

Tumor(neoplasia)

Tumors, general data

DEFINITIONS

- Neoplasia literally means "new growth" and the new growth is a "neoplasm" or "tumor".
- A neoplasm, as defined by Willis, is "an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change."
- In common medical usage, a neoplasm is often referred to as a *tumor*, and the study of tumors is called *oncology* (from *oncos*, "tumor," and *logos*, "study of").
- Now oncology is the study of tumors or neoplasm. In oncology, the division of neoplasms into benign and malignant categories is important.
- Knowledge of non-neoplastic proliferation is helpful in understanding neoplasia.
- Neoplastic cells lose control and regulation of replication and form an abnormal mass of tissue.

DEFINITIONS

- All tumors have two basic components: proliferating neoplastic cells that constitute their parenchyma and supportive stroma made up of connective tissue and blood vessels
- The term "tumor" was originally applied to the swelling caused by inflammation.
- Now this term is used for neoplasm too.
- At the same time cancer is the common term for all malignant tumors.
- Cancer is the second leading cause of death in the World; only cardiovascular diseases exact a higher toll.
- Cancer is not one disease but many disorders that share a profound growth dysregulation.

Tumors etiology.

Carcinogen agents and their interaction with cells

- physical,
- chemical and
- biological agents which are called carcinogens.

Tumors etiology.

Physical carcinogens

- Radiation carcinogenesis.*
- Physical carcinogens* include ionizing radiation and to a lesser extent – ultraviolet rays. Ionizing radiation acts indirectly, through highly active free radicals distorting DNA structure. Ultraviolet rays prevent its reparation.

Tumors etiology.

Carcinogen agents and their interaction with cells.

chemical agents

- Over 75% of human beings' cancerous diseases are caused by environmental factors, and in first turn – by chemical compounds. First experimental proofs of chemical compounds' carcinogenicity, were Yamagiva's and Ishikava's researches (1915). They induced rabbit's ear skin cancer by applying there coal-tar pitch for the period of 15 months.
- Chemical carcinogens* are wide-spreaded in environment and the majority of them are of antropogenous origin. Same time we shouldn't exaggerate their role in human being pathology as only about 100 compounds and manufacturing processes are acknowledged as carcinogenous for human beings.

Chemical carcinogens

- The most important of chemical structure carcinogens are follows:
- a) polycyclic aromatic hydrocarbons;

- b) aromatic amine and amides;
- c) nitrosoamines and nitrosoamides.

Chemical carcinogens

First group consists of over than 200 substances with three and more benzene rings. Only one of them, namely 3,4-benzopyrene considered to be the one able to cause cancerous diseases of human being. The others cause tumors only in experimental animals.

The biggest amount of this group of carcinogens is

- in tobacco fume,
- exhaust gases of automobiles,
- blast furnaces smoke,
- asphalt,
- waste of chemical plants,
- dried and overdone food.

Chemical carcinogens

Substance of polycyclic structure shows mostly local carcinogenous influence. In case during experiment they are applied on skin cancer occurs, in case they are applied under skin – sarcoma occurs. Polycyclic aromatic hydrocarbons are excreted by various organs of organism, so tumors of these organs occur – kidneys, skin, mammary glands.

Chemical carcinogens

(aromatic amine and amides)

The second group of carcinogens are mostly azo dyes, for which two or more azo groups presence is characteristic (mono-azobenzene, 2-naphthylamine, benzidine). These substances are used to color natural and synthetic fibers, in printing industry, cosmetics, color photography, to synthesize medicines, insecticides. Carcinogenous action of amines and amides becomes apparent when they are introduced in digestive tract, subcutaneous or in case they are applied on skin. Tumors appear in organs far from the place of application, the most often in liver, urinary bladder, bowels, kidneys.

