Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

Author:
Grigorii V. Tishchenko, Associate Professor of the Department of Pathological Anatomy, Candidate of Medical Sciences (Ph.D. in Medicine)

METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Tumours: general aspects, carcinogenesis, atypism, diagnostic approach”

Duration: 3 hours

Approved at the meeting of the Department of Pathological Anatomy
(Minutes No. 1 dated 30.08.2025)

2025

EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the general principles of tumour biology, including the definition, nomenclature, and classification of neoplasms. To analyze the fundamental differences between benign and malignant tumours. To examine the mechanisms of carcinogenesis (chemical, physical, and biological factors) and the role of genetic and epigenetic alterations. To define and illustrate the concepts of atypism (morphological, cellular, and molecular) as the hallmark of neoplastic transformation. To master the diagnostic approach to tumours, including clinical, morphological (macroscopic and microscopic), immunohistochemical, and molecular methods. To understand the principles of tumour grading and staging (TNM classification). To emphasize the importance of early diagnosis and the role of the pathologist in oncological practice.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

Know:

- The definition of a tumour (neoplasm) and the basic principles of tumour nomenclature;
- The differences between benign and malignant tumours;
- The main etiological factors and molecular mechanisms of carcinogenesis;
- The concept of atypism (cytological, histological, and functional) and its diagnostic significance;
- The principles of tumour diagnosis (clinical, morphological, immunohistochemical, molecular);
- The TNM classification system for tumour staging;
- The possible outcomes and complications of neoplastic growth.

Be able to:

- Distinguish benign from malignant tumours based on macroscopic and microscopic features;
- Identify major general pathological processes and diseases using histological specimens under light microscopy;

- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body;
- Interpret basic immunohistochemical markers used in tumour diagnosis.

Master:

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

Neoplastic diseases represent one of the leading causes of morbidity and mortality worldwide. Understanding the general principles of tumour biology, carcinogenesis, and the diagnostic approach is essential for all physicians, regardless of their future specialty. Early and accurate diagnosis of tumours significantly improves patient prognosis and survival. Knowledge of the morphological features of neoplasms, the ability to distinguish benign from malignant lesions, and familiarity with modern diagnostic techniques (including immunohistochemistry and molecular pathology) are indispensable for clinical practice, treatment planning, and the analysis of diagnostic errors. This topic forms the foundation for understanding specific tumour types and their clinical management.

QUESTIONS

1. Tumors. Definition. Classification. Properties of tumors.
2. Cellular and tissue atypism.
3. Tumor growth. Examples of tumors with different types of growth.
4. Theories of carcinogenesis.
5. Metastasis. Pathways and stages of metastasis.
6. Clinical aspects of neoplasia. Diagnosis of cancer.

COURSE OF THE SESSION

The term “neoplasia” (from Greek, meaning “new growth”) and its related terms “neoplasm” or “tumor” refer to an abnormal, uncontrolled growth of cells.

In a healthy adult, cellular proliferation and maturation are strictly regulated processes, categorized into three types based on their proliferative capacities:

1) **Labile Cells**: Continuously dividing cells, with ongoing proliferation throughout life (e.g., skin, gastrointestinal lining).

2) **Stable Cells**: Cells with limited capacity to divide, proliferating only when needed (e.g., liver, kidney cells).

3) **Permanent Cells**: Cells that do not normally replicate post-maturation (e.g., neurons, cardiac muscle).

Definition and Characteristics

Neoplastic cells, however, lose this regulatory control, resulting in abnormal cellular replication. They form a mass of tissue that grows autonomously and uncoordinatedly, without functional purpose. Thus, a **neoplasm** or **tumor** is defined as “*a mass of tissue formed due to abnormal, excessive, unregulated, and purposeless cellular proliferation*”

Oncology is the branch of medicine dedicated to studying neoplasms or tumors. Neoplasms are broadly categorized into two types:

1) **Benign Neoplasms**: These are typically slow-growing, localized masses that do not spread and usually pose minimal risk to the host.

2) **Malignant Neoplasms** (Cancer): These are aggressive, rapidly proliferating cells that invade surrounding tissues, spread to distant sites (metastasis), and can lead to host mortality.

Malignant neoplasms are commonly referred to as **cancer**, a term encompassing all forms of these potentially fatal tumors.

Etiology and pathogenesis

Extensive clinical, experimental, and epidemiological research in oncology aims to uncover the causes of cancer and elucidate the transformation of normal cells into neoplastic (tumor) cells. It is well understood that no single factor is solely responsible for tumor development. Some causative factors have established roles in neoplasia, while others are supported by epidemiological data, and many potential factors remain unknown.Based on current knowledge, the factors contributing to neoplastic transformation can be categorized into two main groups:

1) **Predisposing Epidemiologic Factors or Carcinogenic Cofactors**

This category includes a range of internal (endogenous) host factors and external (exogenous) environmental influences that can increase susceptibility to cancer.

- **Endogenous Factors**: Genetics, age, sex, and hormonal imbalances.
- **Exogenous Factors**: Lifestyle, diet, tobacco use, and exposure to certain environmental carcinogens.

Etiology and pathogenesis

2) **Carcinogenesis**

This category focuses on exogenous agents directly involved in triggering cancerous transformation. These agents include:

- **Chemical Agents**: Tobacco, industrial chemicals, and certain medications.
- **Physical Agents**: Radiation (e.g., UV light, ionizing radiation).
- **Hormonal Agents**: Excessive or abnormal hormone exposure, particularly relevant in hormone-sensitive tissues.
- **Biological Agents**: Viral infections (e.g., HPV, hepatitis B virus), indirect effect of some bacteria (e.g., Helicobacter pylori).

These two groups highlight the complexity of cancer causation, involving both intrinsic host susceptibilities and external carcinogens that initiate and promote the neoplastic process.

