Clinical oncology

educational script and notes

Edited by: prof. MUDr. Samuel Vokurka, Ph.D. **Coauthors:** doc. MUDr. Ondřej Fiala, Ph.D., MUDr. Alena Metelková, Ph.D., MUDr. Tomáš Svoboda, Ph.D., MUDr. Radovan Vojtíšek, Ph.D.
The main literature source: ***Onkologie v kostce. Current Media, Praha, 2018,*** ISBN 978-80-88129-37-0. **Authors:** S Vokurka, P Tesařová, J Abrahámová, V Bajčiová, M Budinský, T Büchler, P Holečková, J Chrastina, E Janů, P Klener, J Klimeš, K Kopečková, Š Kozáková, J Kulhánková, R Lakomý, R Lohynská, J Mraček, D Pavlišta, Z Pechačová, A Poprach, E Sedláčková, L Semerád, M Staník, I Šubrt, P Tesařová, J Tomášek, R Tupý, M Zemanová

Department of Oncology and Radiotherapeutics, Charles University, Faculty of Medicine in Pilsen and University Hospital, Czech Republic
prof. MUDr. Jindřich Fínek, Ph.D., MHA,
Head of the Department, Dean of the Faculty of Medicine in Pilsen

8/2020

- **Carcinogenesis - general characteristics and phases of malignant transformation of cells, genetic basis of carcinogenesis: oncogenes, tumor suppressor genes, DNA repair genes, basic characteristics of tumor cells (Hanahan-Weinberg theory)**

The essence of cancer origin and development (carcinogenesis, malignant transformation) is **damage or mutation of genes** (depending on the circumstances, activating or inhibiting mutations), encoding either proteins promoting cell division and growth (proto-oncogenes turning into oncogenes) or proteins suppressing cell growth and promoting apoptosis (tumor suppressor genes), or proteins providing correction of DNA changes (mutations) (DNA-repair genes). These changes result in intensive cell division - **increased proliferation** and / or **reduced programmed cell death** - apoptosis.
Mutations can be congenital (hereditary), or they are acquired and arise spontaneously during life or by the action of exogenous risk factors (**carcinogens**). The mutation created or present in the cancer-transformed cell (cancer stem cell) is then passed on to the cancer daughter cells forming the **cancer clone** with the presence of any other new mutations. Thus, there may be several individual cell clones with different aggressiveness, sensitivity to oncological treatment, in one tumor (**tumor heterogeneity**).
Carcinogenesis is also conditioned by the failure of anti-tumor immunity and the action of the tissue microenvironment (fibroblasts, endothelium, macrophages, lymphocytes) forming a tumor stroma. The microbial colonisation of the gastrointestinal tract (microbiome) probably also has a role in the function of antitumor immunity.
The course of carcinogenesis is divided into several stages:
Initiation: an initial mutation of a critical gene - the cell has the potential for malignant transformation.
Promotion: takes years - other factors stimulate the growth of a malignant clone
Conversion: malignant clone arises (characterised by deregulation of proliferation and apoptosis).
Progression: accumulation of genetic changes, tumor growth, invasion.
Metastasis: matastatic spread to the lymph nodes and formation of distant metastases.

From the point of view of biological behavior, tumors can be divided into benign and malignant. **Malignant tumors** grow rather faster, more aggressively, infiltratively into the environment and have the ability to metastasize. **Benign tumors** grow slowly and do not metastasize.
In 2000, R. Weinberg and D. Hanahan defined six basic properties of a malignant cell: immortality (unrestricted division), insensitivity to signals leading to cell cycle arrest, elimination of apoptosis, production of own growth signals, increased angiogenesis, capability of tissue invasion and metastasis, deregulation of energy metabolism, ability to escape from the anti-tumor immune response.

- **General course and phases of oncological disease clinically, metastasis, relapse, progression, remission, resistance**

See also the previous chapter. Initially, the tumor grows asymptomatically. The time of first manifestation depends on the localization and growth rate. Imaging methods (CT, MRi) are usually able to diagnose lesions of about 0.5-1cm. However, $1cm^3$ of tumor mass already contains 10^9 cells. The growing population of tumor cells, the growth of the primary tumor and its metastases gradually begin to burden the patient with their local manifestations (eg pain, impaired organ function), but also possibly with so-called paraneoplastic symptoms (see in the separate chapter).
The spread of malignant tumor cells from the site of origin (primary tumor) to other parts of the body and the formation of secondary foci (metastases) - is a gradual process called *the metastatic cascade*. Tumor cell dissemination can occur by infiltration into the surrounding area (per

continuitatem), but also via the lymphatic vessels (eg squamous cell carcinoma of the head-and-neck region metastasizing into the neck lymph nodes) or via blood stream (typically sarcoma metastasizing to the lungs or liver), or as imprint metastases (vulvar cancer). Malignant tumors can also spread in all the above mentioned ways at the same time.
Depending on the type of the malignancy, the natural course of oncological disease can last for a few days (eg acute promyelocytic leukemia) or even several years. Oncological treatment can minimize the manifestations of the disease, slow down its course, or even suppress (cure) it completely. In the course of an oncological incurable disease, the following phases can be distinguished:

a) ***Compensated disease -*** *it can last months or years, oncological treatment contributes to the control of symptoms, intensive and resuscitation care is also provided.*
b) ***Disease in the breaking point phase (decompensation, preterminal phase) -*** *oncological treatment fails, complications develop, the condition worsens, the prognosis is unfavorable within mostly weeks to months, palliative care is provided, indication of intensive and resuscitation treatment is individual.*
c) ***Terminal phase -*** *irreversible worsening, within days to weeks, fully symptomatic, nursing, palliative, hospice care without intensive and resuscitation care is indicated.*

Generally used definitions for evaluation of treatment response and disease state:
Relapse, relapse - return of malignancy activity, after the complete remission was present.
Resistant, refractory disease - after treatment, practically the same extent of malignancy persists, there si insensitivity of the malignancy to the administered treatment.
Progression - worsening and increasing extent of malignancy.
Regression - reduction of malignancy mass and extent.
Partial remission - partial (usually at least one-third or half) regression of malignancy after oncological treatment.
Complete remission - disappearance of malignancy, inability to detect it clinically, by imaging methods, or even ideally by microscopy, however, minimal residual disease at submicroscopic (eg molecular-genetic) level cannot be fully excluded.

- **Paraneoplastic syndromes - the most common types and their treatment (cachexia, hormonal paraneoplastic syndromes, thromboembolism)**

Paraneoplastic symptoms (or symptoms, syndromes) typically in lung cancer patients, pancreatic, gynecological cancer, lymphoma and thymoma, there are symptoms and changes that accompany and are associated with cancer, however, they occur outside the organ and the area affected by the tumor itself or its metastasis. The symptomes can be induced by tumor production signaling agents (eg, cytokines, interleukins, hormone active agents, enzymes, serotonin, etc.) or on an autoimmune basis, eg. onconeuronal antibodies (anti-Hu, anti-Yo) in paraneoplastic neurologist symptoms. The paraneoplastic symptoms may precede weeks, months, or years before the tumor detection. When malignancies are cured they can disappear, but they may also leave some permanent damage (eg autoimmune neurological damage).
General symptoms: fatigue, night sweats, anorexia, weight loss and cachexia, fevers of unknown origin, immunodeficiency (herpes zoster, recurrent infections).
Hematological: hypercoagulation, anemia of chronic (tumor) diseases, leukopenia, leukocytosis, thrombopenia, thrombocytosis. The presence of a tumor increases the risk of thromboembolic events by several times more. The treatment of deep vein thrombosis or pulmonary embolism follows standard medical practice guidelines. In palliative care, however, there may be specific situations in patients with limited prognosis or risk of bleeding and anticoagulation can be

contraindicated. Prophylaxis with low molecular weight heparin is recommended in patients with cancer and limited mobility.
Neurological: myasthenia gravis (typically in thymoma)
Hormonal - endocrinological: caused by the production of a hormone-active molecule corresponding to eg parathromone (hypercalcaemia and hypophosphatemia), antidiuretic hormone (SIADH, Schwartz-Bartter sy. - oedema, hyponatremia), insulin (hypoglycaemia).
Cachexia is a multifactorial syndrome characterized by weight loss with progressive loss of muscle mass and cannot be fully corrected by conventional nutritional support. It results from a combination of reduced food intake and abnormal metabolism (insulin resistance, increased lipolysis, increased production of acute phase proteins and cytokines with systemic inflammatory response). There is anorexia present. Prevalence depends on several factors, the main being the type and stage of the cancer. Approximately 25-30% of cancer patients die from cachexia.
Cutaneous: pruritus, acanthosis nigricans, keratoses, hypertrichosis, cold sores.
Rheumatological: paraneoplastic polyarthritis (seronegative), dermatomyositis, myositis.
Other: nephrotic syndrome, serotonin syndrome in neuroendocrine tumors (flushing, diarrhea, right-heart valve damage).

Treatment and care are based on the specific type of disability and complication. In symptomatic treatment, corticotherapy with eg Prednisone, ideally at the lowest effective dose and in the short term, can generally be used as an option to influence paraneoplastic symptoms.