Chemical carcinogens

(nitrosoamines and nitrosoamides)

Nitrocompounds (nitrosoamines and nitrosoamides) are characterized with alkyl radical presence. They are utilized as antioxidants, pesticides, paints solvents, semi-products under paints, medicines and polymers synthesis. Their carcinogenicity for human being is not proved but experimental data causes oncologic alertness. Possibility of nitrocompounds synthesis of nitrites, nitrates, nitric oxide in human being's intestinal tract is proved. Nitrites are widely used as conserved agents for foodstuff.

Viral carcinogenesis

There are various biologic agents able to cause malignant growth. The biggest group consists of viruses. Indisputable proofs were acquired regarding viral origin of many tumors – hens' Rous sarcoma, rabbits' Shope fibroma and papilloma, mice mammary glands cancer (virus is transferred through milk), Burkitt's lymphoma, rhinopharyngitis cancer, carcinoma of uterine cervix.

Viral carcinogenesis

- Viruses causing tumors are called oncogenes.
- They are divided into two groups depending of genome's molecular structure - RNA-containing and DNA-containing.
- Major group consists of RNA oncogenous viruses, forming the group of retroviruses.
- Retroviruses are the major cause of human's malignant growths, however they point the way to understand basic mechanism underlying these diseases. They became model system by means of which the most modern data was received of fine molecular distortions occurring under cellular transformations.

Pathogenesis of tumors. Molecular grounds of cancerogenesis

The question arises: what kind of DNA damage is realized into tumor? The answer to that is not at all simple.

- Based on modern knowledge scientific theory was formulated which is known as oncogene concept.
- It combines all forms of carcinogenesis (chemical, physical and viral) into one universal mechanism.
- There are really many causes of cancer, but all of them similar to water through watering-can should pass through one critical channel – DNA and leave trace in it, meaning damage. This damage is specific. It will lead to normal cell transformation into malignant cell (transformation phenomenon)

Pathogenesis of tumors. Molecular grounds of cancerogenesis

□ As a rule, cellular oncogenes are represented in DNA in one copy but it was proved that copies quantity can increase in the result of DNA replication abnormality. This phenomenon is called *amplification* (augmenting). Cellular oncogenes copies amount increase causes enhanced division of cells. This mechanism acts in human neuroblastoma and carcinoma of large intestine creation.

Pathogenesis of tumors. Molecular grounds of cancerogenesis

□ Anyway, point mutations independently of their cause are considered to be major mechanism of proto-oncogene transformation into active cancer oncogene. It is proved that that's enough to change in human urine bladder cancer only one base – guanine for the other one - thymine as inactive proto-oncogene becomes transforming. Totality of scientific ideas of mutations' decisive force in tumor etiology forms the grounds of mutation concept of cancerogenesis.

Stages of cancerogenesis

- Tumors occurrence and progress is multistage process.
- There are three main stages
- transformation (initiation),
- promotion and
- progression.
- Proto-oncogene activation finishes first stage – stage of initiation.

Stages of cancerogenesis

□ Tumor growth risk factors.

□ These provocative factors could be additional doses of chemical or physical cancerogenes, retroviral superinfection as well as various agents which do not cause tumors as they are, but are able to take immortalized cells out of latent state.

□ Factors activating pre-cancerous cells are called *promoters*. Under their influence transformed cells go into new stage of development – promotion stage for which cellular oncogenes expression is characteristic.

Stages of cancerogenesis

□ *Progression* is the final phase of tumor progress. Under this term persistent, irreversible qualitative changes of tumor to malignization are understood. For example hormone-dependent neoplasms became hormone-dependent, tumor reacted medicines stopped to react them. Progression is the last and the most long lasting stage of tumor progress lasting up to organism death.

The most important clinicopathologic implications of tumor growth.

- Tumor negative influence on organism depends
- -on its type (non-malignant or malignant),
- - localization,
- - temps of growth and
- - directions of metastasis.

Tumor directly injures organ in which it progresses disturbing its structure and functions. Surrounding organs are subject to atrophy and deformation, lumens of cavity organs narrows. Due to chronic intoxication with decay products and insufficient feeding cachexia develops. Hematosis depression, excessive hemolysis and chronic hemorrhage cause anemia.