Epidemiologic factors

Cancer Incidence and Epidemiological Patterns

The incidence of cancer in a population is determined through systematic cancer case registration (cancer registries) and by analyzing cancer-related mortality rates. Currently, cancer is estimated to account for approximately 20% of all deaths. Cancer incidence patterns vary by sex and geographic location, with some types showing marked regional and temporal differences.

Familial and Genetic Factors in Cancer

Familial predisposition and genetic inheritance are recognized as contributing factors in cancer development. Individuals with a family history of cancer face an almost threefold increased risk of developing the disease compared to those without such a history. However, it is estimated that purely genetic cancers make up less than 5% of all cases, underscoring that while genetic factors play a role, most cancers arise from a combination of environmental and genetic influences.

Familial and genetic factors

1) **Familial Adenomatous Polyposis (FAP)**

An autosomal dominant condition, FAP, also known as familial polyposis coli, is characterized by the development of numerous adenomatous polyps in the colon, typically starting in adolescence. Without intervention, nearly all individuals with FAP will develop colorectal cancer by the age of 50.

2) **Hereditary Breast and Ovarian Cancer (HBOC) Syndrome**

Mutations in the BRCA1 and BRCA2 genes are associated with a significantly elevated risk of breast and ovarian cancers. Female relatives of breast cancer patients have a 2- to 3-fold increased risk of developing breast cancer, especially in families with BRCA mutations.

3) **Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)**

Lynch syndrome is an autosomal dominant condition that raises the risk of colorectal cancer as well as other cancers, including endometrial, stomach, and ovarian cancers. It is caused by inherited mutations in mismatch repair genes.

4) **Li-Fraumeni Syndrome**

Caused by mutations in the TP53 tumor suppressor gene, Li-Fraumeni syndrome predisposes individuals to a variety of early-onset cancers, including sarcomas, breast cancer, brain tumors, and adrenal cortical carcinomas.

5) **Von Hippel-Lindau (VHL) Disease**

This autosomal dominant disorder results from mutations in the VHL tumor suppressor gene. VHL disease is associated with various tumors, including renal cell carcinoma, pheochromocytoma, and hemangioblastomas of the central nervous system.

6) **Peutz-Jeghers Syndrome (PJS)**

An autosomal dominant condition caused by mutations in the STK11 gene, PJS is characterized by gastrointestinal polyps and an increased risk of several cancers, including gastrointestinal, breast, pancreatic, and ovarian cancers.

Racial and geographic factors

While genetic predisposition can play a role, environmental and lifestyle factors, including climate, diet, infection rates, and cultural practices, have a substantial impact on cancer risk in different populations.

1) **White Europeans and Americans** commonly experience high incidences of lung, breast, and colon cancers, while liver cancer is relatively uncommon.

2) **Black Africans.** In African populations, cancers of the skin, penis, cervix, and liver are more prevalent. Environmental exposures, such as high UV radiation and endemic infections (HPV for cervical cancer, hepatitis viruses for liver cancer).

3) **Japanese.** The incidence of stomach cancer in Japan is five times higher than in American and European populations. This is thought to be related to dietary factors, including high consumption of salted, smoked, and pickled foods.

4) Nasopharyngeal cancer is more common among **South-East Asians** of **Chinese** descent. This is thought to be linked to high intake of salted fish and exposure to Epstein-Barr virus.

5) **Indigenous Australians and Pacific Islanders** experience elevated rates of liver and biliary cancers, often related to chronic hepatitis B, and certain regions within these populations also show high rates of esophageal cancer, possibly due to consumption of very hot beverages.

6) Among **South Asians**, oral cancer is common, especially in India and Pakistan, due to the widespread practice of chewing betel quid, areca nut, and tobacco. Gallbladder cancer is also more frequent in northern India and Bangladesh.

Environmental factors

We are constantly exposed to carcinogens in our environment, which we ingest, inhale, and come into contact with.

1) **Cigarette Smoking**: The most significant environmental factor for cancers of the oral cavity, pharynx, larynx, esophagus, lungs, pancreas, and urinary bladder.

2) **Alcohol and Tobacco**: Combined use significantly increases the risk of cancers in the upper aerodigestive tract, esophagus, and liver.

3) **Occupational and Environmental Carcinogens**: Many industrial substances, such as arsenic, asbestos, benzene, vinyl chloride, and naphthylamine, are carcinogenic and pose occupational hazards to certain populations.

Age factors

Cancer incidence tends to increase with age, particularly after the 5th decade of life, with the majority of cancers being diagnosed in older individuals.

This rise in incidence could be due to several factors, including **longer exposure** to environmental carcinogens, **accumulation of genetic mutations** over time, and a **decline in immune function** that impairs the body's ability to detect and eliminate cancerous cells.

Some cancers, such as acute leukemias, have two distinct peaks in incidence: one in early childhood and another in older adults.

Additionally, the behavior of tumors in children often differs from that in adults, with some pediatric cancers exhibiting more aggressive features, even when histologically similar to adult cancers.

Sex factors

Cancer incidence also varies by sex, with many cancers being more common in men than women.

For instance, cancers of the prostate, lung, and liver are more prevalent in men, while cancers of the breast, gallbladder, thyroid, and hypopharynx occur more frequently in women.

These differences can often be attributed to the influence of **sex hormones**.

For example, the higher incidence of **breast cancer** in women is strongly linked to **estrogen** and **progesterone**, which stimulate tumor growth in hormone-sensitive breast tissues.

In contrast, the higher incidence of **prostate cancer** in men is influenced by androgens, such as **testosterone**.

Premalignant lesions (tumour progression)

Premalignant lesions are conditions that predispose individuals to cancer development. These lesions often display cellular changes such as increased nuclear-cytoplasmic ratio, pleomorphism and increased mitotic activity.

1) **Intraepithelial neoplasia** (IN) occurs when cytological features of malignancy are present, but the malignant cells are confined to the epithelium without crossing the basement membrane. This condition can range from mild to severe, with carcinoma in situ representing the most advanced stage. If left untreated, IN has a high risk of progressing to invasive cancer.

