Federal State Budgetary Educational Institution of Higher Professional Education "North Ossetian State Medical Academy" of the Ministry of Health of the Russian Federation

Guidelines

"ONCOLOGY" IN CLINICAL RESIDENCE

Section 2. Biology of tumor growth. pathogenesis of clinical symptoms.

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Teaching sections of the discipline "oncology" in clinical residency: guidelines for teachers Associate Professor S.M. Kozyreva - Vladikavkaz: SOGMA, 2016. - 92p. head department, d.m.s. Associate Professor Khasigov A.V., Art. laboratory assistant Sautieva M.G.

Methodological recommendations are intended to help teachers of medical universities in organizing the educational process at the departments of oncology of postgraduate medical education. The recommendations are drawn up in accordance with the work program of the discipline "Oncology" of the main professional educational program of postgraduate professional education for students in residency in the specialty "Oncology". The recommendations provide for theoretical and practical forms of organizing training for clinical residents, the sequence of classes to systematize knowledge on the clinical course, diagnosis, treatment, and prevention of malignant neoplasms.

SOGMA, 2018
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TOPIC 2. "BIOLOGY OF TUMOR GROWTH. PATHOGENESIS OF CLINICAL SYMPTOMS".

1. Duration: 4 academic hours (1 academic hour - 45 minutes).
2. Venue: oncology dispensary.
3. The purpose of the lesson:
To teach residents the concept of carcinogenesis, its stages, types of carcinogens, the main signs of a malignant tumor, the anatomical forms of tumor growth, the pathways of tumor spread, the pathogenesis of clinical symptoms. To unify the concepts of obligate and facultative precancer, forms of growth of malignant tumors, their clinical phenomena, principles of classification according to TNM.
For this you need:
3.1. To systematize knowledge about the biological essence of the tumor,
3.2. To study the principles of constructing a classification of neoplasms.
3.3. Train residents on the principles of building a clinical diagnosis of malignant neoplasm based on the international classification of malignant neoplasms (TNM).
3.4. The educational value of the topic: the analyzed material serves to develop the clinical skills of the residents in examining patients and building a clinical diagnosis of a malignant neoplasm based on the international classification of malignant neoplasms (TNM).
3.5. The origins of the topic: the residents acquired basic knowledge at the departments: normal and pathological anatomy, pathological physiology, histology and cytology, surgery, therapy.
3.6. Output of the topic: the knowledge and skills acquired in the classroom are necessary to build a clinical diagnosis of a malignant neoplasm.

Motivation of the theme of the lesson. Mastering by clinical residents the concept of carcinogenesis, the stages of development of a malignant tumor, the characteristics of tumor cells, the idea of tumor morphogenesis, the main clinical phenomena of cancer, gaining knowledge about the classifications of tumors and the clinical stages of the tumor process, the principles of constructing a clinical diagnosis of a malignant neoplasm. Obtaining basic knowledge by clinical residents on the growth rate of tumors, clinical examination of patients with precancerous and background diseases, dysplasia, necessary for their subsequent work.

Lesson plan.
1. Control test tasks.

2. Oral-speech survey on theoretical material (Biology of tumor growth. Pathogenesis of clinical symptoms. Carcinogenesis. Modern understanding of tumor morphogenesis. Biological types and anatomical forms of tumor growth. Metastasis. Recurrence. Classification of malignant neoplasms).
Test questions:
List the main signs of a malignant tumor.
Define carcinogenesis, types of carcinogens.
Define metastasis and its stages.
Define a malignant tumor.
List the signs of malignant tumor growth.
What are the stages of carcinogenesis?

What are the anatomical forms of tumor growth?
What does relapse mean?
What are the criteria for primary multiplicity of tumors?
What is dysplasia?
What is the difference between obligate and facultative precancers?
Can precancerous disease be asymptomatic?
When staging cancer, what is T, N, M?
What is cancer in situ?

3. Listening and discussion of abstracts:
- Types of carcinogens, Exogenous and endogenous carcinogenic factors
- The concept of carcinogenesis and its stages
- Modern understanding of tumor morphogenesis
Growth and characteristics of tumor growth (signs of malignant tumor growth, biological types of growth, anatomical forms of growth, direction of tumor growth, metastasis)
Ways of tumor spread
Features of tumor recurrence

4. Practical work of residents:
4.1. Training in the method of establishing the stage of the tumor process by the size of the tumor, the presence and level of damage to the lymph nodes, the presence of distant metastases;
Mastering the methods of making a diagnosis according to the international TNM classification;
Establishment of the stage of a malignant disease in 4-5 patients according to outpatient cards.