- **Etiology of cancer - main etiological factors of the external environment (physical, chemical, biological), precancerous (premalignant) lesions, hereditary dispositions**

The origin and development of a tumor (cancer, malignant transformation) is firstly **damage or mutation of genes affecting cell division and growth, apoptosis, or DNA repair.** The onset of cancer is also caused by the failure of anti-tumor immunity and by the microenvironment effect.
Mutations and damage may be congenital and hereditary, or they are acquired and arise spontaneously in the course of life or due to the effects of cancer risk factor (carcinogens).
Carcinogens: chemical molecules, physical and biological effects stimulating tumor transformation - eg UV radiation (typically melanoma), HPV virus (uterine cervix carcinoma, oropharynx), EBV virus (lymphomas), HBV virus (liver cancer), nicotinism (lung cancer), ionizing radiation, radon, polycyclic hydrocarbons, benzpyrene, asbestos, nitrosamines, aflatoxins and others.
Precanceroses - cell and tissue changes, not having the character of malignant tumor, but in a shorter or longer period (up to decades) they can develop into a malignant tumor. There is increased proliferation, increased accumulation of mutations. E.g. dysplasia changes according to the degree of cellular atypia and increasing risk of transition to invasive carcinoma may be of mild, moderate or severe (I, II, III) grade, and **carcinoma in situ is pre-stage of invasive malignancy** (cell changes are already identical to a malignant tumor, however, the basal membrane is preserved and there is no invasion of malignant cell throught it into the of surrounding structures, there are no metastasis - eg ductal carcinoma in situ of the mammary gland). Pre-canceroses most often in the area of mucous membranes are of the clinical character of whitish areas (leukoplakia) or possibly with erythema (erythro-luekoplakia, erythroplakia), or they may may have the character of polyps (typically in gastrointestinal tract), Barrett's esophagus (metaplastic change in the mucosal cells caused by long-term gastroesophageal reflux and chronic inflammation), cervical intraepithelial neoplasia (CIN) of the cervix in association with HPV infection, and myelodysplastic syndrome in hematopoiesis.
Hereditary disposition - there is an increased incidence of malignancies in the family - “inclination” to malignancies. There is no evidence of a clearly defined hereditary severe mutation of a specific gene. The patient inherits poor quality "antitumor" protection (dysfunction of DNA

repair, suppressor genes, antitumor immunity) and it is easier to develop malignancy through carcinogens action. Gradually, over generations, this inclination and disposition to develop cance may decrease.

- **Hereditary cancer syndromes - the most common types (BRCA associated malignancies, FAP, Lynch syndrome)**

Hereditary (hereditary) syndromes are a group of diseases with autosomal dominant inheritance with often high penetrance in the majority of cases. Mostly, there is an inherited germline **mutation affecting tumor suppressor genes or DNA-repair genes.** The affected individual significantly increases the likelihood of cancer, its shifting to a younger age and with the possibility of developing multiple malignancies. **On this basis of inheritance, about 5-10% of malignancies arise.** Suspicion of hereditary cancer is increased in case of development of malignancies at a young age (especially in breast, ovarian and colorectal carcinoma), in case of recurrent cancer, or in case of increased incidence of malignancies in the family. It is advisable to consult a clinical geneticist who, based on the medical history data, can further carry out specific genetic examinations and recommendations. **The most important syndromes include:**

Hereditary syndrome of breast and ovarian cancer - BRCA gene mutation - For carriers of this mutation, the lifetime risk of breast cancer is 80-90%, ovarian cancer is up to 60%, there is also a higher risk for other cancers (in men, prostate cancer is very often). Early close gynecological monitoring and breast control (USG, MRi, mammography) is recommended from practically 20 years old. Prophylactic mastectomy with breast reconstruction and preventive adnexectomy (at the age of about 35-40 years) are recommended, which significantly reduce the risk of developing cancer (up to 5%).
Familial adenomatous polyposis (FAP) - mutation of the APC gene. The development of hundreds to thousands of colorectal polyps with a high risk of early malignant transformation in early adolescence. They may also be found in the stomach and small intestine and there is a high risk of other malignancies. Follow-up and endoscopic controls begin as early as childhood and early prophylactic colectomy is recommended.
Lynch's syndrome - Hereditary non-polyposis colorectal cancer - mutation of Mismatch Repair (MMR) genes MLH and MSH. There is a roughly 75% risk of developing colon cancer (polyps are not often developed), up to a 60% risk of uterine cancer and others. Since the age of twenty, regular checks are recommended, especially colonoscopic, gynecological and others.

Other syndromes: Li-Fraumeni (CNS, leukemia, breast cancer, sarcomas), MEN - Multiple endocrine neoplasia 1 and 2 (tumors of endocrine glands, often thyroid, parathyroid, pheochromocytoma and others).

- **Epidemiology of cancer - occurrence of the most common malignancies in the world, explanation of terms: incidence, prevalence, mortality**

Epidemiology in Oncology - it maps, collects and analyzes data on the incidence and mortality of cancer in populations and population groups. It helps to identify the causes of possible fluctuations of the incidence and morality and describes the reflection of changes directed against malignancies (eg the impact of cancer screening, introduction of new therapy methods).
National Cancer Registry: there have been malignant neoplasms registered systematically and nationwide in the Czech Republic since the end of the 1950s. Any patient with newly developed malignanci must be registered.

Incidence - *number of newly diagnosed cancers during a certain period (eg within one calendar year, within 5, 10 years, etc.).*
Mortality - *the number of deaths from disease during one calendar year (or more years).*
Prevalence - *the total number of patients with a certain malignant disease on a specific date. It is the sum of all diseases newly diagnosed with all diseases diagnosed at any time before, if their carriers are alive at that date.*

In addition to cardiovascular disease, malignancy is the second leading cause of death. There is an increase in incidence and prevalence and a slight decrease in mortality. The increasing survival of cancer patients translates into increasing prevalence rates.
The most numerous group of malignancies are non-melanoma skin tumors. Prostate cancer is the most common cancer in men, and breast cancer is the most common cancer in women. In both sexes, colorectal carcinoma is the second and lung cancer in the third. In an international comparison, the Czech Republic has a significant lead in the incidence of renal cancer. The incidence of colorectal cancer in the Czech Republic is one of the highest in Europe.

- **Cancer prevention and screening – primary, secondary and tertiary prevention, screening programs, the importance of follow-up observation**

Primary prevention – reduces a risk of development and incidence of malignant tumor, eliminates high-risk and inducing factors. Proven precautions are:
Healthy lifestyle – physical exercise, enough sleep, healthy diet, low level of stress, reduced risky sexual behavior, quit smoking and alcohol abuse
Prevent skin from UV-light, long exposure to sunlight and sun parlors
Healthy environment – reduce carcinogenic substances in the air, water and food (i.e. radon, asbestos, nitrosamines, aflatoxines)
Treatment and prevention from infections – eradication of *Helicobacter pylori* in chronic gastritis, vaccination against hepatitis B and HPV infection
Secondary prevention – includes precautions, which enable to detect malignant tumors in early stages and reduce mortality. It involves screening programs, breast and testicles self-examination, monitoring groups of people with increased risk (i.e. with hereditary syndromes or precancerous condition)
Tertiary prevention – the aim is to detect local relapse, distant metastases or detect secondary malignancies as soon as possible. That means follow-up care after the oncological treatment including physical examination, lab tests (tumor markers) and imaging procedures (i.e. CT - computer tomography, ultrasound, MRI - magnet resonance imaging). Frequency of follow-up controls usually starts at 3 months, after 2 years it stretches to 6 months and then every 12 months if there is no sign of relapsed disease 5 years after the last oncological treatment.
Screening programs are conducted by general practitioners in cooperation with gynecologists.

- Cervical cancer – first gynecological examination in 15 years of age, then once a year including cervical swab for cytology test
- Breast cancer – mammography every two years in women aged 45 or more (in the Czech Republic, it differs in each state) in accredited breast health centers
- Colorectal cancer – fecal occult blood test - once a year in people aged 50-54, every two years in people older than 55 or colonoscopy every ten years

- **Cancer diagnostics – medical history, physical and laboratory examination, tumor markers, biopsy, imaging techniques, endoscopic methods**

Anamnesis: Family history – enables to reveal a hereditary predisposition. **Personal history** – diseases in relation with malignant tumor (chronic gastritis, HPV infection, Crohn's disease or ulcerative colitis, cryptorchism). **Abusus** – alcohol, smoking. **Professional history** – carcinogenic substances at a workplace. **Social history:** carcinogenic substances at home, possibilities of homecare. **Allergies** – higher risk for allergic reaction to cytostatics (taxanes). **Medication** – possible drug interactions.
Present disease: Symptoms of the tumor, paraneoplastic syndromes, how long did the symptoms occur (shorter anamnesis of symptoms can mean more aggressive behavior of the disease)
Physical examination and Performance status: Examination of palpable tumor, lymph nodes, metastases and Performance status to quantify general well-being and activities of daily life. It is used to determine whether the patient is fit enough to receive oncological treatment. There are two scales to use to classify the performance status:
Karnofsky performance scale 0-100 % (classifies patient according to their functional impairment): 0 % = dead; 10 % = dying; 50 % = requires considerable assistance and frequent medical care; 100 % = normal, no evidence of diseasea.
WHO (ECOG) performance status (0-5): 0 = fully active, able to carry on all pre-disease activities without restriction; 1 = restricted in physically strenuous activity but able to carry out work of a light nature; 2 = capable of self-care, but unable to carry out any work activities; 3 = capable of only limited self-care, confined to bed or chair more than 50 % of waking hours; 4 = completely disabled, can´t carry on any self-care, totally confined to bed or chair; 5 = dead.
Laboratory examination: Blood tests (metabolic changes and complications), analysis of genetic alterations (PCR, FISH, cytogenetics)
Tumor markers: are biomarkers produced directly by the tumor or by non-tumor cells as a response to the presence of a tumor. They can be found in blood, urine or body tissues. An elevated level can indicate the presence of cancer, but there can also be other causes of the elevation (false positive values). No tumor marker is completely sensitive or specific. It is used in diagnostics, during follow-up care to detect a relapse and it can help estimate prognosis. Examples: PSA (prostatic specific antigen) in prostate cancer, CEA (carcinoembryonic antigen) in colorectal, breast or lung cancer, AFP (Alpha fetoprotein) in germ cell tumors or hepatocellular.
Biopsy or cytology: is crucial for setting the diagnosis. Nowadays, many types of cancer are defined by specific genetic alterations, i.e. non-small-cell carcinoma, a subgroup of acute leukemia.
Imaging techniques: X-ray: mammography. Ultrasonography: for soft tissues or parenchymatous organs. Endosonography (EUS) combines ultrasonography with endoscopy (upper GI, pancreas, rectum, female reproductive system). Computer tomography (CT): universal imaging procedure. Magnet resonance imaging (MRI): used to clarify unclear findings, best for pelvic cavity and central nervous system. PET/CT or PET/MR: informs about morphology, metabolic activity and proliferation in tissues. **Endoscopy:** diagnostics in gastroenterology, otorhinolaryngology and urology, stent insertion

- **Basic principles and importance of grading and TNM staging**

Staging – is a process of determining the extent to which a cancer has developed by growing and spreading. **Stage** – depends on a size and localization of primary tumor or metastases. It is crucial for choosing the best therapeutic strategy and for therapeutic response evaluation. The main staging classification in malignant tumors in general is the **TNM (Tumour, Node, Metastasis)** staging system. **Tumor (T0 – T4)** describes the size and location of the tumor, including how much the tumor has grown into nearby tissues. **Node (N0 - N3)** stands for regional lymph nodes. Most

often, the more lymph nodes with cancer, the larger the number assigned. **Metastasis (M0-M1)** indicates whether the cancer has spread to other parts of the body, called distant metastasis (M1) or not (M0). **According to results of TNM system, we differ four stages (I-IV) of malignant disease** (i.e. stage I – localized tumor, IV – advanced, metastatic or inoperable tumor).
There are more staging systems, specific for particular types of cancer – i.e. FIGO system for gynecological tumors, Ann Arbor system for lymphomas
Staging can be "clinical" or "pathological." Clinical staging (cTNM) is based on the results of clinical tests, such as physical examinations and imaging scans. **Pathological staging** (pTNM) is based on what is found by examining biopsy and histology samples after surgery.
Grading, grade - measures reversion of differentiation in the sampled tumor and is based on the resemblance of the tumor cells to the tissue of origin (G1- G4) and may help the doctor predict how aggressively the tumor would behave. Different types of cancer have different methods to assign a cancer grade. Poorly differentiated (High grade, G3) tumors are more aggressive, however, usually more sensitive to treatment.