2) **Chronic inflammatory conditions** can increase the risk of cancer. For example, chronic ulcerative colitis increases the likelihood of developing colorectal cancer. Chronic gastritis, especially when caused by Helicobacter pylori infection, can predispose to gastric cancer. Chronic pancreatitis is associated with an elevated risk of pancreatic cancer.

3) Certain **hyperplastic conditions** also predispose to malignancy. For example, endometrial hyperplasia can lead to endometrial carcinoma, particularly when it is associated with atypia. Similarly, actinic keratosis, a skin condition caused by chronic sun exposure, can progress to squamous cell carcinoma. These hyperplastic lesions often exhibit cellular changes that increase the potential for malignancy.

Carcinogenesis

Carcinogenesis refers to the complex process by which normal cells transform into cancerous cells, eventually leading to tumor formation. This process involves a series of genetic, epigenetic, and environmental changes that drive the uncontrolled proliferation of cells. Carcinogenesis can result in both **benign** and **malignant tumors**.

The term carcinogenesis is often used interchangeably with **oncogenesis** and **tumorigenesis**, which all describe the biological mechanisms underlying tumor formation. *Oncogenesis* refers specifically to the formation of tumors driven by oncogenes, which are mutated versions of normal genes (proto-oncogenes) that promote cell growth and division. *Tumorigenesis* emphasizes the overall process of tumor formation, which involves both genetic mutations and the influence of environmental factors.

Carcinogenesis is influenced by both **intrinsic factors** (such as genetic predisposition) and **extrinsic factors** (such as exposure to carcinogens).

Stages of Carcinogenesis

1) **Initiation**: This is the first step, where a normal cell undergoes genetic damage (mutation) that can make it more prone to uncontrolled growth. Initiation is often caused by exposure to carcinogens such as chemicals, radiation, or viruses.

2) **Promotion**: During this stage, the initiated cell undergoes further changes that enhance its growth and survival, usually under the influence of specific promoters (e.g., hormones, inflammatory mediators, or chronic irritation). This step is reversible and does not by itself result in cancer, but it increases the likelihood of the initiated cell progressing to a malignant state.

3) **Progression**: This phase involves the accumulation of additional mutations, leading to the development of a malignant tumor. These mutations enable the tumor cells to become increasingly aggressive, allowing them to invade surrounding tissues, evade the immune system, and acquire the ability to metastasize to distant organs.

4) **Metastasis**: In this final stage, tumor cells spread from their original site to distant organs through the bloodstream or lymphatic system, forming secondary tumors. This is characteristic of malignant cancers, making them more difficult to treat.

Groups of Carcinogens

1) **Chemical Carcinogens**

These are substances that directly damage DNA or affect cellular processes, leading to cancer. Examples include tobacco smoke, industrial chemicals (e.g., benzene, asbestos), and certain food additives.

2) **Physical Carcinogens**

These include various forms of radiation that can damage DNA and promote tumor formation. Ionizing radiation (e.g., X-rays, radon) and ultraviolet (UV) radiation from the sun are common examples.

3) **Hormonal Carcinogens**

Hormones can act as carcinogens when they influence cell proliferation. For example, prolonged exposure to estrogen is linked to the development of breast and endometrial cancers, while androgens may contribute to prostate cancer.

4) **Biologic Carcinogens** (*mainly viruses*)

Certain viruses can induce carcinogenesis through their ability to integrate into the host genome and alter cellular functions. Examples include human papillomavirus (HPV) in cervical cancer, hepatitis B and C viruses in liver cancer, and Epstein-Barr virus (EBV) in nasopharyngeal cancer.

Biologic carcinogenesis

Some of the most well-known cancer-causing **viruses** include:

1) **Human Papillomavirus (HPV)**: This virus is strongly linked to cancers of the cervix, anus, and oropharynx. HPV, particularly the high-risk strains (e.g., HPV-16 and HPV-18), can cause cellular changes that lead to cervical dysplasia and eventually cervical cancer. HPV also plays a role in the development of other cancers, such as vulvar, penile, and head and neck cancers.

2) **Hepatitis B and C Viruses (HBV, HCV)**: These viruses are major contributors to liver cancer (hepatocellular carcinoma). Chronic infection with HBV or HCV causes persistent liver inflammation, leading to cirrhosis and an increased risk of developing liver cancer.

3) **Epstein-Barr Virus (EBV)**: EBV is associated with several cancers, including nasopharyngeal carcinoma, Burkitt lymphoma, and certain types of Hodgkin lymphoma. It can infect B cells and induce genetic changes that promote tumorigenesis.

4) **Human T-Cell Lymphotropic Virus (HTLV-1)**: This virus is linked to adult T-cell leukemia/lymphoma (ATL). It infects T-cells, leading to genetic mutations and cellular transformation.

Biologic carcinogenesis

In addition to viruses, some **parasites** have been identified as contributors to cancer development. One of the most well-known examples is schistosomiasis, caused by the **Schistosoma** species of parasites. Chronic infection with Schistosoma haematobium is linked to an increased risk of bladder cancer, particularly in regions like Egypt, where the infection is endemic. The parasite causes long-term inflammation and scarring in the bladder, which can eventually lead to carcinogenesis.

In more recent years, certain **bacteria** have also been implicated in carcinogenesis. One of the most prominent examples is Helicobacter pylori, a bacterium that infects the stomach lining. Chronic infection with H. pylori is a major risk factor for gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. The bacterium induces inflammation and alters the local environment of the stomach, leading to DNA damage and mutations that can result in cancer.

DNA Oncogenic Viruses

DNA oncogenic viruses are classified into five subgroups, each capable of producing neoplasms in different hosts. These viruses play a significant role in carcinogenesis by either integrating their genetic material into host DNA or by promoting cellular changes that lead to uncontrolled cell growth. The five major subgroups of DNA oncogenic viruses include **Papovaviruses**, **Herpesviruses**, **Adenoviruses**, **Poxviruses**, and **Hepadnaviruses**.