4.2. Situational tasks
- staging tasks,
- writing obligate and facultative cancers for all localizations of malignant neoplasms.

TUMORS (Neoplasm, Eng) - uncontrolled cell growth due to a violation of the cell cycle and the predominance of proliferation processes over differentiation processes

The tumor process is a process accompanied by the addition of cell mass. Neoplasms are characterized by an autonomous type of growth. Normally, the number of cells is regulated by a precise balancing of two opposite processes - cell division and cell elimination. In oncological diseases, the addition of cell mass outstrips cell death either due to the activation of proliferation processes, or due to inhibition of apoptosis processes, and most often - with a combined violation of these processes. Significantly, the imbalance in cell number regulation is caused by the inability of the transformed clone to respond to external cues; thus, the volume of the cell mass ceases to depend on the needs of the body, which is what is meant by the concept of "autonomy".
Throughout the 20th century, scientists tried to formulate what specific features distinguish tumor cells and tissues from their normal predecessors. Progress in this area, which is the basis for the development of antitumor therapy, was hampered by the biological diversity of

the manifestation of neoplasms. Nevertheless, to date, it has been possible to identify and classify several clear trends supported by molecular genetic data. The clearest generalization of these signs are presented in the work of the founders of molecular oncology D. Hanahan and R. Weinberg, which appeared on the pages of the journal Cell (? 1 for 2000). According to the authors, all or almost all tumors are characterized by several inherent features.

1. Self-sufficiency in relation to proliferation signals associated with autoproduction of growth factors, corresponding receptors, or other components of the promitotic signaling cascade (Fig. 5.1). It is significant that a normal cell never divides by itself; to launch a proliferative program, a signal is needed from the outside, delivered by the endocrine system (hormones), paracrine mechanisms (tissue growth factors), or through the synaptic endings of neurons (neurotrophic). Thus, an increase in the number of cells normally occurs only if the multicellular host organism produces signals to increase the cell mass. The transformed cell produces such signals for itself, regardless of the needs of the body, which leads to the non-stop division of the tumor clone.

2. Loss of sensitivity to signals inhibiting the proliferation process due to inactivation of suppressor (antimitotic) proteins (Fig. 5.2). Clones with an abnormal ability to autostimulate the proliferative cascade can occur quite often in the body, which is associated with a constant mutation process in the cells of the body. However, in the process of evolution, all multicellular representatives of wildlife have developed several levels of defense systems that prevent unauthorized accumulation of cells. In the event of the appearance of cells with the ability to autocrine stimulation of division, the host organism produces inhibitory signals delivered to the cells in the form of humoral factors and aimed at stopping proliferation. Transformed cells, unlike normal ones, have lost the ability to perceive such signals. Such insensitivity to suppressive influences may occur as a result of the loss of the corresponding membrane receptors or other components of the signaling cascades involved in the transmission of the extracellular signal to the cell nucleus.

3. Slowing down the processes of programmed cell death, mediated by an imbalance in the biochemical regulation of apoptosis processes (Fig. 5.3). In everyday life, the word "death" always implies a negative emotional connotation. On the contrary, under the conditions of functioning of multicellular living systems, the physiological significance of cell death largely depends on the context of this event. It is customary to distinguish 2 main types of cell death: non-programmed and programmed. Unprogrammed cell death (necrosis) occurs as a result of pronounced adverse effects (hypoxia, burns, etc.). Such an event can negatively affect the structure and function of the organ and be accompanied by the formation of scar tissue. Programmed cell death, unlike necrosis, is a highly controlled, energy-consuming process aimed at preserving and maintaining the morphological and functional characteristics of organs and tissues. The most studied type of programmed cell death - apoptosis - provides a "scheduled" elimination of cells; this process is especially pronounced in tissues with a high intensity of cell renewal - in the epithelium of the gastrointestinal tract, skin, and blood. In addition, the cell is able to recognize its own DNA damage and other biochemical changes that pose a threat from point of view of malignant transformation. When such disorders appear, a “suicidal” program is launched, leading to the self-destruction of potentially dangerous cells. Cancer cells, unlike normal cells, have lost the ability to self-eliminate, which allows them to remain viable despite the presence of DNA damage and the stressful conditions of existence associated with hyperproliferation.

