dyspepsia, neurological disorders, toxic organ damage).

Delayed complications can be in different organs and hemopoiesis in a few weeks after completion of chemotherapy. Toxic effect in hematopoiesis is the most common chemotherapy side effect. Most often there is a decrease of granulocyte and thrombocyte germs, red germ is less exposed to the toxic action. Simultaneous inhibition of all three hematopoietic germs is a consequence of the predecessor myelopoiesis or stem cell lesion.

It is considered that chemotherapy treatment can be given when white blood cell count is at least $4x10^9$/l and platelet count is $120x10^9$/l.

Agranulocytosis (decrease in leukocyte count below $1x10^9$/l) can cause infectious complications. Endogenous and exogenous microbial flora becomes the source of infection and during this period dramatically increases the danger of inner hospital infection. The most frequently observed diseases are necrotic angina, pneumonia, abscess, and other suppurative complications, which are followed by hyperthermia.

Thrombocytopenia can cause the development of hemorrhagic diathesis. The critical level of platelet count is $20x10^9$/l. During this period there may be nasal, gastrointestinal and cerebral hemorrages.

Severe mielodepression development risk factors include previous drug and radiation therapy (mainly with exposure of the sternum bone and pelvis).

Chemotherapy toxically effects the gastrointestinal tract and manifests itself as stomatitis, enteritis, diarrhea, nausea and vomiting.

Many of the most effective antineoplastic agents produce toxic effects on heart. Antitumor antibiotics (adriamycin, pharmorubicin and rubomycin) have been associated with cardiotoxicity. The early manifestations of it are: blood pressure decrease, sinus tachycardia and arrhythmia, pain in the heart, the later manifestations of cardiotoxicity are: myocarditis and pericarditis syndrome with rhythm disorder, left ventricle disorders, myocardium infarct (infarcted myocardium). Late effects of cardiotoxicity can develop weeks or years after completion of

chemotherapy and they are degenerative cardiomyopathy with left ventricle failure and even the development of dilated congestive cardiomyopathy.Tachycardia, dyspnea, heart size enlargement, blood circulation decompensation.

Chemotherapy – induced pulmonary toxicity has been observed less frequently. It causes the development of interstitial pneumonitis with resulting fibrosis. Symptoms usually develop over a period of several weeks to 3-4 years after undergoing chemotherapy. Bleomycin administration causes pulmonary toxicity in 5 – 20% of cases.

Platinum compounds have been associated with urinary excretion system lesions and renal functions failure.

Chemotherapy treatment leads to skin toxicity. Skin and its appandages toxicity includes erythema, urticaria, hyperkeratosis, hyperpigmentation.

Alopecia (hair loss) is an adverse effect that although not life – threatening, often causes significant patient distress. Allopecia is a manifestation of skin appendages and develops as a result of the hair follicles epithelium proliferation suppression. Chemotherapy associated alopecia is reversible. Total scalp hair regrowth begins 3to 6 months after cessation of therapy.

The development of toxic phlebitis after several injections of cytostatics is the local effect of chemotherapy. Some chemotherapeutic agents (anthracyclines, actinomycin, vinalkaloids et al.) can cause necrosis under the skin.

It is common that chemotherapy can cause complications, so systematic monitoring and follow up of blood, functional state of the liver, kidneys, cardiovascular system, as well as timely correction of possible violations is necessary.

Hormone therapy

Hormone therapy is the other type of drug therapy. Unlike chemotherapy, which is entirely based on the use of alien to the body chemicals, hormone therapy uses hormone preparations existing in the body – hormones or their synthetic analogues. This method is based on the property of cells of hormone dependent tumors (prostate, breast, ovary cancers) to use for their development hormones, in the absence of which cells stop their devision.

A substantial body of experimental and clinical evidence indicates that hormones play a major role in the cause of several human cancers. There are epidemiologic hypotheses relating specific hormones to cancers of breast, endometrium, and prostate. According to these hypotheses excessive hormonal simulation of the particular target organ increases the number of cell divisions, random genetic errors accumulate during the process of repeated cell divisions and can lead to neoplastic phonotypes.