Tumor of mediastinum

The most important clinicopathologic implications of tumor growth.

□ In case tumor consists of hormone-active cells diseases occur connected with corresponding hormone hyperproduction or paraneoplastic syndromes of endocrinopathy, neurological aspects (dementia, neuropathy), skin implications, hematologic implications (hyper coagulability of blood, anemia, thrombocytopenia, polycythemia).

□ Pheochromocytoma (cancer of adrenal glands cerebral layer, producing adrenalin) causes arterial hypertention progress, insulinoma (tumor of islet of Langerhans β -cells) causes hypoglycemia, gastrinoma (pancreatic tumor producing gastrin - gastric secretion stimulator) causes stomach ulcer.

Tumors structure.

Their appearance can remind

- mushroom,
- cauliflower,
- node or intumescence.

In section tumors are mostly of

- white,
- grey and
- red color.

The following is often found in them:

- hemorrhages,
- necrosis and
- cysts cavity of which is filled with mucus or bloody mass.

Some tumors are of brown color, for example, melanoma.

melanoma

Tumors structure.

□ Tumor size depends mostly of its origin, location and growth period. In some cases they can reach giant sizes (fibroid tumors) in the other cases they can be seen only microscope (microcarcinomas). Tumors localized close to vitally important centers as a rule are of rather small size.

Lymphoma

Tumors structure.

□ Tumor consistency is defined first of all by the type of outgoing tissue and ratio between stroma and parenchyma.

□ Tumors of bone (osseous) tissue, cartilage tissue and fiber conjunctive tissue are of dense consistence.

Malignant growth of epithelium in which stroma is underdeveloped are flaccid and by their consistence they are similar to new-born child's brain (cancer-brainer).

□ Stroma and parenchyma are seen microscopically in each tumor. Parenchyma is its specific part which is represented by malignant cells and determines tumor place in hystologic classification.

Tumors structure.

Tumors structure.

□ Most of tumors looks like organ by their structure, i.e. have parenchyma and completely represented stroma.

□ Such tumors are called *organoid*.

□ In undifferentiated tumors parenchyma prevails and stroma is underdeveloped.

□ They are called *histioid*.

□ Blood circulation insufficiency causing necrosis easily occurs in them. At the same time there are tumors poor with parenchymatous elements and rich with stromal, for example gastric fibrocarcinoma or scirrhus. These tumors cause complications due to stroma's corrugation.

□ They deform organ or narrow its lumen.

Corrugation of organ by cancer

Tumors structure

□ Tumor corresponding structure of the organ it is localized in is called *homologous*, and the one which structure differs from this organ structure is defined as *heterologous*.

□ In case tumor is developed from the cells of organ in which it occurred – this is *homotopy* tumor.

□ In cases it occurs from the cells of embryonal displacement (*heterotopia*), it is called *heterotopic*, for example tumor of bone marrow in uterus.

Biology of tumor growth.

□ Universal and mandatory feature of all the tumors – both non-malignant and malignant – is their ability to endless growth.

□ This is fundamental feature of any tumor.

□ Uncontrolled excessive proliferation of malignant cells doesn't mean at all that they divide faster than homologous cells of healthy tissue.

□ Infinity of malignant cells growth is based on the fact that they are unable to exhaust division resource.

□ Malignant cell has one more feature – uncontrolled growth.

□ On the level of the whole organism tumor growth is controlled with nervous and endocrine systems, and on the local level – with mitogens and keylones.

□ Malignant cell gets out of this hand, that is shows autonomy, independence of growth.

Biology of tumor growth.

□ Peculiar feature of malignant cells is *anaplasia*, which means their persistent dedifferentiation, loss of ability to form specific tissue structures or produce specific substances characteristic for normal cells. In the other words its return to embrional state, structural-chemical organisation simplification.