4. Unlimited replicative potential of cells (overcoming the "Hayflick limit"), associated with reactivation of the expression of the telomerase enzyme and, as a result, the absence of physiological shortening of telomeres (Fig. 5.4). Imagine that a clone of cells has arisen in the body that has the ability to autostimulate division, is not sensitive to mitosis suppressors, and has lost the ability to self-eliminate through apoptosis. Even these cells, which have a whole set of characteristics of malignant transformation, will not be able to form a clinically recognizable tumor! In multicellular organisms, there is another level of protection: limiting the replication potential of dividing cells. In 1961-1962 American scientist L. Naushek found that normal cells can divide no more than 100-150 times, after which the entire clone (i.e., the original cell and its descendants, which have a correspondingly smaller reserve of possible divisions) loses the ability to reproduce itself. This phenomenon, often referred to as the Hayflick limit, underlies at least part of the biological mechanisms of aging: it has been found that the replicative potential of cells decreases with the age of the individual. Moreover, overcoming the Hayflick limit is a necessary condition for malignant transformation; A demonstration of this property is the fact that under laboratory conditions only tumor cells can be cultured for many years, while long-term cultures of normal cells cannot be obtained. The unlimited replicative potential of tumor cells is usually explained by the activation of the telomerase enzyme, which compensates for the physiological shortening of the end sections of chromosomes observed during cell division. Telomerase appears to be one of the most promising molecular targets for anticancer therapy.

5. Stimulation of angiogenesis processes in the tumor, caused by the expression of angiogenic factors by transformed cells and aimed at meeting the increased needs of rapidly dividing neoplastic components for oxygenation (Fig. 5.5). For a long time, tumor cells were attributed to complete self-sufficiency. It was assumed that the transformed clone proliferates on its own, and all other elements of the tumor - stroma, vessels, fibroblasts - are only passive auxiliary components. The change in these ideas is associated with the name of the outstanding American scientist J. Folkman, who combined the daily work of a surgeon with fundamental, fundamental research in the field of experimental oncology. J. Folkman suggested and experimentally proved that tumor cells can form a clinically recognizable neoplasm only if they produce neoangiogenesis factors. Thus, the formation of the tumor vasculature does not occur by itself, but due to active biological processes controlled by the transformed cells. To date, dozens of factors that provoke or, conversely, inhibit angiogenesis have been identified. It is noteworthy that the development of anti-angiogenic drugs is considered one of the most promising areas in oncology. The fact is that in an adult body there is practically no formation of new vessels (the exception is post-traumatic tissue regeneration and some processes associated with the reproductive cycle in women). It is assumed that anti-angiogenic drugs should have an excellent therapeutic index, i.e. effectively inhibit the growth of the tumor mass without any side effects on the body.

6. The ability to invade and metastasize, associated with the production of histolytic enzymes (proteases) by the tumor, as well as factors that suppress local immunity (Fig. 5.6). This feature of malignant transformation is almost always cited as a key component of tumor growth. Attention to invasion and metastasis is associated with the clinical significance of these processes: they compromise the results of surgical treatment of cancer

and lead to death in cancer patients. In the context of the above, we note that none of the listed signs of tumor growth is sufficient for the clinical manifestation of the oncological process. In particular, the process of metastasis of non-transformed cells is characteristic of the disease of the female reproductive system - endometriosis, which is by no means an oncological pathology.
7. Genomic instability mediated by inactivation of DNA repair systems and disturbances in the molecular control of the cell cycle (Fig. 5.7). A tumor cell is characterized by an accelerated accumulation of mutations, which is at least partly associated with a decrease in the efficiency of DNA repair processes. This feature leads to extreme biological plasticity of neoplasms, which are able to quickly adapt.

to changing metabolic conditions and various therapeutic effects. It is significant that genomic instability seems to be the main property of tumor cells, which provides a "therapeutic window" when prescribing cytostatic drugs. Previously, it was believed that the mechanism of the therapeutic action of cytostatics is associated with selective suppression of dividing cells. This statement remains valid, but needs an important addition. The antitumor effect of chemotherapy and radiation is associated with the induction of DNA damage, which really manifests itself only in the process of cell division; However, tumor cells, at least in theory, are more sensitive to DNA-damaging agents, since their ability to repair chemical changes in the structure of nucleic acids is lower than that of the unchanged components of organs and tissues.