- G1 - Well differentiated (Low grade)
- G2 - Moderately differentiated (Intermediate grade)
- G3 - Poorly differentiated (High grade)
- G4 - Undifferentiated (High grade)

- **Clinical conditions of initiation of cancer treatment and basic types of systemic treatment (adjuvant, neoadjuvant, palliative, curative, concomitant, induction, consolidation, maintenance), importance of supportive care**

Basic treatment methods: surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and others. **The treatment may be initiated assuming that:**

The diagnosis (type of malignancy) and the extent of the disease (stage) are made.
The patient's general condition and co-morbidity are known and the patient is bearable for the treatment.
The treatment strategy is ideally assessed within a multidisciplinary team.
The patient agrees with the treatment.

Contraindications: generally very poor, unstable performance status, the disease not indicated for this type of treatment, patient disagreement.

From the point of view of therapeutic intent, cancer therapy is intended as:
Curative - to eradicate tumor cells and „to cure" the patient (eg. in some types of acute leukemia, localized cancers).
Palliative - to eliminate or at least alleviate the symptoms of cancer (pain, bleeding, obstruction, etc.), mostly in advanced and metastatic diseases.
Adjuvant - to eradicate the presumed residual microscopic disease, reducing the risk of recurrence of the disease with the possibility of improving survival (eg. postoperative treatment after radical resection of colorectal cancer, breast cancer, stomach cancer etc.).
Neoadjuvant – to shrink the tumor usually before surgery (preoperative), which in many cases can achieve the operability of the originally inoperable tumor, or it is possible to achieve a reduction in the extent of surgical intervention (eg. preoperatively in breast cancer).
Concomitant – the administration of chemotherapy together with radiotherapy in order to improve the effect of radiotherapy as well as to provide systemic treatment (eg. in head and neck cancers or cervical cancer).
Induction - initial chemotherapy inducing the remission of the malignancy (eg. in acute leukemias).
Consolidation – following the inducing treatment and further suppressing malignancy residues,(eg. in acute leukemias).

Maintenance - ensuring the control of the achieved remission of the malignancy (eg. in acute leukemias).

Supportive care is an obligatory part of the cancer care - it solves the complications of the cancer treatment and the cancer itself. **Symptomatic and hospice treatment:** it focuses on maintaining the quality of life of the patients, suppressing their problems with some hope of longer survival. Hospice care is primarily focused on the symptomatic treatment in the pre-terminal and terminal stages of the disease.

- **Radiotherapy – basic principles of effect and types of radiotherapy (photon and proton beam radiotherapy, brachytherapy, teleradiotherapy, stereotactic radiotherapy) and possibilities of its´use**

Radiotherapy – uses the ionizing radiation, whose quantum have such a high energy, that are capable to emit electrons from the atomic shell and thereby to ionize the substance. A key molecule for radiobiological activity is DNA. The cell's response to radiation can be cell death, stopping cell division, or a change in genetic information passed on to next generation of cells, i.e. mutation. The main aim of radiotherapy is to deliver the sufficient dose of radiation to the precisely defined target volume with the maximum possible accuracy while sparing healthy tissues as reasonably achievable; in other words, to deliver the correct dose to the correct place and not to harm. **Dose** D is the energy of radiation absorbed in a substance of a certain weight. Its **unit is gray (Gy),** 1 Gy = 1 J/kg.

Photon radiotherapy: The most frequently used types of radiation in radiotherapy are electromagnetic (photon) radiation γ (gamma) and X. Photon radiation emitted from the atomic nuclei is called radiation γ, while braking electron radiation is called radiation X (X-rays). The most commonly used source of ionizing radiation in photon radiotherapy is **linear accelerator**, which is currently standard equipment of radiotherapy departments. It uses high-energy photon beams, however, it can also emit electron beams.
Proton beam radiotherapy (corpuscular radiation): can also be used. Proton beam radiation has very similar biological effects to photon radiation, but its advantage, however, is better physical dose distribution. In the proper indications, it is possible to reduce the side effects of radiation and to improve the therapeutic results in terms of local control and overall survival in selected tumors (e.g. ocular melanomas, brain tumors in children).

External beam radiotherapy (EBRT) - the radiation source is located outside the body of the patient. Basic preparation of the patient is usually performed on the X-ray simulator, a machine, working on the principle of skiascopy. This allows to locate the target volume position and to simulate the radiation conditions after the radiation plan was created. The fixation of the patient is the crucial condition for correct and accurate radiotherapy. The aim is to provide a stable, comfortable and well reproducible patient position. Planning CT scan (native or contrast) aims to obtain accurate geometric and anatomical data about the patient that are necessary for a correct and accurate definition of target volumes as well as to get current information about the extent of the cancer. In certain situations, it is preferable to use CT scan fused with a different imaging method – MRI in prostate, brain and cervical tumors, PET scan in lung tumors and head and neck tumors. The total dose delivered to specific target volumes (i.e. tumour, tumour bed or lymphatic areas) has to be divided (fractionated) into several smaller doses (fractions). When using standard (conventional) fractionation, daily dose of 2 Gy per fractions is used, 5 days a week. The total delivered dose depends on the treatment purpose, the localization and the type of the tumour. It is usually in the range of 30-80 Gy.

Stereotactic radiotherapy and radiosurgery (SRT, SRS) – special techniques of EBRT that can be performed using the following radiotherapy machines: Leksell gama knife, X knife and CyberKnife. Using these techniques, a high dose can be applied to a relatively small target volume in a few fractions. They can be used in the treatment of brain metastases (Leksell gama knife, X knife), localized lung tumours and also lung metastases of various primary tumours (CyberKnife).

Brachytherapy (BT), or „short-distance irradiation", is a form of radiotherapy that achieves a very high dose of radiation in the area of application with its very steep fall into the surrounding area (radiation intensity decreases significantly with increasing distance). This makes it possible to be applied locally and in shorter time as compared to external beam radiotherapy. It is a suitable treatment method for small, well-accessible and circumscribed tumors. BT is, in many cases, an invasive treatment method that requires a specially equipped brachytherapy unit and, in certain cases, performig general anesthesia or analgosedation. **BT uses self-shielded irradiators** whose size is very small (eg. the iridium source has a diameter of about 1 mm and a lenght of 5 mm) and are most often shaped into grain or roller shapes. Typically, they emit **gamma radiation**. **Intracavitary BT** – the source of radiation is placed in the hollow organ from which the tumor originates (eg. BT of endometrial and cervical cancer). **Intraluminal BT** – the source of radiation is placed in the lumen of tubular organ (eg. BT of malignant stenoses caused by lung or extra-biliary duct cancers). **Interstitial BT** – the source of radiation is inserted directly to the tumor or to the tumor bed by plastic catheters or metal needles. The application is performed during surgery by placing catheters into the tumor bed (tumor bed after partial breast resection or after resection of sarcoma) or without surgery directly into the tumor (eg. prostate cancer). This implantation may be either **temporary**, in which the source is removed after the end of irradiation (prostate and breast cancers, sarcomas), or **permanent**, in which the sources are left permanently in the organ (prostate cancer) and where the sources of radiation are ^{198}gold or ^{125}iodine. **Surface mould BT –** the applicators are placed on the affected skin or mucose membrane surface.

Radiotherapy can be used as a separate method, but sometimes the combination with chemotherapy (**concomitant radiochemotherapy**), or targeted therapy is used.
Radiosensitivity: In theory, all tumors can be healed by radiation, the problem is the presence of surrounding healthy tissues, which do not allow the delivery of the sufficient lethal dose. **Extremely sensitive to the radiation are** lymphomas and germ cell tumors, moderately sensitive are carcinomas, **relatively radioresistant are** gliomas and sarcomas.

- **Hormonal therapy – basic principles of action, types and uses**

The production and the effect of estrogens and androgens is related to development of endometrial, breast and prostate carcinoma, respectively. The direct association between tumor growth and hormone production is due to the presence of hormone receptors on the surface of tumor cells. The main goal of hormone therapy is usually to reduce tumor exposure to hormone production. In practice, hormonal therapy is mainly applied in breast cancer (hormone-dependent tumors account for 60-70%), prostate cancer (all tumours are initially hormone-dependent), endometrial cancer (hormone treatment is one of the palliative treatment options) and neuroendocrine tumors (eg. carcinoid – the inhibition of somatostatin receptors on the surface of tumor cells is used).