Biology of tumor growth

□ Tumor occurs from single parent cell subject to genous mutation. Malignant cells differs in several parameters from their common normal ancestor. This difference relates to cell's and its organoids' structure, metabolism, specific features and functions. Therefore morphologic, biochemical, physical-chemical, immunologic and functional anaplasia is differentiated.

morphological anaplasia

□ The essence of *morphological anaplasia* comes to tissue, cellular and subcellular atypicity occurrence.

□ Polymorphism is inherent to malignant cells – they acquire smaller as well as bigger size and shape which is not peculiar for normal cells.

□ Interrelation between nucleus and cytoplasm is shifted in favor of nucleus due to its enlargement.

□ Multinuclear cells, nucleus hyperchromatosis are observed caused by nucleic acids accumulation in them, nucleolus amount increase and their migration into cytoplasm.

□ Of subcellular structures mitochondrions are subject to most prominent changes. Their quantity and size are decreased, membranes became thinner, cristas also become thinner and disappear.

□ At tissue level structures' created by malignant cells size and shape changes are observed. This referes for example to glandular follicles in adenocarcinomas and focuses of ossification in osteosarcomas. Sometimes tumor completely losses morphologic features indicating its origin from the certain differentiated tissue.

Biochemical anaplasia

□ is peculiarities of malignant cells' metabolism caused by theirs genetic apparatus change.

□ As the result of that malignant cells enzymatic range changes. Intracellular enzyme insufficiency occurs - some enzymes are inhibited but the other ones activates or start to synthesize absolutely new substances which didn't exist in normal cells.

□ It is found that all tumors, subject to progression start to look like each other by their enzymes set independently of what cells they come from.

□ Unification of tumors izoenzymal range independently of their histogenesis is very characteristic manifestation of malignization.

The most peculiar biochemical features of malignant cells relate to proteins and carbohydrates metabolism. Proteins synthesis prevails their decomposition. To build own proteins tumor captures aminoacides of the other organs ("tumor - trap for nitrogen").

Biochemical anaplasia

Peculiarities of tumors power supply are as follows:

a) activation of anaerobic glycolysis and enzymes providing it - pyruvatekinase, hexokinase, fructokinase;

b) presence of aerobic glycolysis for which normal cells are not able (exceptions – leukocytes, spermatozoon, eye retina cells);

c) breath oppression with glycolysis (Crabtree effect), to say exact – with powerful system of glycolytic enzymes, which intercept substrates – inorganic phosphorus, coenzymes.

Biochemical anaplasia

Among physical-chemical features of malignant cells the following should be emphasized:

acidosis in the result of lactic acid accumulation,

intracellular aqutation,

potassium ions accumulation,

electroconductivity increase,

colloids density reduction,

membrane negative charge increase,

their surface tension decrease.

Antitumor immunity

Under immune anaplasia changes of malignant cell's antigene features is understood. These changes is the result of protein metabolism rebuilding. It is known that each tissue synthesizes a set of antigenes specific for it. This set is changed in tumor.

Tumor antigenes. Antigene simplification and antigene complication are differentiated. Antigene simplification is characterized with antigenes synthesized by malignant cell numerous times decrease.

Antitumor immunity

Antigene complication is manifested with antigene divergence and antigene reversion.

Antigene divergence means that malignant cells start to synthesize antigenes which are not characteristic for healthy cells, but these antigenes are usually synthesized by the other cells.

For example hepatic tumor can synthesize antigenes of spleen or kidneys.

Tumor's synthesis of embrional antigenes is called antigene reversion.

Renal carcinoma of human being synthesizes α -fetoprotein, which serves as the test for its diagnosis.

Functional anaplasia

is manifested with loss or distortion of function fulfilled by cell.

In thyroid gland malignant cells' thyroid hormones synthesis can reduce or increase up to myxedema or thyrotoxicosis occurrence. Bilirubin conjugation is stopped in hepatoma (liver cell carcinoma).

In some cases tumors start to synthesize the products not peculiar to them. For example pulmonary and bronchi tumors can synthesis hormoniform substances.