I. **Papovaviruses**

This group includes the Human Papillomavirus **(HPV)**, **Polyoma virus**, and **SV-40** (Simian Vacuolating Virus). HPV is particularly significant in causing skin warts (**papillomas**), **epidermodysplasia verruciformis**, and **squamous cell carcinoma**, particularly in sun-exposed areas where warts are present. Some strains of HPV are linked to the development of **genital warts** (condyloma acuminata) and are implicated in **cervical cancer**. HPV is also associated with the formation of **juvenile laryngeal papillomatosis** in children, which results in the growth of multiple papillomas in the larynx.

DNA Oncogenic Viruses

II. Several members of the **herpesvirus** family have been implicated in oncogenesis:

1) Epstein-Barr Virus **(EBV)** is linked to **Burkitt's lymphoma** and **nasopharyngeal carcinoma** (anaplastic type).

2) Herpes Simplex Virus Type 2 **(HSV-2)** is associated with **genital cancers**, particularly in immunocompromised individuals.

3) Human Herpesvirus 8 **(HHV-8)** is strongly linked to **Kaposi's sarcoma**, a vascular malignancy that occurs more frequently in individuals with **AIDS**.

4) Cytomegalovirus **(CMV)** and other viruses like **Lucke's frog virus** and **Marek's disease virus** in animals can also have oncogenic potential, though their role in human cancers is less well-established.

DNA Oncogenic Viruses

III. While **Adenoviruses** are primarily known for causing upper respiratory infections and **pharyngitis** in humans, they are not directly linked to oncogenesis in humans. They are, however, used experimentally in gene therapy and cancer research due to their ability to infect cells and their potential for gene delivery.

IV. **Poxviruses** are known for causing skin lesions and can induce **squamous cell papillomas** in certain cases. The most notable poxvirus, **Molluscum contagiosum virus**, causes benign, wart-like growths on the skin. Poxviruses are not typically linked to malignancies but may induce abnormal cell proliferation in some instances.

V. The Hepatitis B Virus **(HBV)**, a member of the **Hepadnavirus** family, is a major etiological agent in **liver cancer** (hepatocellular carcinoma). HBV causes **acute hepatitis**, and in some cases, it leads to a **chronic carrier state**, increasing the risk of **chronic hepatitis**, **hepatic cirrhosis**, and subsequent development of liver cancer.

RNA Oncogenic Viruses

RNA oncogenic viruses are mainly **retroviruses**, which contain the enzyme **reverse transcriptase**, enabling the conversion of viral RNA into DNA. This viral DNA can then integrate into the host genome, potentially causing cancer. Retroviruses are classified into three groups based on how they induce cancer:

1) **Acute Transforming Viruses**
These retroviruses carry **oncogenes** that directly cause rapid transformation of cells into cancerous ones. Example: **Avian Sarcoma Virus**, which causes tumors quickly in animals.

2) **Slow Transforming Viruses**
These viruses do not carry oncogenes but induce cancer through the insertion of their viral DNA near **proto-oncogenes** in the host genome. Example: **Murine Leukemia Virus (MLV)**, which causes leukemia in animals over time.

3) **Human T-cell Lymphotropic Virus (HTLV)**
HTLV-1 causes **Adult T-cell Leukemia/Lymphoma (ATLL)** in humans by infecting T-cells and inducing cancer over a long period. The viral protein **Tax** promotes cell growth and malignancy.

Theories of carcinogenesis

Carcinogens may induce neoplasms through various mechanisms, and often, multiple mechanisms are involved in the development of cancer. Some of the prominent theories explaining carcinogenesis include:

1) **Genetic Theory**

This is the most widely accepted theory, suggesting that neoplastic transformation occurs due to **DNA alterations**. Mutations in critical genes lead to uncontrolled cell growth, and these mutated cells pass on their altered genetic material to subsequent generations of cells.

2) **Epigenetic Theory**

This theory posits that carcinogenic agents do not directly alter genes but instead affect **gene regulators**, such as activators or suppressors. This leads to abnormal gene expression, contributing to tumorigenesis without altering the genetic code itself.

3) **Multi-Step Theory**

Carcinogenesis is viewed as a **multi-step process**, involving **initiation** (genetic mutations) and **promotion** (stimulation of growth by external factors). Over time, successive mutations accumulate, leading to the activation of oncogenes and inactivation of tumor suppressor genes, ultimately resulting in invasive carcinoma. Some cancers follow a stepwise progression from dysplasia to carcinoma in situ, and then to invasive cancer.

4) **Immune Surveillance Theory**

This theory suggests that an **immune-competent host** can detect and destroy emerging tumor cells. In contrast, an **immune-incompetent host** fails to mount an effective immune response, allowing tumor cells to evade destruction and proliferate.

5) **Monoclonal Hypothesis**

Strong evidence supports the idea that most cancers arise from a **single clone** of transformed cells. This hypothesis suggests that a single genetic mutation or set of mutations initiates the neoplastic process, leading to the clonal expansion of the cancer cells.

Classification of tumours

1) **Epithelial Tumors** (**Organ-Nonspecific**) arise from epithelial cells but do not have a specific organ origin. They can occur in various tissues, including skin and mucous membranes. Example: Squamous cell carcinoma of the skin.

2) **Epithelial Tumors of Exocrine and Endocrine Glands** (**Organ-Specific**)

Tumors that originate from the epithelial cells of glandular tissues. These can be further categorized based on whether they are exocrine (e.g., pancreatic adenocarcinoma) or endocrine (e.g., thyroid carcinoma). These tumors are often localized to the organ of origin.

3) **Mesenchymal Tumors** develop from mesodermal tissues, which include connective tissues, muscles, bone, and cartilage. Examples include fibrosarcoma (from connective tissue) and osteosarcoma (from bone).

4) **Tumors of Melanin-Forming Tissue** arise from melanocytes, the pigment-producing cells of the skin. The most well-known example is melanoma, a malignant tumor of melanocytes, often associated with sun exposure.