8. Restructuring of stromal components, creating more favorable conditions for the evolution of a malignant clone (Fig. 5.8). For a long time it was assumed that the elements of the stroma form only a passive framework for proliferating tumor cells. In recent years, it has been established that such a statement is far from the truth. Numerous facts indicate that the stromal components of tumors differ markedly from those in normal tissues; some researchers even insist
on the fact that fibroblasts infiltrating epithelial neoplasms contain somatic mutations that are different from those in tumor cells and are necessary for the vital activity of a malignant neoplasm. Numerous cases of symbiosis of transformed cells and surrounding fibroblasts have been demonstrated. In particular, the independence of the malignant epithelium from external proliferative signals may be provided not by autocrine stimulation as such, but by the secretion of growth factors by fibroblasts inhabiting the tumor. In turn, epithelial cells secrete a whole range of biologically active substances that regulate the adaptation of stromal elements to the needs of tumor growth.

Such a "dissection" of the key features of tumor growth is of significant practical importance. The empirical approach, associated with a random enumeration of thousands of biologically active chemicals, is gradually being replaced by a scientifically based, molecular-directed search for truly specific anticancer agents aimed at activating or inactivating the key biochemical components of tumor transformation. The first such tools have already been introduced into practical medicine. Apparently, their number will increase tenfold in the coming years, which will lead to a significant improvement in the results of antitumor therapy.

Carcinogenesis is the process of development of tumors of any type. The last stage of tumor growth, with visible manifestations, manifestation is called malignancy (canceration).
General signs of malignancy:
1. The cell acquires the ability to uncontrolled, unrestrained reproduction, division
2. Hyperplasia in parallel with uncontrolled cell division, there is a violation of differentiation, remains immature, young (this property is called anaplasia).
3. Autonomy (independent of the body), from the controlling, regulating processes of vital activity of stimuli. The faster the tumor grows, the less differentiated the cells are, as a rule, and the more pronounced the autonomy of the tumor.
4. A benign tumor is characterized by a violation of proliferation, there is no violation of differentiation, with the growth of a benign tumor, the cells simply increase in number, pushing or squeezing the surrounding tissues. And malignant tumors are characterized by the so-called infiltrative growth, tumor cells germinate (like cancer cells) destroying surrounding tissues.
5. Ability to metastasize. Metastases are cells that can spread throughout the body through the hematogenous, lymphogenous way and form foci of the tumor process. Metastases are a sign of a malignant tumor.
6. Tumor tissue has a negative effect on the body as a whole: intoxication caused by the products of tumor metabolism, tumor decay. In addition, the tumor deprives the body of the necessary nutrients, energy substrates, and plastic components. The combination of these factors is called cancer cachexia (depletion of all life support systems). The tumor process is characterized by pathological proliferation (uncontrolled cell division), impaired cell differentiation and morphological, biochemical and functional atypism.
Atypism of tumor cells is characterized as a return to the past, that is, a transition to more ancient, simpler metabolic pathways. There are many features that distinguish normal cells from tumor cells:
1. Morphological atypism. The main thing is the change in the cell membrane.
In tumor cells, the contact surface area decreases, the number of nexuses - contacts that ensure the adhesiveness of cell membranes - decreases, the composition of membrane glycoproteins changes - carbohydrate chains shorten. Embryonic proteins, unusual for mature cells, begin to be synthesized in the cell, the amount of phosphotyrosines increases. All this leads to a violation of the properties of contact inhibition, increases the lability, fluidity of the membrane. Normally, cells, coming into contact with each other, stop dividing (self-regulation of the division process takes place). In tumor cells, the absence of contact inhibition leads to uncontrolled proliferation.