Principles of action:
Ablation and suppression of gonads: bilateral orchiectomy in men with prostate cancer causes tumor regression as well as bilateral ovarectomy in premenopausal women with breast cancer. The application of injection LH-RH agonists (luteinizing hormone releasing hormone, LH-releasing hormone, gonadoliberin, GnRH) causes the stimulation and consequently, due to the negative

feedback reaction, the inhibition of the function of the hypothalamus-pituitary gland-gonads axis and can thus achieve the castration status and replace the surgical castration of the gonads in breast or prostate cancer patients.
The inhibition of enzymes involved in hormone synthesis: the aromatase enzyme converts androgens to estrogens in the adrenal gland and in the adipose tissue. In postmenopausal women with hormone-dependent breast cancer, aromatase inhibitor therapy (anastrozole, letrozole, exemestane) is very effective because the adrenal gland and adipose tissue are the major source of estrogens after the menopause.
Antagonists of receptors and subsequent signaling pathways: Antiestrogens - tamoxifen, fulvestrant - inhibit estrogen receptors on the surface of estrogen receptor positive breast cancer cells and block the action of physiological hormones. **Antiandrogens** play the role in some treatment regimens in prostate cancer, eg. enzalutamide and apalutamide act at multiple sites within the androgen receptor signaling pathway. **Somatostatin analogues** - hormone active gastrointestinal and lung tumors (neuroendocrine tumors, carcinoid, insulinoma, etc.) with a number of clinical manifestations (diarrhea, abdominal pain, shortness of breath, rush and hot flushes) can be blocked by binding somatostatin analogues (e.g. lanreotide, octreotide) to the somatostatin receptors of the tumor cells.
Other: Gestagens (medroxyprogesterone, megestrol) are used in the treatment of advanced breast and uterine tumors. Alternatively, they can be used to increase appetite, weight, performance status. **Corticosteroids** (Prednisone, Dexamethasone) suppress nausea, vomiting and allergies. They also have anti-edematous effect in brain metastases, anti-tumor effect in hematological malignancies (eg. myeloma, lymphomas) and they can correct hypercalcaemia.

Oral hormonal contraceptives: Slightly increase the relative risk of breast and cervical cancer. It has a protective effect on endometrial, ovarian and colorectal carcinoma (by suppressing endometrial cell proliferation, ovulation, and decreasing bile acid concentration).

Side effects of hormone therapy are most often related to the loss of their physiological function. These may include flushing, mood swings, menstruation disorders, osteoporosis, thinning and hair loss, sexual dysfunction, fatigue, loss of libido, erectile dysfunction or gynecomastia in men, etc.

- **Chemotherapy - basic principles of action and types of cytostatics (antimetabolites, alkylating agents, intercalating agents, topoisomerase inhibitors, inhibitors of polymerization / depolymerization of microtubules), methods of application**

Chemotherapy is a treatment modality using individual chemical molecules, or drugs called **cytostatics**, which have the ability to block cell division - for example, by blocking the synthesis, replication, function of DNA, RNA, or function of microtubules.
Chemotherapy is a systemic treatment that is not specific in its effect (unlike the so-called targeted treatment) and has a cytostatic effect on tumor cellls as well aso on the healthy tissue cells. However, tumor cells are in most cases more sensitive to the action of cytostatics leading to a therapeutic effect. There are several types of agents according to their mechanism of action.
Antimetabolites (block nucleic acid synthesis): purine antagonists (e.g. mercatopurine, fludarabine), pyrimidine antagonists (e.g. 5-fluorouracil, capecitabine, gemcitabine, cytarabine), folic acid antagonists - antifolates (e.g. methotrexate, pemetrexed), hydroxyurea.
Alkylating agents (DNA binding, covalent bond) - e.g. cyclophosphamide, ifosfamide, busulfan, melphalan, lomustine, dacarbazine, temozolomide, cisplatin, carboplatin, oxaliplatin, mytomycin C.
Intercalating agents (DNA binding, hydrogen bond) - e.g. mitoxantrone and anthracyclines (doxorubicin, idarubicin, daunorubicin, epirubicin).

Topoisomerase inhibitors (developmental disruption, DNA replication) - topotecan, irinotecan, etoposide.
Mitotic poisons, inhibitors (polymerization / depolymerization) of mitotic spindle microtubules - vinca alkaloids (vicristine, vinblastine, vinorelbine), taxanes (paclitaxel, docetaxel).

Chemotherapy is usually applied in a validated treatment protocol in a precisely defined dosage and timing in order to ensure the best effect with the lowest risk of toxicity (for example every 3 weeks).
It is usually administered cyclically, when the phase of application of the cytostatic alternates a period of rest allowing the regeneration of healthy tissues and organs. The duration of chemotherapy is limited either by a defined number of cycles to reduce the accumulation of toxicity, or until the development of intolerance and toxicity of the treatment or treatment failure with progression of malignancy.
One cytostatic (monotherapy) or a combination of two or more can be administered in order to enhance the antitumor effect by different mechanisms of action. It can be alone or, for example, with radiotherapy, immunotherapy, hematopoietic stem cell transplantation.
Chemotherapy is usually administered as a p.o. tablets, but more often as i.v. infusion or s.c. injection, optionally in the form of lavage of the sinuses (bladder, pleural cavity, abdominal cavity) or superficially.
Chemosensitive tumors – e.g. acute leukemia, lymphoma, germinal tumors
Chemoresistant tumors – e.g. kidney cancer

Patient care requires regular monitoring of clinical status and laboratory results (blood count and biochemistry), provision of basic supportive care and care including sufficient to increased fluid intake, antiemetics and others with regard to the type of cytostatics (eg granulopoiesis growth factors, hyperhydration, allopurinol, etc.).

- **Targeted treatment - basic principles of action and types of targeted drugs (monoclonal antibodies, kinase inhibitors)**

Targeted treatment is based on knowledge of the pathophysiology of individual cancers, affecting specific structures or mechanisms involved in the development of cancer. **The antitumor effect can be targeted not only to the tumor cells**, but also to the **tumor microenvironment and antitumor immunity** (e.g. blockade of angiogenesis, activation of antitumor immune response). **The effect is realized in such a way that the drug, for example, specifically blocks** the ligand (usually growth factors) or their receptors on the cell surface, or it can block signaling pathways targeting intracellular signaling proteins, resp. enzymes from the group of kinases. The final effect can be inhibition of proliferation, angiogenesis or induction of anti-tumor immune reaction. From the point of view of the nature of the molecule and the mechanism of action, **monoclonal antibodies** (i.e. macromolecules, or proteins, or biotherapy) and **small molecules of small intracellular inhibitors** (e.g. protein kinases inhibitors) can be included in the group of targeted treatment, as well as **hormonal therapy**.
Targeted therapy is used in a number of malignancies, which are usually characterized by the presence of a specific "feature" which can be a target for a specific treatment. Such a specific „feature“ can be called a **predictive (bio)marker** - usually a gene mutation or cell-surface antigen (e.g. mutated form of BRAF gene in melanoma is a predictive marker for targeted therapy with BRAF inhibitors, HER2/neu overexpression in breast cancer is a predictive factor for the use of anti-HER2 monoclonal antibody). It is a type of systemic oncological treatment. It is usually performed on an outpatient basis with regular use of tablet forms or as a cyclic administration of

injections / infusions. In terms of structure and mechanism, it has two main groups - monoclonal antibodies and small molecules (inhibitors).
Monoclonal antibodies - see Immunotherapy.
Small molecules - inhibitors: a various group of small molecule drugs that act inside a tumor cell. According to the specific mechanism of action, they are devided into a number of subgroups. There is used the suffix -nib in the name of the drug. The main subgroups include, for example, inhibitors of intracellular tyrosine kinase parts of receptors or intracellular kinases - kinase inhibitors (e.g. erlotinib for lung cancer, pazopanib for renal cell carcinoma and sarcomas), inhibitors of cyclin-dependent kinases (e.g. palbociclib for breast cancer), protease inhibitors (e.g. bortezomib for multiple myeloma), PARP poly-ADP-ribose polymerase inhibitors (e.g. olaparib for BRCA positive ovarian cancer).

Malignancies with a common use of targeted treatment include: metastatic colorectal carcinoma (inhibition of angiogenesis, blockade of epidermal growth factor receptor), metastatic melanoma (inhibition of BRAF mutation, immunotherapy), advanced non-small cell lung cancer (inhibition of EGFR mutation, immunotherapy), advanced renal cell cancer (inhibition of angiogenesis, immunotherapy).

- **Immunotherapy - basic mechanism of action and types of immunotherapy (cytokines, monoclonal antibodies, checkpoint inhibitors, cancer vaccines, cellular immunotherapy)**

Immunotherapy - includes drugs that are part of or affect anti-tumor immunity (note: some immunotherapy agents can be included due to the macromolecular protein structure in the group of biotherapy (so-called **biological treatment**) or due to its mechanism of action among targeted treatment - typically monoclonal antibodies.
Cytokines (interleukins and interferons) - non-targeted immunomodulatory molecules, a certain effect, for example, in metastatic renal cell carcinoma, melanoma or hemato-oncological diseases, due to poor tolerance of use in the clinical practice is already minimal.
Monoclonal antibodies - proteins, immunoglobulins produced by one clone of B-lymphocytes, either as fully human immunoglobulins or with a smaller or larger component of a part of the mouse molecule (humanized or complexed chimeric immunoglobulins). The target structures of monoclonal antibodies include various antigens or ligands (e.g. vascular endothelial growth factor - VEGF), receptors (e.g. epidermal growth factor receptor - EGFR), specific cell surface antigens (e.g. CD20 antigen on the surface of B-lymphomas) or a receptor involved in regulation of anti-tumor immunity - PD-1 on the surface of T-lymphocytes (check-point inhibitors). Depending on the type of drug and tumor, the antibody binding blocks proliferation signaling, triggers apoptosis or an immune response with subsequent tumor cell destruction. In some drugs (so-called conjugates), a cytostatic molecule is also bound to the antibody, and this cytostatic can thus be delivered to the tumor cell in a targeted manner. The **-mab suffix** is used for the names of individual antibodies and includes, for example: bevacizumab (anti-VEGF-vascular endothelial growth factor in the treatment of colorectal cancer), trastuzumab (anti-HER-epidermal receptor in the treatment of HER2 antigen-positive breast cancer), nivolumab (so-called check-point inhibitor, or anti-PD1 on the surface of T-lymphocytes in the treatment of melanoma, lung and kidney cancer).
CAR-T cells - Chimeric antigen receptor (CAR) - a recombinant T cell receptor prepared by fusing a portion of a T cell receptor and a monoclonal antibody directed against a selected surface antigen.
Antitumor vaccines - directed against tumor-specific antigens or oncogenic viruses, are prophylactic (vaccines against tumors that are of viral origin) and therapeutic – e.g. based on

peptides, nucleic acids, dendritic cells, recombinant viruses and killed, genetically engineered tumor cells.
Cellular immunotherapy - dendritic cells induce an immune response by activating T-lymphocytes. Dendritic cells (monocytes) of the patient's blood are cultured with tumor antigens (peptides, lysates) and the activated dendritic cells are then given back to the patient as an anti-tumor vaccine to stimulate and overcome tolerance to tumor cells and enhance anti-tumor immunity.
Other: allogeneic hematopoietic stem cell transplantation.