First evidence of the successful treatment of three patients with advanced breast cancer by ovariectomy was published by George Beatson, a surgeon from Glasgo, in 1896. At that time nobody knew about hormones produced by the ovaries. Depending on the veterinary experience of the castrated cows, the intuition helped him to guess the probability of mammary glands (including tumors) atrophy in ovaziectomized women too.

Hormone therapy is devided into **ablative** and **additive.**

Abblative hormone therapy includes partial or complete exclusion of the function of the endocrine glands, affecting the growth and development of hormone dependent tumors (ovariectomy, orchiectomy, adrenalectomy, hypophysectomy).

Additive or drug hormone therapy includes the use of drugs competing with hormones for control of the tumor cell. This type of hormone therapy is performed by sreproductive system hormones (androgens, estrogens, progestines) and anti – hormones (antiestrogens, antiandrogens and antigestagens).

Antihormones block the cytoplasmic receptors by which the tumor cell captures hormones it needs. Antiestrogen drug tamoxifen (zitazoneum) is used for breast cancer treatment.

Biologic response modifiers and tumor immunology

Biologic response modifiers, in a broad sense, are all substances of both natural and synthetic origin, which produce antitumor effect on the tumor – bearing host. Biologic therapy is promising but this field is still is in its infancy.

The use of biologic response modifiers as adjuvant therapy in patient who undervent surgical removal of the tumor or have complete

clinical remission after chemotherapy or radiotherapy is most promising treatment.

Strategies for the immunotherapy can be divided into active and passive approaches.

Active immunotherapy refers to the immunization of the tumor – bearing host with materials designed to elicit an immune reaction capable of eliminating or retarding tumor growth. Active immunotherapy can be subdivided into specific or nonspecific immunization. Tumor cells (vaccines) or tumor – cell extract are used in specific immunology. Treatment with BCG vaccine, levamisole, interferon or interleukin – 2 is a form of nonspecific active immunotherapy.

Passive immunotherapy

Various materials including drugs, toxins, or radionuclides, are conjugated to monoclonal antibodies to aid in their antitumor effectiveness.

The advantages of monoclonal antibody therapies include their relative selectivity for tumor tissue and the relative lack of toxicity associated with their administration.

Passive immunotherapy presupposes injection into the tumor – bearing host immune factors. They can be immune competent cells or specific antibodies affecting tumor development. Lymphocytes are used as cells and monoclonal antibodies are used as antibodies.

There is a variety of immune therapeutic mechanizms which include different approaches:

1. Different microorganisms, their components and metabolic products are used for nonspecific activation of antitumor immunity. An example of successful application of BCG for instillational therapy for bladder cancer.
2. Living, inactivated and treated with various substances tumor cells are used for creation of nonspecific immunity.
3. Lymphocytes stimulation of the tumor – bearing host in vitro with the fallowing their injection into the organizm.
4. Biologically active substances that can mediate various immune modulatory effects, such as the thymus preparations are used.
5. Various synthetic immunomodulators are used.

Rehabilitation of cancer patients

Specific methods of cancer treatment in most cases encompass not only a tumor itself but a sufficient margin of normal tissue. Especially it is characteristic of surgical therapy, in which the surgical resection of bulk disease in the treatment of selected cancers may impair functioning of body systems (respiratory, digestive, etc) and often leads to patients permanent disability. Surgery can lead to the loss of a limb or of important functional elements. Prolonged bed rest can lead to severe deconditioning and significant psychological morbidity.

New treatment strategies may be associated with disability and with new challenges to the rehabilitation specialist. Limb – salvage procedure may preserve anatomy and body image, although occasionally at the expense of function. Early envolvement of the cancer rehabilitation team can help to predict the degree of disability and to help the patient make an informed desision about a variety of treatment options.

Rehabilitation should begin soon after diagnosis and continue until the patient has reached maximal functional benefit.

Rehabilitation is a system of socioeconomic, medical, psychological and other measures aimed at restoration of health and ability to work of disabled persons. There are medical, lab our and social rehabilitation.