Biochemical atypia. Atypism of energy metabolism is manifested in the predominance of glycolysis - a more ancient metabolic pathway. In tumor cells, a negative Pasteur effect is observed, that is, intense anaerobic glycolysis does not decrease when changing from anaerobic conditions to aerobic ones, but persists (increased glycolysis in tumor cells causes their high survival rate under hypoxic conditions). The tumor actively absorbs nutrients. The phenomenon of substrate traps is observed, which consists in an increase in the affinity of the enzyme for the substrate (glucose), in tumor cells, the activity of hexokinase increases by 1000 times. Tumor cells are also a trap for protein, which also leads to cachexia.

The predominance of glycolysis leads to an increase in the concentration of lactic acid in the tumor cells, acidosis is characteristic, leading to disruption of the cell itself (the necrosis zone is usually located in the center of the tumor).
Atypism in the regulation of growth and differentiation of tumor cells. Growth processes, differentiation of division are normally under the control of central endocrine regulation, which is carried out by growth hormone, thyroid hormones, and insulin. In addition to these common factors, each tissue has its own growth and differentiation factors (epidermal growth factor, platelet factor, interleukin). Induction of growth and differentiation begins with the interaction of the growth factor with the growth factor receptor on the cell membrane (in a tumor cell, this stage may be impaired). At the next stage, secondary messengers are formed - cyclic adenosine and guanosine monophosphate, and normal growth and differentiation are characterized by the predominance of cyclic adenosine monophosphate (cAMP). The formation of cyclic guanosine monophosphate is combined with increased proliferation. This is a typical feature in tumor cells. At the next stage, active protein kinases are formed, the function of which is phosphorylation of cellular proteins. Normally, protein kinases phosphorylate proteins for serine, threonine, and histidine. In tumor tissue, protein kinases are tyrosine-dependent, that is, protein phosphorylation proceeds via tyrosine. Stimulation of proliferation is associated with the formation of proteins phosphorylated by tyrosine.
Regulation of tumor cell growth and differentiation is also associated with calcium-dependent protein kinase. Normally, calcium-dependent protein kinase functions as a modulator and balances the processes of growth and differentiation. A tumor cell is always characterized by hyperreactivity of calcium-dependent protein kinase, while it acts as a proliferation inductor, it stimulates the formation of phosphotyrosine and enhances uncontrolled cell reproduction.
Theories of the development of the tumor process.

In 1755, English scientists published a study “On cancer of the skin of the scrotum in chimney sweeps”. Cancer in this work was considered as an occupational disease that chimney sweeps suffered at the age of 30-35 years (the question of the localization of the tumor in the scrotum is still unclear). Chimney sweeps, cleaning chimneys, rubbed soot into their skin and after 10-15 years developed skin cancer . The explanation of the mechanisms of development of this form of cancer was the beginning of a new era in the study of the tumor process. It was found out 2 main factors causing the development of cancer - constant irritation, damage; the action of certain substances (soot), which have been called carcinogens. Many carcinogens are now known. This model of the disease was reproduced by Japanese scientists who rubbed soot into the ear of a rabbit for a year and got first a benign (papilloma) and then a malignant tumor.
Carcinogenic substances that are in the external environment are called exogenous carcinogens: benzpyrenes, phenanthrenes, polycyclic hydrocarbons, amino-azo compounds, aniline dyes, aromatic compounds, asbestos, chemical warfare agents, and many others. There is a group of endogenous carcinogens - these are substances that perform a certain useful function in the body , but under certain conditions can cause cancer. These are steroid hormones (especially estrogens), cholesterol, vitamin D, tryptophan conversion products. Cancer has even been obtained by injecting substances such as glucose, distilled water under certain conditions. Tumor processes belong to the group of polyetiological diseases, that is, there is no one main factor that would contribute to tumor development. It

occurs when a combination of multiple conditions and factors, hereditary predisposition or natural resistance matters. Nuller animal lines have been bred that never get cancer.
The action of carcinogens is very often combined with the action of physical factors - mechanical irritation, temperature factors (in India, skin cancer in carriers of vats of hot coal, in northern peoples there is a higher incidence of cancer of the esophagus due to the consumption of very hot food: hot fish. In smokers, the following factors contribute to the development of lung cancer - high temperature, which is created when smoking, chronic bronchitis - causing active proliferation, and tobacco contains methylcholanthrenes - strong carcinogens.Sailors have an occupational disease with skin cancer of the face (exposure to wind, water, ultraviolet radiation of the sun) , radiologists have an increased incidence of leukemia.