- **Side effects of anticancer treatment - the most common side effects of chemotherapy and basics of their treatment**

Chemotherapy can damage tumor cells but also a normal cells of healthy tissues with the development of various side effects. **The incidence and severity of side effects depend on the type and dose of the cytostatic as well as on individual susceptibility.** They may develop early or later, with the risk of cumulative toxicity adding up the side effect of the cytostatic with each additional dose and the risk of damage, especially to the liver, kidneys and myocardium (typically when treated with anthracyclines).
General side effects: include transient toxic damage to healthy and especially rapidly regenerating tissues, such as bone marrow hematopoiesis (anemia, leukopenia, thrombocytopenia), oral and gastrointestinal mucosa (oral mucositis, diarrhea), hair follicles (alopecia) and gonads (temporary or permanent infertility).
Early side effects develop within minutes to weeks and include: loss of appetite, nausea and vomiting, hematopoietic toxicity (anemia, neutropenia / leukopenia, thrombocytopenia), mucosal damage (oral mucositis, diarrhea), hair loss (alopecia), irritant phlebitis and extravasation, hyperuricaemia (increase in serum uric acid levels with risk of urolithiasis and gout), tumor lysis syndrome (sudden tumor or leukemia, release of ions and metabolites, renal failure, cardiac arrhythmias), allergic reactions, weakened immune system.
Late side effects develop and last for months and years and include: gonadal disorders (infertility, decreased libido, disorders or disappearance of the menstrual cycle), secondary malignancies (chemotherapy increases the risk of new malignancies, especially leukemia and lymphomas up to several years apart).
Specific side effects - are typical for a specific cytostatic and are not general: e.g. **cardiotoxicity** - heart failure and arrhythmias after repeated anthracycline treatment; e.g. **neurotoxicity** - peripheral polyneurpathy after vinca alkaloids (vincristine, vinblastine) and taxanes (docetaxel, paclitaxel).
Treatment, e.g.: Sufficient hydration - generally always during chemotherapy, p.o. or i.v., optionally up to hyperhydration to reduce nephrotoxicity, especially with cisplatin and methotrexate. Nausea - prevention with antiemetics. Hematopoietic toxicity - growth factors of granulepoiesis and eryropoiesis, transfusion of erythrocytes or platelets. Infectious complications - antibiotics, antifungals, antivirals - in high-risk (leukemias, bone marrow transplantation) and prophylactically, otherwise therapeutically.

- **Side effects of anticancer treatment – the most common early and late side effects of radiotherapy and their treatment**

Despite the optimization of the treatment and the latest radiotherapy techniques, part of the radiation also affects healthy tissue and causes a variety of side effects.

Systemic symptoms and signs usually occur when irradiating larger volumes, and are manifested by fatigue, anorexia, nausea, vomiting or psychic changes. Other systemic side effects include haemotological toxicity that occurs when large amounts of bone marrow are irradiated, and these are mainly leukopenia, thrombocytopenia and anemia.
Local symptoms and signs directly affect irradiated areas and have a varied clinical picture depending on the site of the disorder.

Acute (early) side effects occur during the radiotherapy course and within three months of its ending. The most striking are in fast-growing tissue such as skin epithelium, mucous membrane and haematopoietic system. These side effects are reversible. The most commonly occurring are radiodermatitis, mucositis, enteritis or cystitis.
Chronic (late) side effects occur several weeks, months or years after the end of radiotherapy (usually 2-3 years). They occur predominantly in tissue with low cellular turnover, i.e. connective tissue, blood vessels, lungs, heart, kidneys, nervous tissue, liver and muscels. Unlike acute changes, late changes are irreversible. In particular, there are fibrotis changes in the skin and subcutaneous tissue, atrophy of the skin, damage of microvascularity resulting in lymphedema, cataract, corrugation of the bladder or osteoradionecrosis.
Very late side effects occur several years after the end of radiotherapy (5-15 years) and are caused by mutations resulting from irradiation. This is mainly about the emergence of so-called secondary malignancies. An example is secondary breast cancer after radiotherapy of mediastinal Hodgkin´s disease in childhood.

Brachytherapy: brachytherapeutic procedures may be complicated by the non-optimal introduction of applicators into the target organs or by the damage of these organs (eg. uterine perforation during uterovaginal brachytherapy). Late side effects, in terms of chronic inflammatory changes (e.g. proctitis, cystitis, vaginal synechia, etc.), prevail over other side effects due to the use of high fraction doses.

The treatment of the postradiation reactions is symptomatic with regard to the type and localization of the reaction (moisturizing gels, creams, beware of sunlight, mechanical abrasions, hot - freeze). It is extremely important to prevent the occurrence of side effects by careful radiotherapy planning, by appropriate radiotherapy technique, as well as adherence to preventive regimens by the patient.

- **Side effects of anticancer treatment - the most common side effects of targeted treatment and immunotherapy**

Although targeted treatment and immunotherapy, in contrast to non-specific (non-selective) chemotherapy, are more specific and focused mainly on tumor cells, tumor microenvironment and anti-tumor immunity regulation, there are also side effects with a number of risks. The nature of the side effects usually depends on the type and mechanism of action of the used therapeutic agent.
Monoclonal antibodies: some side effects occur practically within minutes during or shortly after application and resemble allergic reactions such as chills, itchy skin, rash, fever, or shortness of breath and collapse. They are common, especially in the treatment of patients with leukemia or lymphoma. Other complications occur within days, but also months. They manifest themselves primarily as skin rashes and itching, fatigue, flu-like syndrome (fever, joint or muscle pain, weakness), or as intestinal inflammation with pain and diarrhea. Disorders of the nature of autoimmune diseases may also occur, typically during treatment with immunoterapy using agents so-called check-point inhibitors (monoclonal antibodies targeting PD1, PD-L1) affecting anti-tumor immunity leading to the risk of development of endocrinopathies, pneumonitis, colitis, dermatitis, ocular inflammations, etc.

Kinase inhibitors: the most common side effects include skin rash, hand-foot syndrome (palm-plantar erythrodysesthesia), disorders of skin and hair pigmentation, fatigue, hypertension, diarrhea, wound healing disorders and bleeding events.
Hormone therapy: most often associated with a loss of physiological hormonal function. These can be hot flashes, mood swings, menstrual disorders, osteoporosis, thinning and hair loss, sexual dysfunction, fatigue, loss of libido, erectile dysfunction or gynecomastia in men, etc.

- **CNS tumours – basic types and their characteristics, symptoms, diagnostics**

The most common intracranial and brain tumours are secondary tumours – metastases (typically breast, lung and renal cancers). The others are meningiomas and tumours arising from neuroglial (supportive) brain tissue - gliomas. Rarely lymphomas, ependymomas, pituitary adenomas and meduloblastomas in children.
Excluding secondary tumours, 700-800 patients, mostly gliomas and meningiomas, are diagnosed annually in the Czech Republic. The cause can usually not be determined. Ionizing radiation and immunosuppression are known risk factors.
Tumours localized in the brainstem and in the proximity to important centers and pathways manifest at relatively small sizes. A slow-growing tumour in a clinically silent location of the hemispheres can grow up to several centimeters. Gliomas grow infiltratively, meningiomas press on brain tissue.
Neurological manifestations - motor, sensation and speech disorders, cranial nerves lesions, visual field defects, often epileptic paroxysms. **Intracranial hypertension syndrome** - increasing headache, nausea and vomiting, somnolence, disorientation, visual impairment and optic nerve papilla edema.
Diagnosis and examination: The key role play CT and MRI, in children under one year ultrasound via fontanels. Histological examination of a specimen from neurosurgical resection or navigated biopsy. Lumbar puncture (attention of the intracranial hypertension and the development of occipital conus) and analysis of the cerebrospinal fluid - negative cytology result does not exclude CNS tumor! In leukemias and lymphomas, cytostatics are usually administered intrathecally (i. t.) in lumbar puncture. The part of the diagnosis of brain tumours is also examination of the eye background (verification of papilla congestion during intracranial hypertension), EEG examination and basic blood analysis. There are no specific tumour markers.

Meningeomas - meningeal tumors, 90 % benign, slow growth, asymptomatic for a long time, more often in elderly and in women (they have estrogen and progesterone receptors). Postoperative relapses and residues can be irradiated (Gamma knife).
Gliomas – arising from the supportive brain glial tissue with a number of subtypes. Low-grade gliomas (WHO grade I-II) with slow infiltrative growth e.g. diffuse astrocytoma, oligodendroglioma. Highly aggressive high-grade gliomas (WHO grade III-IV) e.g. anaplastic astrocytoma, glioblastoma (glioblastoma multiforme) with aggressive growth, prognosis within months.
Ependymomas – arising from the cerebral ventricles or central spinal canal ependyma, hydrocephalus is usual, as well as implant metastases. The therapy is radical resection and radiotherapy.
Meduloblastoma - aggressive tumor in children, the therapy includes resection, radiotherapy and chemotherapy.

In general, patients with multiple metastatic brain involvement have the worst results, with a mean survival of approximately three months after palliative radiotherapy. In addition, patients with glioblastomas have also very poor prognosis.