5) **Tumors of the Nervous System** arise from the cells of the nervous system or its supporting structures, including the brain, spinal cord, and meninges. Examples include gliomas (from glial cells) and meningiomas (from the meninges).

6) **Hematologic Tumors** originate in the hematopoietic system, including blood and lymphatic cells. These include leukemias (cancers of blood-forming tissues) and lymphomas (cancers of the lymphatic system).

7) **Tumors of the APUD System** (amine precursor uptake and decarboxylation) system includes cells that produce hormones or neuropeptides. Tumors from these cells, such as carcinoid tumors and paragangliomas, are classified here and often occur in the gastrointestinal tract or other neuroendocrine sites.

8) **Teratomas** are the tumors that contain tissues from multiple germ layers (ectoderm, mesoderm, and endoderm), often arising from germ cells in the gonads (ovaries or testes) but also in midline locations. Mature teratomas may contain a variety of tissues, such as hair, teeth, and bone.

Characteristics of tumours

Majority of neoplasms can be categorized morphologically into **benign** and **malignant** on the basis of certain characteristics, the most important being the degree of differentiation of the tumour cells.

1) Macroscopic features
2) Microscopic features
3) Growth rate
4) Local invasion (direct spread)
5) Metastasis (distant spread)

Macroscopic features

The macroscopic appearance of tumors can vary significantly even within the same tumor type, and gross examination alone is often not sufficient for a definitive diagnosis. However, certain features are commonly observed in tumors, distinguishing them from the surrounding normal tissue. These features include differences in **color**, **texture**, and **consistency**.

Gross descriptions used to characterize tumors include terms like **papillary** (finger-like projections), **fungating** (irregular, cauliflower-like growth), **infiltrating** (spreading into surrounding tissue), **hemorrhagic** (containing blood), **ulcerative** (causing surface ulceration), and **cystic** (containing fluid-filled spaces).

In hollow organs, tumors can exhibit different growth patterns: **exophytic** growth, where the tumor grows outward into the organ lumen; **endophytic** growth, where the tumor grows inward into the organ wall; or **mixed growth**, where the tumor grows both into the lumen and the wall.

Types of tumor growth

1) *Benign Growth*:

- **Expansile Growth**: Benign tumors tend to grow in a localized and expansile manner, pushing aside normal tissues without invading them.
- **Encapsulation**: Benign tumors are often encapsulated, meaning they are surrounded by a well-defined fibrous or connective tissue capsule that separates them from the surrounding normal tissue.
- **Slow and Uniform Growth**: Benign tumors typically grow slowly and maintain a uniform appearance. They do not invade adjacent tissues or spread to distant parts of the body.

2) *Mixed Pattern of Growth*:

- **Locally Invasive but Non-Metastatic**: Some tumors may display characteristics of both benign and malignant growth, being locally invasive but not capable of metastasizing. These are sometimes referred to as locally aggressive tumors.

3) *Malignant Growth*:

- **Invasive Growth**: Malignant tumors, on the other hand, often display invasive growth, infiltrating surrounding tissues and organs. This invasion can make complete surgical removal challenging.
- **Metastasis**: Malignant tumors have the ability to metastasize, meaning they can spread to distant sites through the bloodstream or lymphatic system, forming secondary tumors in other parts of the body.
- **Angiogenesis**: Malignant tumors stimulate the formation of new blood vessels (angiogenesis) to ensure a blood supply, facilitating their rapid and uncontrolled growth.
- **Variable Growth Rate**: Malignant tumors can exhibit variable growth rates, with some areas growing more rapidly than others, contributing to their heterogeneity.

Microscopic features

1) **Microscopic Pattern**

Epithelial tumors typically exhibit structures such as **acini**, **sheets**, **columns**, or **cords** of epithelial cells, often arranged in either solid or papillary patterns. Benign and low-grade malignant tumors often retain the original tissue architecture closely, making them relatively easy to identify and classify. In contrast, **anaplastic** or **high-grade tumors** often show significant deviations from the normal structure of the tissue, which can complicate their classification.

2) **Tumor Differentiation**

Differentiation refers to the extent to which tumor cells resemble normal cells in both structure and function. Tumors that closely resemble normal cells are considered **well-differentiated**, which is typically seen in most benign and low-grade malignant tumors. Conversely, **poorly differentiated**, **undifferentiated**, or

dedifferentiated tumors show significant deviations in structure and function, reflecting a loss of normal cell characteristics.

Tumor atypia

1) **Tissue atypia** involves changes in the spatial arrangement of cells while maintaining their basic structure.

2) **Cellular atypia** refers to changes in the cell's structure, such as pleomorphism, hyperchromatic nuclei, increased mitotic activity, and a high nucleocytoplasmic ratio.

3) **Biochemical atypia**: Changes in metabolic activities of tumor cells.

4) **Histochemical atypia**: Altered enzyme activity or cellular staining properties.

5) **Antigenic atypia**: Altered expression of cell surface antigens, often affecting immune recognition.

6) **Functional atypia**: Loss or alteration of normal cell functions, such as secretion or motility.

Growth rate

Tumor cells typically proliferate more rapidly than normal cells. While benign tumors generally grow slowly and malignant tumors grow rapidly, there are exceptions. The rate of tumor enlargement depends on three main factors:

1) **Rate of Division and Destruction of Tumor Cells**

The rate at which tumor cells divide is influenced by two factors: the **mitotic index** (the proportion of cells undergoing mitosis) and the duration of the mitotic cell cycle. High cell division rates can lead to **ischemic necrosis** in the tumor center due to insufficient nourishment. As a result, despite rapid cell division, tumor enlargement may slow down if the tumor outgrows its blood supply.

2) **Non-Neoplastic Elements in the Tumor**

These elements include the **connective tissue stroma**, **mucoid material**, **cartilaginous matrix**, and other components that support the tumor but do not contribute to its malignancy. The presence and composition of these elements can impact the rate of tumor growth by affecting structural integrity and blood supply.