Medical rehabilitation. After treatment has been completed, the cancer patient may need continued treatment to maintain strength and range of motion, control pain, and return to normal activity. There may be residual effects of the disease or its treatment, and the patient may suffer from nutritional deficits and from a loss of physical capacity.

Labour rehabilitation. Vocational counseling and retraining are important aspects of returning the cancer patient to the community. Adaptive strategies are needed to facilitate the return to work. Job discrimination may interfere with the rehabilitation process.

Psychosocial issues may be a critical factor. The disabled person often has an impaired body image and patients always perceive themselves as being different from the rest of the world.

Social rehabilitation is aimed at the employment of disabled persons, their adaptation in the family and society.

The basic principles of rehabilitation are: as early onset of rehabilitation as possible and its continuity; complex character of this discipline, involving the interaction of numerous treatment providers, each with a particular area of training (oncologists, surgeons, psychologists, sociologists, physiatrists, occupational and physical

therapists, speech and language pathologists, vocational counsellors and variety of other professionals as determined by the particular needs of the individual patient); individuality of rehabilitation of disabled persons in the team (eg. ostomy patients society, patients who underwent mastectomy); earlier return of cancer patients to work. The goal of medical rehabilitation is to maintain mobility through the use of exercises and adaptive devices to maximize patient independence, minimize the burden to others and fascilitate the return to work.

Patients with artificial unnatural anus experience difficulties, because a bowel training program is not instituted for colostomy patients and they don't know about ostomy collections systems collection bags. Support groups for ostomy patients, and patient information materials are not available. So patients do not know how to regularize emptying and as the result self – isolate themselves and refuse to visit public places, because they perceive themselves as being different from the rest of the world. They have reduced or completely lost ability to work.

Urination disorders, decreased sexual activity and impotence contribute to significant psychological mobidity and depression.

Rehabilitation practice of patients with artificial anus (colostomy patients) includes proper clean techniques such as the use of appropriate diet, the use of drugs regulating the intestinal peristalsis, the use of mechanical methods of bowel cleansing. Colostomy training should be a regular part of the cancer patient's rehabilitation process. Patients should get information on how to care for an artificial anus, how to regulate bowel motility, means to regulate uncontrolled discharge of gases and odors. Education should be conducted by trained health specialists or colostomy patients who had previously undergone treatment.

The second group of patients with urgent need of rehabilitation are patients with malignant neoplasms of the lower extremities in which the primary surgical option is amputation. This operation relates to a crippling and causes infringement of motor function (mobility). It should be noted that musculoskeletal system tumors are the most common ones in the patients aged 10 to 30 years. So this group of patients has many psychological, social are physical impacts.

Express – prosthesis of the oncologic lower limb amputees on the operation table or on the 10^{th} – 14^{th} day after operation is undoubted progress in the rehabilitation. The main advantage of the method is the fact that the patient can stand in the upright position 1 – 3 days after amputation using educational and training gait prosthesis and thus load the stump of the amputated limb, which contributes to a stump formation

and strengthens its muscle tone. This methods controls pain in the immediate post operative period and reduces the frequency of phantom pain.

Express prosthesis is of great psychological importance since the patient has a hope for a quick restoration of the lost mobility function and eliminates the stress resulting from the operation.

Cancer patients consider this diagnosis fatal due to low level of knowledge about the nature and results of malignant tumor treatment. So when the person is to be examined and treated in the oncology clinic he has an acute psychological reaction, sometimes turning into reactive psychosis, very often the person has suicidal thoughts or actions.

Depressive syndrome is the second most common mental disorder. In this regard many cancer patients need psychotherapeutic support in the period of the survey and diagnosis justification. Psychotherapy should be included in the rehabilitation plan after oncologic treatment.

Rehabilitation system in cancer patients requires a multidisciplinary approach medical, social, psychological, and sociological. Rehabilitation is a phased process, which should begin soon after diagnosis, continue in the process of treatment until the patient has reached maximal functional benefit and follow – up medical examination.

Return of cancer patient after radical treatment to work, into the community produces beneficial effect on psyche and contributes to the recovery of the individual and the restoration of his social status.