- **CNS tumours – surgery, radiotherapy, chemotherapy, corticotherapy and i.t. application of chemotherapy**

The treatment is modified according to the clinical condition, comorbidities and age of the patient. **The basis is the effort to complete surgical removal of the tumor**. The tumor is resected with an ultrasound aspirator, the standard is MR imaging navigation, intraoperative ultrasound monitoring, fluorescent tumour imaging and peroperative electrophysiological monitoring for the accurate location of the elocvent area and its relationship to the tumour.
The alternative to surgery for radically inoperable or inaccessible tumours or metastases are stereotactic radiotherapy and radiosurgery techniques (Gamma knife, Cyber knife). For multiple metastases or postoperatively, standardized fractionated radiotherapy (typically high-grade gliomas in combination – concomitantly - with chemotherapy) is used to improve disease control and relapses.

Chemotherapy is an essential part of the comprehensive treatment of high-grade gliomas. However, the possibilities of chemotherapy are limited, due to the lower sensitivity of the gliomas and the limited penetration of cytostatics through the blood-brain barrier, except for the lesions in leukemias and lymphomas and germ tumours, that are ususally sensitive. Oral administration of temozolomide is the standard type of chemotherapy for high-grade gliomas. Special protocols (medulloblastoma) may be used for other types of tumors or relapses, and intrathecal administration is also applicable for lymphomas and leukemias.

In general, patients with multiple metastatic brain involvement have the worst results, with a mean survival of approximately three months after palliative radiotherapy. In addition, patients with glioblastomas have also very poor prognosis.

Supportive and complementary treatment: corticosteroids - dexamethasone (4-8 mg 1-3x daily) reduces brain edema around the tumour and at least temporarily contributes to reduce the clinical manifestations of the expansive process.

- **Head and neck tumours - causes, localization, manifestations, diagnostics and prevention**

Squamous cell carcinomas (80%) derived from squamous cell epithelium predominate in the head-and-naeck area tumours, and there can also be adenocarcinomas, melanomas, lymphomas, sarcomas and metastases. Maximum incidence is in around 60 years of age, annually there are about 2000 new patients in the Czech Republic with a predominance of men.
Causes: Chemical effects (alcohol and smoking), physical effects (UV radiation in lip tumor, ionizing radiation in salivary and thyroid tumors) and biological effects (viral etiology in EBV-induced nasopharyngeal carcinoma and HPV-induced oropharyngeal carcinomas). Most oropharyngeal cancers are now associated with HPV infection. Unlike larynx cancer, where smoking and alcohol-induced cancers account for the vast majority of cases.
The carcinomas of the head-and-neck region grow predominantly locally invasively and, primarily via the lymphogenic pathway, they metastasize to the cervical lymph nodes. The poor socio-economic status of patients with alcohol abuse and nicotinism is also the reason for late diagnosis in the advanced stage of the disease. These tumors threaten patients mainly by reducing food intake with the development of malnutrition and early establishment of percutaneous endoscopic gastrostomy - PEG - is recommended, there is also risk of airway obstruction requiring the establishment of tracheostomy, and speech disturbance.

Tumors of the nasal cavity and paranasal sinuses - they are manifested mainly by unilateral nasal obstruction and purulent (often smelly) secretion from the nose, or as recurrent epistaxis, paraesthesia in the area of n.trigemin branches etc.
Nasopharyngeal cancer - nodal cervical metastasis is the most common first symptom. Similar to nasal cavity and paranasal sinus carcinoma, nasal secretion and bleeding or lying down of the ear and hearing impairment due to impaired Eustachian tube function may be present.
Carcinoma of the lips or oral cavity - it appears to be non-healing ulcer or visible lump and can cause pain when talking and eating. An admixture of blood in saliva may be present. There may be limited movement of the tongue leading to deterioration of pronunciation, foetor ex ore.
Oropharynx carcinoma - is manifested by pain or scratches when swallowing or by the feeling of a foreign body in the throat.
Larynx carcinoma - there is a hoarseness as a typical symptom. In later stages, swallowing pain, dysphagia, inspiratory shortness of breath and aspiration of fluids can occur.
Salivary gland cancer - usually manifests as painless resistance or gland enlargement.

Diagnosis and examination: The basis for diagnosis is the clinical examination with probatorial excision and histological verification. The sonography of the neck, CT or MR, PET/CT or PET/MR will help to determine the extent of the disease.
Prevention: Stop alcohol and smoking abuse, HPV vaccination.

- **Head and neck tumours - surgery, radiotherapy and systemic treatment**

The main treatment modality is surgery (tumor resection with or without cervical node dissection), in case it can be performed with regard to the location and extent of the tumor and the risk of permanent damage to surrounding structures.
In advanced tumors, radiotherapy or chemoradiotherapy is the alternative traetment. In larger tumors, the combination of more modalities is neeeded - surgery, radiotherapy, chemotherapy, nutritional support. In metastatic patients, palliative chemotherapy and palliative radiotherapy dominate.

Patients with Head-and-neck tumors are at risk nutritional risk. Especially in curative chemoradiotherapy, percutaneous gastrostomy (PEG) is very often provided to prevent reduced oral intake of food for approximately 2-3 months, as acute radiation mucositis is painful and risky for malnutrition development. Nutritional support is an essential issue. Tracheostomy is often required in laryngeal carcinomas.

In the early stages I and II of the disease, the results of surgery and radiotherapy are the same, and about 80% of patients with stage I disease have a long-term survival. Advanced Stages III and IV have a long-term survival well below 40%. Less than 5% of patients in metastatic disease (lungs, liver, skeleton) survive. Most local tumor relapses are most commonly within two years.

- **Tumours of endocrine glands - thyroid carcinoma - types and possibilities of treatment**

The most common endocrine malignancy with the fastest growing incidence. There is an increase in incidence and in the Czech Republic more than 1,000 patients, and especially women, fall ill annually. **Most of the thyroid malignancies, about 90%, are differentiated cancers (very common (75%) papillary),** which have a generally good prognosis with a 5-year survival of 98% with an indolent course of several years even in the presence of pulmonary metastases.
Rare medullary carcinoma (up to 10%) from parafollicular C-cells produces calcitonin, does not accumulate radioiodine and is caused by mutations in the proto-oncogene RET.

Rare anaplastic carcinoma (2%) is very aggressive, with resistance to chemotherapy and radiotherapy and less than 10% survives for 3 years.
Rarely, lymphomas, sarcomas and secondary tumors (metastases of breast, lung, kidney) may occur in the thyroid gland.
It often manifests as asymptomatic nodules or patients may feel pressure from increasing nodes. Voice changes, hoarseness, imperative diarrhea in advanced medullary carcinoma. The most common is metastasis to the lungs and skeleton.
In the etiology of thyroid carcinoma radiation burden (so-called "radiogenic carcinomas" several years after radiation of the neck area) may play role, hormonal changes (female sex hormones may be involved in malignant transformation of thyroidal tissue), some rare hereditary oncological diseases (eg syndrome) multiple endocrine neoplasia (MEN).

Examination: physical, sonography, thin needle aspiration biopsy, CT, PET/CT imaging with 18F-fluorodeoxyglucose (FDG) or more sensitive DOPA. For the diagnosis of medullary carcinoma (and pheochromocytoma) scintigraphy with the radiopharmaceutical 123I-MIBG (meta-iodobenzylguanidine) is suitable, as well as Octreoscan (octreotide). Calcitonin, thyroglobulin and CEA may be also important for further monitoring.

Surgical resection is the basis of treatment. **Radioactive iodine (radioiodine)** is applied postoperatively to destroy residual tissue and reduce recurrence. The same can be used to treat metastases. Some tumors develop radioresistance or are already primarily resistant (eg, medullary carcinomas do not accumulate radioiodine) and only 10-20% of such patients survive for ten years.
Targeted systemic therapy with tyrosine kinase inhibitors (eg sorafenib) is possible in selected patients. **External radiotherapy** of the neck is indicated in unresectable or locally recurrent cancers.

- **Tumours of endocrine glands - pheochromocytoma, paragangiloma - basic characteristics and symptoms**

Pheochromocytomas are derived from chromaffin cells (neuroectodermal tissue) of the adrenal medulla with the ability to produce catecholamines, but I can also develop outside the adrenal glands (extraadrenally) alongside the autonomic nervous system as so-called **paragangliomas** (e.g. Zuckerkandl organ in the periaortic area).

Pheochromocytoma (paraganglioma) is a rare tumor with an incidence of approximately two cases per million inhabitants. The incidence of paragangliomas localised along the autonomic nervous system from the neck to the pelvis is more common than the adrenal pheochromocytoma.
Most tumors are functional, producing catecholamines. Persistent hypertension occurs in 50% of patients, 40-45% have paroxysmal hypertension accompanied by headache, anxiety, flushing, palpitations, tremor or sweating.
Scintigraphy with the 123I-MIBG (metaiodobenzylguanidine) radiopharmaceutical is suitable for diagnosis, and 111In-Octreoscan (octreotide) is also possible. Serum levels of catecholamines and their metanephrine metabolites, respectively, can be analysed..

The basic treatment of feochromocytoma, resp. paraganglioma, is based on surgical excision. Pre-operative preparation with alpha-blockers is important as large amounts of catecholamines may be released during the operation and life-threatening hypertensive crisis may occur. A laparoscopic approach is also possible, maintaining adrenal cortex without the need for lifelong corticoid substitution. Experience with chemotherapy is limited and the **radiopharmaceutical 131I-MIBG (meta-iodobenzylguanidine) is the most effective known treatment, used at higher doses than in diagnostics.**

- **Endocrine tumours of hypophysis and pancreas - basic characteristics and symptoms**

Pituitary adenomas and endocrine pancreatic tumors are rare and should be considered. Tumors can cause mechanical problems (oppression, pain, bleeding, obstruction), but can also be associated with specific hormonal syndromes according to the type of secretion. Most tumors are well differentiated (grade 1) and low-aggressive, but some may have the character of already aggressive neuroendocrine carcinoma (grade 3).

Hormonally inactive pituitary adenoma: by oppression it reduces the function of the pituitary gland and hormone secretion (hypopituitarism, panhypopituitarism), oppresses the pathway of the n.opticus (bitemporal hemianopsia).
Hormone active pituitary adenoma: hormone production syndrome - mostly prolactinoma, STH or ACTH, TSH and gonadotropin.