Secondary changes in tumor.

Secondary metabolism disorders can develop in tumors,

like sliming,

hyalinosis,

adiposity,

calcification.

Blood circulation functional insufficiency is characteristic for malignant growth as parenchyma always grows faster than stroma. Besides that, blood vessels are often thrombosed causing progress of necrosis on background of which ulcers, hemorrhages, perforations occur.

Necrosis and hemorrhages *in tumor of liver*

Secondary changes in tumor of kidney

Secondary changes in tumor of ovary

Non-malignant growth and malignant growth.

Depending on the stage of differentiation,

speed and character of growth,

inclination to metastasis and recurrence,

secondary changes in tumors,

their influence on organism,

they are distributed into non-malignant, malignant and the ones with local destructive growth.

Non-malignant tumors

- or mature tumors are built of cells from structure of which it is always could be determined from what tissue they grow.

- In case they do not locate near vital important centers

- they are manifested with local changes and

- their influence on organism is minor.

But these tumors can transform into malignant ones – malignize.

Malignant (immature) tumors

are built of low-differentiated or nondifferentated cells which lose structural similarity to cells they originate from.

Apart from non-malignant tumors they

gives metastasis,

recur,

manifest themselves with local changes and influence on the whole organism

non-transforming into differentiated forms.

Tumors with local destructive growth occupy intermediate position between non-malignant and malignant.

They have the features of infiltrating growth, but do not metastasis.

These are hemangioma, desmoid tumor.

Basic differential features of non-malignant and malignant growth.

Non-malignant growth

Have minor deviations

Expansive growth

Grow slowly

Reach big size

Rare are subject to ulceration

Do not give metastasis

Recurrence is not characteristic

Minor influence on patient's

Malignant growth

Expressed atypism: tissue from parent tissue

Infiltrative growth

Grow fast

Rare reach big size

Often are subject to ulceration

Give Metastasis

Recur often

Have major influence on

General condition of organism

and cells

Tumors' growth and spread in organism.

Depending on differentiation level the following forms of tumor growth are differentiated:

expansive,

opposition and

infiltrative (invasive).

First form is peculiar for non-malignant growth,

and second and third – for malignant ones.

Tumors' growth and spread in organism

Tumor which grows *expansively* increases as a node, moving aside surrounding tissues.

Cells surrounding atrophy and stroma is subject to collapse causing pseudocapsule formation and sharpness of tumor boarder.

Opposition growth is intermediate between expansive and infiltrative. Tumor grows from multiple spots of growth – focal proliferates forming “tumor field”. Tumor transformation (malignization) is done consequentially from the center to peripharia and is finished with malignization focuses fusion into single node.

Infiltrative growth is characterized with tumor elements spreading into the least resistance directions and ingrown surrounding tissues destructing them.

Tumors' growth and spread in organism

In respect to organ's cavity *endophytic* and *exophytic* growth are differentiated. Pre-invasive or intraepithelial neoplasia is observed as specific form. Hystologically epithelium displasia of epithelium, atypism are found, its normal distribution into layers disappears, but basal membrane is not injured.

Tumors which grow expansively do not spread out of organ's boarder. In case infiltrative growth tumor spreads not only inside the organ but also out of it. Continuous contact tumor spread and metastasis are differentiated.

Metastasis (dissimination)

is malignant cells transfer from primary focus into distant parts with their further settle down and secondary focuses creation.

Several ways of tumor dissemination exists:

hematogenic,

lymphogenic,

perineural,

implant,

mixed.

Hematogenic metastases

occur when malignant growth's cells come into blood circulation system and moves by venous or arterial blood stream.

Spreading through veins is the most often way of metastasis. In this case two possible direction exist:

first is through vena cava system when malignant cells from primary focus (uterum, kidney, skeleton bones) are transferred into lungs, and

the second one - through portal vein, when gastric, intestine carcinoma, tumor of pancreas metastasis in liver.