3) **Degree of Differentiation**

In general, the growth rate of a malignant tumor is inversely related to its degree of differentiation—more poorly differentiated tumors tend to grow more rapidly. Some tumors that grow steadily may experience a sudden increase in growth rate due to the emergence of more aggressive clones of malignant cells.

Conversely, certain tumors may stop growing after a time, and rarely, a malignant tumor like **choriocarcinoma** or **malignant melanoma** may regress spontaneously, potentially due to immune responses, only to recur as secondary tumors at distant sites.

Local invasion (direct spread)

Most **benign tumours** form **encapsulated** or **circumscribed masses** that push aside the surrounding normal tissues without actually invading, infiltrating or metastasizing. Malignant tumours also enlarge by expansion and some well-differentiated tumours may be partially encapsulated as well. But characteristically, they are distinguished from benign tumours by **invasion**, **infiltration** and

destruction of the surrounding tissue, besides distant metastasis (described below). In general, tumours invade via the **route of least resistance**, though eventually most cancers recognize no anatomic boundaries.

Often, cancers extend through **tissue spaces**, permeate **lymphatics**, **blood vessels**, **perineural spaces** and may penetrate a bone by growing through **nutrient foramina**. More commonly, the tumours invade thin-walled capillaries and veins than thick-walled arteries. Dense compact collagen, elastic tissue and cartilage are sufficiently resistant to invasion by tumours.

When the tumour cells cross the basement membrane, it is referred to as invasive cancer.

Metastasis (distant spread)

Metastasis is defined as **spread of tumour by invasion** in such a way that discontinuous **secondary tumour mass/masses** are formed at the site of lodgment. Metastasis is the most important feature to distinguish malignant from benign tumours. Usually **benign tumours do not metastasize** while malignant tumours do, with a few exceptions (CNS gliomas, basal cell carcinoma of the skin).

Generally, larger, more aggressive and rapidly-growing tumours are more likely to metastasize but there are numerous exceptions.

Metastasis is a **common event in malignant tumours** which greatly reduces the survival of patient. In the biology of tumour, metastasis is a form of unusual cell differentiation in which the tumour cells form disorderly masses at ectopic sites and start growing there.

This random phenomenon takes place in a stepwise manner involving only a subpopulation of tumour cells selectively.

Routes of metastasis

Cancers may spread to distant sites by following pathways:

1) **Lymphatic spread** occurs primarily in carcinomas and leads to regional lymph node involvement, which can be an early sign of cancer metastasis.

2) **Hematogenous spread** is common in sarcomas and some carcinomas, and involves cancer cells traveling through the blood to distant organs, such as the liver, lungs, bones, and brain.

3) **Implantation** occurs when tumor cells invade adjacent tissues or organs, especially in body cavities, and may happen spontaneously or due to surgery or trauma. This is common in cancers like ovarian, mesothelioma, and endometrial cancers.

Lymphatic spread

Lymphatic spread occurs when cancer cells invade nearby lymphatic vessels and travel to regional lymph nodes or distant areas of the body. The lymphatic system is a primary pathway for carcinomas (cancers of epithelial origin) to spread. The lymphatic vessels, which carry lymph (a fluid that circulates immune cells), provide a direct route for cancer cells to reach nearby or distant lymph nodes, and from there, they may travel to other organs.

1) **Breast Cancer:** Typically spreads first to axillary (underarm) lymph nodes. If it advances, it can travel to distant nodes or organs such as the lungs, liver, and bones.

2) **Squamous Cell Carcinoma (SCC):** In cancers like SCC of the head and neck or skin, lymphatic spread can cause swelling and enlargement of nearby lymph nodes.

3) **Gastrointestinal Cancers:** Colorectal cancer often spreads to regional lymph nodes and then to distant organs such as the liver, as the lymphatics drain into the portal circulation.

Mechanism: Cancer cells use the lymphatic system to move from primary tumors into lymph nodes, where they may grow and form secondary tumors. This form of spread is often used as a diagnostic tool since lymph node involvement is closely associated with cancer staging.

Hematogenous spread

Hematogenous spread involves the dissemination of cancer cells through the bloodstream. Cancer cells gain access to blood vessels (mainly veins), circulate through the body, and settle in organs that have a rich blood supply, forming secondary tumors. Blood vessels such as veins, capillaries, and arteries all serve as transport systems for these cells, but veins are typically more involved because they have thinner walls and lower pressure compared to arteries.

1) **Renal Cell Carcinoma:** Often spreads hematogenously to the lungs, liver, and bones. The tumor may invade the renal vein and from there enter the inferior vena cava, which allows the cancer to reach distant sites through the bloodstream.

2) **Colorectal Cancer:** Spreads primarily through the portal venous system to the liver. Colorectal tumors often metastasize to the liver first because of the venous drainage of the colon into the hepatic portal system.

3) **Lung Cancer:** Can spread through both the blood and lymphatics. Hematogenous spread may lead to metastasis in the brain, bones, and liver.

Mechanism: After entering the bloodstream, cancer cells must survive immune surveillance and the shear stress of blood circulation. They eventually lodge in organs with smaller capillaries, like the liver, lungs, or bones, where they can establish new tumors.

Implantation

Implantation, also known as **direct spread**, occurs when cancer cells physically invade neighboring tissues or body cavities. This form of spread is typically seen in cancers that arise near body cavities or organs, and it may happen through mechanical factors like surgery or trauma, as well as natural growth and invasion. Cancer cells spread to adjacent tissues or distant sites within the same cavity by seeding.

1) **Ovarian Cancer:** Frequently spreads by implantation into the peritoneum, causing peritoneal carcinomatosis. Ovarian tumors may shed cells into the abdominal cavity, where they implant on the peritoneal surfaces or other organs like the liver or intestines.

2) **Mesothelioma:** A cancer of the pleura, peritoneum, or pericardium can spread within these body cavities, especially in the case of asbestos exposure. The tumor invade the peritoneum and pleura and then implant in tissues within the same cavity.