Endocrine pancreatic tumors (about 1% of all pancreatic tumors) may be hormone-dysfunctional, but mostly(80%) they are with hormone production eg:

Gastrinoma *- gastrin production, Zollinger-Ellison sy (hyperacidity, ulcers, diarrhea)*
Insulinoma - *production of insulin, hypoglycemia*
Glucagon - *production of glucagon, hyperglycemia*
VIP - *production of VIP (vasoactive intestinal peptide) - watery diarrhea*
Carcinoid - *serotonin production - typical flushing*

Diagnostics: Clinical symptomatology, changes in biochemical laboratory. The typical marker is serum chromogranin A (CgA) and Neuron-specific enolase (NSE). Specific hormones can also be analysed - for example, insulin and its precursors and metabolites for insulinoma, serum gastrin, glucagon, somatostatin and vasoactive intestinal peptide (VIP) as well as serotonin catabolite - 5-hydroxyindole acetic acid (HIAA) in 24-hour urine collection after diet.
Imaging methods include CT, MR, classical 18F-FDG PET / CT, OctreoScan (scitnigraphy with detection of somatostatin receptors typical of neuroendocrine tumors).

- **Neuroendocrine tumours as a general group - manifestations, diagnostics, serotonin syndrome, treatment with somatostatin analogues**

Most often they present as tumors from diffuse neuroendocrine tissue, especially in GIT, pancreas and lungs. They can occur more or less everywhere. This group includes also tumors of the pituitary gland and adrenal medulla (pheochromocytoma, paragangliomas). Many tumors escape the diagnosis during the patient's life. In the Czech Republic about 300 patients a year get sick. Most have a good prognosis of survival. The causes are often unknown, there can be predispossition e.g. genetic syndromes (eg MEN - multiple neuroendocrine neoplasia type 1 and 2, neurofibromatosis).
We distinguish little aggressive neuroendocrine tumors (grade 1 and 2) and highly malignant neuroendocrine carcinoma (grade 3). The older **name carcinoid is used for** lung tumors or for tumors that produce serotonin and have clinically expressed carcinoid syndrome.
The manifestations are given by localization (eg pains or symptoms from oppression) and by the type of hormone production if they have the ability to secrete it (gastrin, insulin, glucagon, serotonin, vasoactive intestinal peptide). **Carcinoid (serotonin) syndrome** may be accompanied by typical flushing and diarrhea, as well as retroperitoneal and subendocardial fibrosis (carcinoid heart disease).
Diagnostics: Clinical symptomatology, changes in biochemical laboratory. The typical marker is serum chromogranin A (CgA) and Neuron-specific enolase (NSE). Specific hormones can also be

analysed - for example, insulin and its precursors and metabolites for insulinoma, serum gastrin, glucagon, somatostatin and vasoactive intestinal peptide (VIP) as well as serotonin catabolite - 5-hydroxyindole acetic acid (HIAA) in 24-hour urine collection after diet. **Imaging methods** include CT, MR, classical 18F-FDG PET / CT, OctreoScan (scitnigraphy with detection of somatostatin receptors typical of neuroendocrine tumors).
Treatment: Surgical removal is essential in therapy. In hormone-active neuroendcrine tumours, special attention should be paid to pre-operative preparation and peri- and post-operative medication to prevent the occurrence of complications in the form of a carcinoid crisis (administration of somatostatin analogues).
Somatostatin analogues - Somatostatin is a natural hormone that inhibits the secretion of growth hormone and thyroid stimulating hormone (TSH) in the adenohypophysis. It also inhibits secretion of gastrin, cholecystokinin and other hormones GIT, glucagon and insulin, inhibits secretion of gastric and pancreatic juice, motility of GIT. Its synthetic analogs are eg octreotide (Sandostatin), lanreotide (Somatuline Autogel). **Somatostatin analogues block hormone secretion and cell division, and are of great use in the treatment of neuroendocrine tumors.**

- **Lung and pleural tumors - small cell lung cancer and pleural mesothelioma - causes, manifestations, diagnosis and treatment**

Lung cancer originates from bronchial epithelial cells or lung parenchyma. **Malignant pleural mesothelioma** arises from the mesoderm, the serous lining of the body cavities. Every year, more than 6,000 patients in the Czech Republic become ill with lung cancer, its incidence in men is 2-3 times higher than in women, but the incidence trend in women is increasing. Malignant pleural mesothelioma is a rare malignancy with incidence about 100 cases per year in the Czech Republic.
With regard to histological characteristics, lung cancer is divided into **two basic types - small cell lung cancer (SCLC)** and more common (85%) **non-small cell lung cancer (NSCLC)**.
The main risk factors are tobacco smoking (nicotinism), exposure to asbestos, heavy metals (chromium, arsenic, beryllium, nickel, lead), organic solvents, radon and ionizing radiation. The development of mesothelioma is typically associated with asbestos exposure.
Symptoms: **Cough** - may manifest as new, long-lasting cough, or as a change of the character of chronic smokers cough. Anyway, cough lasting for 3-4 weeks and more should be an indication for further examination, minimaly including a chest X-ray! **Haemoptysis**; **recurrent inflammation** (retention pneumonia, so-called pneumonia behind stenosis); **pain**; **dyspnoea**; **hoarseness** (caused by compression of n. laryngeus recurens leading to paresis of the left vocal cord); **upper vena cava syndrome**; **endocrine manifestations** (caused when tumor can produce hormonally active molecules, e.g. parathromone (development of hypercalcaemia and hypophosphataemia), antidiuretic hormone (development of swelling and hyponatraemia) or ACTH (development of Cushing's syndrome with hypokalemia).
Diagnostics: Chest X-ray, CT is the "gold standard". Morfological verification is necessary – taking biopsies by transparietal puncture in peripheral tumor localization and / or bronchoscopy by biopsy or cytology in central tumors.
Small cell lung cancer (SCLC) - highly aggressive with typically rapid growth and early dissemination, mostly diagnosed at an advanced stage (approximately 70% already with metastatic disease). Due to its aggressive nature and frequent advances, it is rarely possible to provide surgery. It responds well to chemotherapy (cisplatin, etoposide) and radiotherapy (80-90%), but the treatment response is usually temporary and the overall prognosis is unfavorable. Due to the high risk of CNS metastases, prophylactic brain irradiation is recommended in order to eradicate undetectable brain micrometastases.

Malignant pleural mesothelioma - highly aggressive, clinically manifested mainly by irritating cough and increasing dyspnea caused by pleural effusion. In general, treatment options are very limited and the prognosis is extremely unfavorable. Only a small number of patients is able to undergo radical surgery (i.e. resection of the lung, parietal and visceral pleura, pericardium and diaphragm). Other treatement options represent chemotherapy or chemoradiotherapy, but the risk of complications is high and the results are unsatisfactory.
Complementary treatment of lung cancer: Bronchoscopic interventions - interventional treatment of bronchial hemorrhage, brachytherapy, cryotherapy, electrocoagulation and implantation of stents into malignant stenoses.

- **Lung and pleural tumors - non-small cell lung cancer, causes, manifestations, diagnosis and treatment**

Lung cancer originates from bronchial epithelial cells or lung parenchyma. Every year, more than 6,000 patients in the Czech Republic become ill with lung cancer, its incidence in men is 2-3 times higher than in women, but the incidence trend in women is increasing.
With regard to histological characteristics, lung cancer is divided into **two basic types - small cell lung cancer (SCLC)** and more common (85%) **non-small cell lung cancer (NSCLC)**, which usually has a slower growth rate and greater chance of surgical treatment. NSCLC is further divided into several histological subtypes (adenocarcinoma, squamous carcinoma, large cell carcinoma). **Accurate histological diagnosis and molecular genetic testing is essential for the choice of appropriate targeted therapy.**
The main risk factors are tobacco smoking (nicotinism), exposure to asbestos, heavy metals (chromium, arsenic, beryllium, nickel, lead), organic solvents, radon and ionizing radiation.

Symptoms: **Cough** - may manifest as new, long-lasting cough, or as a change of the character of chronic smokers cough. Anyway, cough lasting for 3-4 weeks and more should be an indication for further examination, minimaly including a chest X-ray! **Haemoptysis**; **recurrent inflammation** (retention pneumonia, so-called pneumonia behind stenosis); **pain**; **dyspnoea**; **hoarseness** (caused by compression of n. laryngeus recurens leading to paresis of the left vocal cord); **upper vena cava syndrome**; **endocrine manifestations** (caused when tumor can produce hormonally active molecules, e.g. parathromone (development of hypercalcaemia and hypophosphataemia), antidiuretic hormone (development of swelling and hyponatraemia) or ACTH (development of Cushing's syndrome with hypokalemia).
Diagnostics: Chest X-ray, CT is the "gold standard". Morfological verification is necessary – taking biopsies by transparietal puncture in peripheral tumor localization and / or bronchoscopy by biopsy or cytology in central tumors. Molecular genetic testing for the presence of some activating mutations (e.g. mutations in the epidermal growth factor receptor gene - EGFR, translocation of the anaplastic lymphoma kinase gene - ALK), which are essential for the choice of appropriate targeted therapy.
In a localized non-small cell lung cancer (NSCLC) tumors (stage I or II) radical surgery (e.g. lobectomy, bilobectomy, pneumonectomy) is preferred, the alternative is stereotactic radiotherapy (application of a high dose of radiation in a small number of fractions to the tumor site). **In advanced tumors** (stage III), radiotherapy is usually used, mostly combined with chemotherapy (platinum derivatives in combination with vinorelbine, paclitaxel or etoposide). Treatment of **metastatic NSCLC** (stage IV) is based on various forms of palliative systemic treatment: chemotherapy (platinum derivatives in combination with paclitaxel, gemcitabine, or pemetrexed); according to the subtype antiangiogenic targeted therapy (bevacizumab); targeted therapy in the form of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (e.g. gefitinib, erlotinib, afatinib) or anaplastic lymphoma kinase (ALK) inhibitors (e.g. crizotinib, alectinib). Where

appropriate, immunotherapy with checkpoint inhibitors is used (e.g. pembrolizumab, nivolumab, atezolizumab). **In case of recurrence of the disease or its worsening (progression) during the initial treatment**, further treatment possibilities are limited. Depending on the type of cancer and its genetic profile, other lines of chemotherapy or targeted therapies (EGFR tyrosine kinase inhibitors, ALK inhibitors, etc.) or immunotherapy may be tried.
Complementary treatment of lung cancer: **Bronchoscopic interventions** - interventional treatment of bronchial hemorrhage, brachytherapy, cryotherapy, electrocoagulation and implantation of stents into malignant stenoses.