The third etiological group is viruses. One of the main confirmations of the viral theory of the occurrence of cancer is the inoculation of a non-cellular filtrate of an animal with a tumor to a healthy one. The non-cellular filtrate contained the virus and the healthy animal became ill. From diseased chickens, leukemia was transplanted into healthy chickens; it was possible to cause leukemia in almost 100% of chickens. More than 20% of various viruses have been described that are capable of causing various forms of the tumor process in almost all experimental animals. Transmission of cancer-causing viruses through milk has been discovered. The offspring of low-cancer mice were placed in a high-cancer female (the mice belonged to low-cancer and high-cancer lines. Low-cancer lines did not spontaneously develop cancer, high-cancer lines developed cancer in almost 100% of cases.). this is how the milk factor of a viral nature was discovered, the virus that causes disease was discovered, and in humans - the Epstein-Barr virus (we cause lymphoma).
So, 3 main theories of carcinogenesis have been formulated, corresponding to the three main etiological groups:
carcinogens
physical factors
biological factors - viruses.

The main theories explaining the pathogenesis of cancer are:
mutational theory of carcinogenesis, which explains the development of the tumor process as a consequence of mutation. Carcinogenic substances, radiation cause a mutation process - the genome changes, the structure of cells changes, and malignancy occurs.
Epigenomic theory of carcinogenesis. Hereditary structures are not changed, the function of the genome is disturbed. The epigenomic mechanism is based on derepression of normally inactive genes and depression of active genes. According to this theory, the basis of the tumor process is the derepression of ancient genes.
virus theory. Viruses can persist in cells for a long time, being in a latent state, under the influence of carcinogens, physical factors, they are activated. The virus integrates into the cell genome, introducing additional information into the cell, causing disruption of the genome and disruption of the cell's vital functions.
All these theories formed the basis of the modern concept of oncogenes. This is the theory of oncogene expression. Oncogenes are genes that contribute to the development of the tumor process. Oncogenes were discovered in viruses - viral oncogenes, and similar ones discovered in cells - cellular oncogenes (src, myc, sis, ha-ras). Oncogenes are structural genes encoding proteins. Normally, they are inactive, repressed, so they are called

protoncogens. Under certain conditions, activation or expression of oncogenes occurs, oncoproteins are synthesized, which carry out the process of transforming a normal cell into a tumor one (malignancy). Oncogenes are denoted by the letter P, followed by the name of the gene, say ras and a number - the molecular weight of the protein in microdaltons.

Characteristics of the tumor - metabolic atypism
Metabolic atypism is manifested in a significant change in the metabolism of nucleic acids, proteins, carbohydrates, lipids, ions and vitamins.
Metabolic atypism leads to functional atypism, which in tumor cells is manifested by hypo-, dis- or hyperfunction.

WHICH GENES MUST MUTE TO DEVELOP CANCER?

The mutations must affect the genes that control six cellular processes.
susceptibility to growth factors,
susceptibility to factors that inhibit growth,
apoptosis
DNA Replication,
angiogenesis, tissue invasion and metastasis

Oncogenes are mutant genes that, in the non-mutated state, accelerate proliferation. In the normal state, these genes are called proto-oncogenes (genes for RF, RF receptors, and signaling proteins such as ras).
Antioncogenes are genes that inhibit proliferation.
Genetic events that convert a proto-oncogene to an oncogene or inhibit anti-oncogenes:
point mutations, chromosomal amplifications,
insertions or deletions, gene silencing,
chromosomal translocations, exogenous viral RNA.

Stages of carcinogenesis:
1. Initiation
2. Transformation
3. Tumor aggression
Under the action of carcinogens in the cell, a certain group of oncogenes is activated. At the stage of initiation, the expression of oncogenes myc and mut is most often observed (the products of these oncogenes are DNA-binding mitogens), uncontrolled proliferation is stimulated. differentiation does not occur, the function is preserved. This is a long latent - latent phase. The duration of the initiation phase is approximately 5% of the life span of the species (in humans, depending on the type of tumor - 5,10,12 years, sometimes much shorter). At the initiation stage, the Hayflick limit is removed. It is typical for a normally developing cell to perform no more than 30-50 mitoses, then division stops and the cell dies. This limitation on the number of mitoses is called the Hayflick limit. This is not the case in a tumor cell; the cell is continuously, uncontrollably dividing. A cell in the initiation phase is called immortal (immortal) since it continuously reproduces itself, the initiation phase is called the immortalization phase. The cell in this phase can return to the path of normal development, or it can go to the next phase of development - the transformation phase.