3) **Endometrial Cancer:** May spread via implantation in the pelvic cavity. Tumor cells can be shed from the uterus and implant on surrounding structures such as the ovaries, fallopian tubes, or bladder.

Mechanism: Tumor cells in direct contact with adjacent tissues or body cavities shed individual cells that are not contained by the basement membrane, allowing them to invade neighboring structures.

TNM classification

T describes the size of the original (primary) tumor and whether it has invaded nearby tissue

N describes nearby (regional) lymph nodes that are involved

M describes distant metastasis (spread of cancer from one part of the body to another)

Clinical aspects of neoplasia

The interaction between a tumor and its host is critical in determining the course of the disease, the prognosis, and the management strategies.

Two main aspects of this interaction are:

1) **Effect of Tumor on Host**

2) **Host Response Against Tumor** (Immunology of Cancer)

Local Effects

1) **Invasion and Compression**: As the tumor grows, it may invade surrounding tissues, causing local damage. This can result in the destruction of normal tissue and the compression of nearby structures. For example, a brain tumor may cause neurological deficits due to compression of the brain tissue.

2) **Obstruction**: Tumors can obstruct the normal function of organs. For instance, a colon tumor can cause bowel obstruction, leading to symptoms such as constipation, vomiting, or even bowel perforation.

3) **Ulceration and Bleeding**: Tumors, especially those in epithelial tissues, can ulcerate and cause bleeding. Gastric cancer may lead to gastrointestinal bleeding, presenting as vomiting blood or black stools.

4) **Pain**: Tumors often cause pain by compressing nerves or infiltrating bone and other sensitive structures. Bone cancers, for example, can result in severe localized pain.

Generalized Effects

1) **Cachexia**: A condition of severe weight loss, muscle wasting, and fatigue that occurs in many cancers, often due to the release of pro-inflammatory cytokines by the tumor. This metabolic wasting is a hallmark of advanced cancer and contributes significantly to morbidity.

2) **Endocrine Effects**: Some tumors produce hormones or hormone-like substances, leading to paraneoplastic syndromes. For example, small-cell lung cancer may produce ACTH (adrenocorticotropic hormone), leading to Cushing's syndrome.

3) **Fever and Systemic Symptoms**: Tumors can induce fever, night sweats, and generalized weakness. These systemic effects are typically related to the body's immune response to the tumor or the production of cytokines by the tumor.

Host Response Against Tumor

1) **Immune Surveillance**: Normally, the immune system can recognize and destroy abnormal or transformed cells. Immune cells such as T lymphocytes, natural killer (NK) cells, and macrophages are involved in recognizing tumor-associated antigens (TAAs) and eliminating the cancerous cells.

2) **Immune Evasion by Tumors**: Tumors can evade immune detection through mechanisms such as the downregulation of major histocompatibility complex (MHC) molecules, secretion of immunosuppressive cytokines, or by inducing immune tolerance. For example, tumors may release programmed death-ligand 1 (PD-L1) to suppress T-cell activity, thereby preventing an effective immune response.

3) **Tumor-Infiltrating Lymphocytes (TILs)**: Tumors may also attract immune cells into the tumor microenvironment. The presence of tumor-infiltrating lymphocytes can sometimes be indicative of a better prognosis, as it suggests the immune system is actively attempting to combat the tumor. However, the tumor may also manipulate these immune cells to promote its own survival, thus leading to an immunosuppressive environment.

Paraneoplastic Syndromes

Paraneoplastic syndromes are immune-mediated, subacute, and progressive conditions caused by remote effects of malignant tumors (not direct infiltration). Around 10-15% of patients with advanced cancer develop paraneoplastic syndromes, and in rare cases, it may be the first sign of latent cancer.

1) **Endocrine Syndromes** (Ectopic Hormone Production):

- Hypercalcemia: Commonly seen in squamous cell lung cancer, kidney, breast cancers, and adult T-cell lymphoma.
- Cushing’s Syndrome: Found in small cell lung carcinoma, pancreatic carcinoma, and neurogenic tumors.
- Polycythemia: Caused by erythropoietin secretion in renal cell carcinoma or hepatocellular carcinoma.
- Hypoglycemia: Due to insulin-like substances from fibrosarcomas, pancreatic islet cell tumors, and mesotheliomas.

2) **Neuromyopathic Syndromes**: Seen in about 5% of cancers, causing peripheral neuropathy, cerebellar degeneration, myasthenia gravis, and polymyositis, likely mediated by immune mechanisms.

3) **Osseous, Joint, and Soft Tissue Effects**: Includes hypertrophic osteoarthropathy and finger clubbing, especially in bronchogenic carcinoma.

4) **Hematologic & Vascular Syndromes**: Includes venous thrombosis (Trousseau phenomenon), disseminated intravascular coagulation (DIC), leukemoid reaction, and anemia. Autoimmune hemolytic anemia can be linked to B-cell tumors.

5) **Gastrointestinal Syndromes**: Malabsorption and hypoalbuminemia can occur in cancers not involving the small bowel.

6) **Renal Syndromes**: Renal vein thrombosis or systemic amyloidosis leading to nephrotic syndrome in cancer patients.

7) **Cutaneous Syndromes**: Acanthosis nigricans (dark, warty lesions in the axillae and groin) often linked to gastrointestinal adenocarcinomas. Other skin changes like seborrheic dermatitis and exfoliative dermatitis may occur in advanced cancers or lymphomas.

8) **Amyloidosis**: Primary amyloid deposits occur in multiple myeloma, while secondary amyloidosis is linked to renal cell carcinoma and other solid tumors.

Diagnosis of cancer

When cancer is suspected based on clinical examination and other investigations, it is essential to confirm the diagnosis. The most reliable method, which has been the gold standard for diagnosis, is histological examination of a biopsy. However, with advancements in medical technology, there are now various other methods available to confirm the diagnosis or complement the histological findings.