Sometimes paradoxical and retrograde metastases are possible. Arterial way of metastasis relates, in the first turn, primary focus localized in lungs. At it metastasis into cerebrum, bone marrow, liver and other organs are possible.

Hematogenic way of metastasis is most peculiar to sarcomas.

Metastases in liver

Metastases in kidney

metastasis

Lymphogenic metastasis is malignant cells transfer into regional, and further on – into distant lymph nodes.

Later on malignant cells come into blood circulation system through thoracic lymphatic vessel.

Perineural metastases could be better characterized as an example of endless spread. Cells are disseminated through perineurium fissures.

Lymphogenic metastasis into lymph nodes
metastasis

Implantation metastasis is called tumor extension through serous cavities or natural channels. When serous tunic is invaded with malignant cells, they can come off and disseminate in serous cavity. In case conditions are favorable, they settle down and new focuses occur – implantation metastases. Macroscopically these metastases look like white plaques or humps.

At that hemorrhagic inflammation occurs. Implantation metastases should be differentiated from lymphogenous metastases (carcinoma of pleura, peritoneum) when similar humps are formed downstream lymphatic vessels.

Implantation metastases on peritoneum

contact metastasis on intestine

metastasis

Metastase cells have parent tumor structure and function. Intensity of metastasis depends on the stage of tumor differentiation and immunologic reactivity of organism. There is no correlation between tumor size and metastasis intensity. Malignant growth is able to metastasis from the moment of its occurrence.

Metastases size often exceed parent tumor's size. Most of cells die when transferred to the other place, so metastases could stay latent for a long time.

Recurrent tumor

is repeated occurrence of the same tumor by its features in the place of removed or treated tumor.

Both non-malignant and malignant tumors recur, the latter - more often.

pretumor conditions

diseases at which the risk of tumor progress is increased and precursors of cancer (histologic ‘;abnormalities’ of tissues).

They are classified in the following types:

a) pathologic regeneration an example of which can be chronic bronchitis with epithelium metaplasia,

mucus tunics' leukoplakia,

chronic atrophic gastritis,

chronic stomach ulcer,

subacute skin ulcer;

b) chronic proliferative inflammation,

first of all polyps of ventricle and large intestine;

c) dishormonal diseases – proliferative mastopathy,

glandular hyperplasia of endometrium,

endocervicitis,

prostatic hypertrophy;

d) tissues development abnormalities – teratomas, nevus pigmentosis and birthmarks.

pretumor conditions

Pretumor processes shouldn't be connected with etiology. Pretumor changes presence do not mean at all that tumor will occur on their ground. So by cancer threat level they are distributed into optional (under which cancer develops rarely) and obligatory (under which cancer develops rather often).

Tumors classification. Terminology.

Modern classification is built by histogenetic principle taking into consideration morphologic structure,

localization,

- structure features in certain organs (organo-specificity),
- non-malignancy or malignancy.
- Tumor name ends with ‘oma’ (mioma, fibroma).
- Malignant epithelium growth are called “cancer”,
- mesenchymal – “sarcoma”,
- tumors of embrional tissues – “blastoma”,
- of several embryonic leafs - “teratomas”.
- Some tumors are called with the name of the author described them – Kaposi's sarcoma (angiosarcoma), Wilms' tumor (nephroblastoma).

Tumors classification. Terminology

□ International TNM system is used in respect to tumor process extention, where T(tumor) – tumor characteristic, N(nodus) – presence of metastases in lymph nodes, M(metastasis) – presence of distant hematogenous metastases.

□ Seven groups of tumors were differentiated combining over 200 names:

□

- **a) epithelial tumors without specific localization (organo-nonspecific);**
- **b) organospecific epithelial tumors;**
- **c) mesenchymal tumors;**
- **d) tumors of melanin creating tissue;**
- **e) tumors of nervous system and cerebral membranes;**
- **f) tumors of hematopoietic and lymphoid tissue;**
- **g) teratomas .**

thanks