Transformation occurs if the initiated cell continues to be affected by a carcinogenic factor and a new group of oncogenes is expressed. In cell culture, the expression of oncogenes of the ras family characteristic of this phase is observed with the greatest constancy; the products of these oncogenes bind guanosine triphosphate. expression of the sis oncogene also occurs at this phase. The expression of these oncogenes leads to the final malignancy of the cell - differentiation and proliferation are disturbed. The formation of single tumor cells does not yet lead to a tumor process. Tumor cells have the property of foreignness (antigens) for the body. It is believed that tumor cells are constantly formed, but with sufficient immune control they are destroyed. The transition to the stage of tumor progression depends on the state of immunological reactivity.

The antigenic properties of a tumor cell are manifested by several mechanisms:
antigenic simplification. A qualitative change in glycoproteins is especially important - carbohydrate chains are shortened.
Antigenic complication - the appearance of unusual components - an increase in phosphotyrosines.
Reversion (return to the past) - the appearance of embryonic proteins in the composition of the membrane of the tumor cell. Embryonic proteins - alpha-ketoprotein, etc.
Divergence.
Appear in the tissues of antigenic components that are unusual for this tissue. Divergence is like an exchange of antigenic fragments. Thus, there is no absolutely foreign antigen, all antigens are modifications of the body's own tissue, these are weak mosaic antigens.
There are several levels of protection against the tumor antigen:
the function of natural killers (natural killers) - they create the main antitumor protection. They recognize the tumor cell by negative information - the absence of long glycoproteins, etc. the killer contacts the tumor cell and destroys it.
Sensitized killer T cells also destroy foreign cells. The role of humoral immunity is controversial. It is believed that the complex of antibodies on the surface of tumor cells prevents the manifestation of the killer effect.

It has been shown that with immunodeficiencies, the risk of developing tumors increases by 1000 times, and sometimes by 10,000 times, as well as with prolonged use of immunosuppressants, glucocorticoids.
The stage of tumor progression is already characterized by clinical manifestations - the mass of the tumor increases, infiltrative growth, metastasis is observed, and ends with cancer cachexia.
The process of vascular development in the tumor is controlled by the oncoprotein angiogenin (now they are trying to use blockers of this protein to treat the tumor).
A constant sign of tumor growth is an increase in the number of T-suppressors in relation to T-helpers (it is not clear whether this is a primary or secondary mechanism).
It is known that tumors are capable of regression. In lizards, newts, tumors often form in the zone of active regeneration (tail), which are able to resolve themselves. Cases of resorption of tumors in humans are described, but the mechanism of this phenomenon has not yet been studied.

Two lines of antitumor defense.

The first line of defense is aimed at protecting the cell's genome. This line of defense is made up of caretaker genes, or caretaker genes in Russian.
Caretaker genes encode proteins that correct errors that occur during DNA replication or as a result of mutations.
The caretaker genes themselves can be mutated. Mutations in caretaker genes increase the vulnerability of cells to ultraviolet radiation and the development of skin cancer.
The second line of defense is activated when the first fails and tumor cells form. This is the immune line of defense.

Antitumor immune defense is based on the fact that the surface of cancer cells contains specific antigens, tumor-specific antigens, or TSA for short.
TSAs are recognized by the body's immune system.

Clinical manifestations of the pathogenic effect of the tumor on the body
* The pathogenic effect of the tumor is manifested in the following clinical symptoms and syndromes
*pain, cachexia, leukopenia,
*anemia, thrombocytopenia and vulnerability to infections.

! Cachexia is the main cause of death in patients.

CACHEXIA SYNDROME:
Changes in protein, lipid, carbohydrate metabolism
Asthenia (significant weakness)
Anorexia (loss of appetite)
Poor performance
early satiety
Taste change
Weight loss
Anemia