1) **Histological Methods (Histochemistry)**: This involves examining tissue samples (from excised tumors or biopsies) under a microscope, supported by clinical data. Histochemistry uses special stains to identify specific substances in tissues, helping to differentiate between tumor types.

2) **Cytological Methods**: These involve studying cells shed into body cavities (**exfoliative cytology**) or collected from a lesion using fine needle aspiration (**FNAC**).

2.1) **Exfoliative Cytology**: Initially used for detecting cervical dysplasia, carcinoma in situ, and invasive carcinoma, this method has expanded to include sputum, bronchial washings, pleural, peritoneal, and pericardial effusions, urine, gastric secretions, and cerebrospinal fluid.

However, a negative result doesn’t completely rule out malignancy due to potential sampling errors.

2.2) **Fine Needle Aspiration Cytology** (FNAC): Superficial masses can be aspirated under direct vision, while deep-seated lesions (e.g., intraabdominal, pelvic, or retroperitoneal) are often investigated using ultrasound (US) or computed tomography (CT)-guided FNAC.

FNAC has a diagnostic accuracy of 80-97%, but it should complement, not replace, clinical judgment or histopathologic biopsy when needed.

3) **Immunohistochemistry**: This method identifies cells by detecting specific components (antigens) in the cytoplasm, cell membrane, or nucleus.

Formalin-fixed paraffin sections or cytological smears are incubated with specific antibodies, which bind to the antigens.

The antigen-antibody complex is then visualized under a light microscope using fluorescent dyes or enzyme systems.

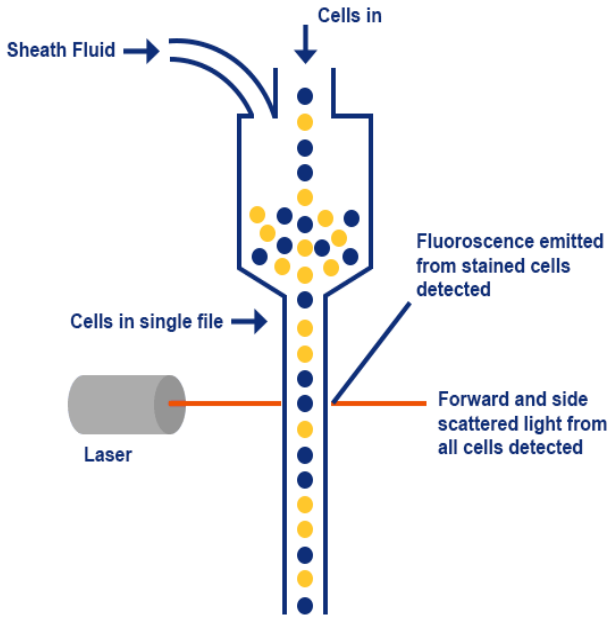
Immunohistochemistry is highly sensitive, providing an objective and reliable means of detecting antigenic components, aiding pathologists in tumor diagnosis.

4) **Electron Microscopy (EM)**: EM provides detailed ultrastructural examination of tumor cells and plays a selective role in diagnostic pathology. It is particularly useful for confirming or supporting diagnoses made through light

microscopy and immunohistochemistry, offering deeper insights into cellular structures and abnormalities.

5) **Modern Methods in Tumour Diagnosis**

5.1) **Flow Cytometry**: Flow cytometry is a computerized technique that analyzes individual tumor cells by measuring their characteristics, such as size, shape, and protein expression. The data collected can be quantified and stored for comparison, aiding in tumor diagnosis and prognosis.



5.2) **In Situ Hybridization**: This molecular technique allows for the localization of specific nucleic acid sequences (DNA or RNA) within intact cells. By using labeled probes, it identifies and maps cellular or viral genetic material directly in tissue samples.

5.3) **Molecular Diagnostic Techniques**: This group includes various DNA and RNA-based methods where genetic material is extracted from cells and analyzed. These techniques are highly sensitive, specific, and fast, providing crucial insights for diagnosing both neoplastic and non-neoplastic conditions, significantly advancing diagnostic pathology.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

1. Pathomorphology : textbook / ed. by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2020. - 327 p., [10] col. inserts : tab.

2. Klatt, E. C. Robbins and Cotran Atlas of Pathology : [with Student Consult Online Access] / Edward C. Klatt. - third edition. - Philadelphia : Elsevier, 2015. - 587 p. : il.

3. Robbins Basic pathology / [ed. by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. - 9th ed. - [Philadelphia] : Elsevier ; Saunders. - 910 p. : ill., scheme, tab.

ADDITIONAL LITERATURE

1. Sobotta. Atlas of human anatomy. [V. 1]. General anatomy and musculoskeletal system / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 400 p. : ill., col. ill.

2. Sobotta. Atlas of human anatomy. [V. 2]. Internal organs / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 259 p. : ill., col. ill.

3. Sobotta. Atlas of human anatomy. [V. 3]. Head, neck, and neuroanatomy / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 370 p. : ill., col. ill.

4. Weir & Abrahams' imaging atlas of human anatomy / ed.: J. D. Spratt [and oth.] ; consultant eds.: J. Weir, P. H. Abrahams. – 5th ed. - [S.l.] : Elsevier, 2017. - xvi, 263 p. : ill.

NORMATIVE LEGAL ACTS AND DOCUMENTS

1. Order of the Ministry of Health of the Republic of Belarus No. 111 of 06/01/1993 "On further improvement of the pathological service of the Republic of Belarus"

Access mode: http://patan.by/menyu/administrativnyie-proczeduryi.html - The date fccess: 20.03.2022.

ELECTRONIC DATABASES

1. Physician's consultant. Electronic Medical Library = Consultant of the doctor. Electronic medical library [Electronic resource] / Publishing group "GEOTAR-Media", LLC "IPUZ". – Access mode: http://www.rosmedlib.ru/ . – Access date: 03/15/2022.

2. Springer Link [Electronic resource] / Springer International Publishing AG. – Access mode: https:link.springer.com. – Date of access: 03/15/2022.