- **Non-melanoma skin tumors - basic types, causes, prevention, treatment**

Non-melanoma skin tumors are a heterogeneous group of malignancies. **The most common epithelial origins include basal cell carcinoma (basal cell carcinoma) and squamous cell carcinoma (spinal cell carcinoma).** Lymphomas and other tumorsa also can occur. The incidence of non-melanoma skin tumors is increasing worldwide, these are the most common tumors in general. In the Czech Republic, over 27,000 patients become ill every year. **The mortality is low.**
The basic risk factors include UV radiation (chronic exposure), ionizing radiation, chronic immunosuppression, chemical carcinogens (tar – historically, carcinoma of the scrotum in chimney-sweeps), genetic factors (xeroderma pigmentosum). In spinaliomas, also chronic scarring diseases (ulcers, fistulas) and HPV infections in tumors of the anogenital area.
Basal cell carcinoma often grows in the form of nodules, ulcerating after years (ulcus rodens). Basal cell carcinoma rarely metastasizes. Rather, it threatens the patient with locally destructive growth, and death is exceptional.
Spinalioma initially has the appearance of a rigid, bumpy deposit, but may ulcerate or grow in the form of an exophyte. Unlike basal cell carcinomas, they have a greater tendency to lymphogenic dissemination and in advanced conditions they also metastatsize hematogenously, e.g. to the lungs.
Diagnostics: Based on a clinical and histological examination. Imaging technics are important to examine locoregional spread, regional lymph nodes or eventualy distant metastases.
The treatment is based on **surgery**. For those unsuitable for surgical treatment (head area, multiple basal cell carcinomas), cryotherapy with liquid nitrogen or radiotherapy can be used. Chemotherapy tends to be less used.
The prognosis of the early stages of basal cell carcinomas and spinaliomas is excellent, 90-95% of patients are cured by radical surgery in the case of spinaliomas.
Prevention is to limit exposure to carcinogens (see above), for anogenital areas HPV vaccination.

- **Malignant melanoma - causes and prevention, surgery, chemotherapy, targeted treatment and immunotherapy**

Malignant melanoma arises from melanocytes. T**he most often occurs on the skin, rare localisations represent mucous membranes and eye.** The incidence is increasing dramatically. There are about 2,500 patients diagnosed every year in the Czech Republic. Genetic factors (familial incidence 5-10%) and environmental factors - UV radiation, especially in phototypes I and II (poorly tanning blonde and red-haired people with a tendency to create freckles) contribute to the development, the UV dose in childhood and shock tanning with sunburn.
Melanoma can occur in pre-existing pigmented nevi (in about 1/3 of cases), but more often it occurs *de novo*. In the initial stages, the symptoms are poor. Itching or bleeding may occur during melanoma ulceration. **Not every melanoma is pigmented** (amelanotic forms of

melanoma). **Suspected changes are defined as ABCDE criteria:** A - asymmetry, B - irregular border, C - color, D - diameter over 5mm, E - permanent enlargement.
Superficially spreading (superficial) melanoma - the most common, initially grows horizontally as an unevenly colored lesion. **Nodular melanoma** - the second most common, growth is vertical, rapid from the beginning, ulceration and bleeding often occur. It has a worse prognosis, it almost always occurs de novo. **Acrolentiginous melanoma** - occurs on the palms, soles and fingers. It can be mistaken for hematoma, bruising or wart. **Lentigo maligna melanoma** - occurs in elderly patients on the face and other sun-exposed areas, usually growing slowly.

Diagnostics: Based on a clinical examination with biopsy sampling; X-ray, USG, CT, PET/CT or MR can be used to visualize regional lymph nodes or distant metastases. No typical laboratory changes.
The treatment of early stages is based on surgery - removal of melanoma, or the first descending lymph nodes (so-called sentinel lymph nodes) and if it is positive, dissection of the nodal area is indicated**. In advanced and metastatic stages**, **targeted treatment** is used in the presence of a BRAF oncogene mutation (positivity in about 40% of patients) or **immunotherapy** with a monoclonal antibody that blocks inhibitory receptors on T lymphocytes (check-point inhibitors). Palliative chemotherapy has little effect and is used in cases where targeted therapy or immunotherapy cannot be given.
The prognosis corresponds to the classification according to clinical stages, respectively the thickness of melanoma - the probability of 10-year survival in tumors with a thickness of ≤ 1 mm is 92% and, conversely, in> 4 mm it decreases to only about 50%. The prognosis with disseminated melanoma during chemotherapy is very poor and about 10% of patients lived more than five years. With modern treatment strategies (targeted treatment and immunotherapy) there is a substantial improvement of patients‘ prognosis.

- **Breast cancer - incidence, causes, symptoms, diagnostics, prevention, screening, genetics**

There are two main histological subtipes: **ductal** (84%) and **lobular** (15%) **carcinoma**. A very aggressive form is **erysipeloid (inflammatory) carcinoma** - it infiltrates the entire breast, which is reddish, painful, with skin damage that has the appearance of an orange peel (peau d´orange), grows rapidly and establishes lymph node and also distant metastases. A special form of ductal carcinoma in-situ is Paget's carcinoma of the nipple, in which tumor cells invading ducts penetrate the epidermis of areola.
Breast cancer is the most commonly diagnosed cancer in women. It is 100 times more common in women than in men. In the Czech Republic about 8,000 new cases are diagnosed every year.
In most cases, it occurs in a sporadic form from the accumulation of mutations in mammary cells and the most significant risks are age and estrogen exposure (i.e. early menarche, late menopause, nulliparity, hormone replacement therapy).
Hereditary forms are seen in 15-20% of breast tumors: familial occurrence (in women with a positive family history, but without an obvious genetic mutation) and hereditary form (they make up 5-10% of all patients and specific gene mutations can be found - the most important genes **BRCA 1 and BRCA 2**). Due to the high risk of breast nacncer and also other cancers - e.g. gynecological malignancies, healthy individuals harboring these gene mutations are preventively monitored and examined (magnetic resonance, sono, mammography), preventive mastectomy and also hysterectomy with bilateral salpingo-ovarectomy is offered.

Thanks to the screening program, more than half of paptients are diagnosed in the early asymptomatic phase. Otherwise, palpable resistance is a typical manifestation. A sign of a

dangerous inflammatory cancer is redness and swelling of the skin of the breast resembling inflammation with the so-called orange peel. Lymphatic metastases are most common in regional lymph nodes - especially axillary. Hematogenous spread with distant metastases to bones, lungs, pleura, liver, ovaries, skin and brain can occur even in a subclinical tumors.
The most common diagnostic methods include mammography and sonography of the breast and regional lymph nodes. The final diagnosis is performed by a biopsy of the tumor under ultrasound control using a core cut biopsy needle. Complete histological information on tumor type, hormone receptor expression, HER2/neu, degree of differentiation (grade) and mitotic activity are required due to the subsequent choice of adjuvant systemic oncological treatment. Preoperative staging includes examination of the lungs, liver and bones, as the most common sites of metastatic spread (X-ray, USG, CT, bone scintigraphy).
A routine mammographic screening program is performed in the Czech Republic. Every two years, the examination is paid for women from the age of 45 years. It leads to the detection of small tumors, which have an excellent prognosis. More than half of patients are diagnosed at a localized stage and there is a trend of declining mortality.

- **Breast cancer - surgery, radiotherapy, hormonal treatment, targeted treatment, chemotherapy**

The comlex treatment procedure is determined by a multidisciplinary tumor board (surgeon, clinical oncologist, radiation oncologist, radiologist, etc.).
Early breast cancer: Surgical treatment of smaller tumors is usually based on local excision of the tumor with a border of healthy tissue and sentinel node biopsy. Preoperative (non-adjuvant) chemotherapy may be started for larger and more aggressive tumors. Breast-saving (partial) surgery is not suitable in some cases (large tumor, multilocular tumors, invasion to the skin, inflammatory cancer), in which mastectomy is necessary. Ultrasound or clinically diagnosed suspicion of metastatic involvement of the axillar lymph nodes requires exenteration of the axilla. After breast-sparing (partial) surgery, it is necessary to undergo adjuvant radiotherapy, which significantly reduces the risk of local recurrence. In estrogen receptor-positive breast cancers (hormone-dependent cancer), adjuvant (postoperative) hormonal treatment is recommended for 5-10 years with anti-estrogens (tamoxifen) or aromatase inhibitors (anastrozole, letrozole). Adjuvant chemotherapy is usually used in young patients with high-risk patients with aggressive cancer, hormone-negative, HER2-positive, and metastatic lymph node involvement. Adjuvant targeted treatment with trastuzumab (anti-HER2 monoclonal antibody) is added in HER2/neu positive tumors.
Metastatic breast cancer: spreads lymphogenically to the axillary and parasternal lymph nodes and hematogenously to the lungs, liver and bones. Hormone-dependent metastatic disease (tumor cells express estrogen receptors) can be treated with hormonal therapy (e.g. anti-estrogen tamoxifen, aromatase inhibitor - anastrozole, letrozole, exemestane), if possibly combined with targeted therapy (e.g. anti-HER2, cyclin-dependent kinase inhibitors, mTOR inhibitors). For palliative chemotherapy, mostly is used monotherapy with various cytostatics (anthracyclines, taxanes, vinorelbine, eribulin, capecitabine, cisplatin, etc.). In patients with HER2/neu positive tumors, a combination of anti-HER2 targeted therapy and chemotherapy is used. Chemotherapy alone is the only systemic treatment option for triple-negative cancers.
Prognosis: 10-year survival is about 90% in a localized stage; median survival in metastatic stage is about 3 years.

- **Esophageal and gastric cancer – causes, symptoms, diagnostics, treatment**

The two main sub-types are **squamous-cell carcinoma** (ESCC), which usually arises from the epithelial cells of upper two thirds of the esophagus and is more common in the developing countries and **esophageal adenocarcinoma** (EAC), which is more common in the developed world. EAC arises from glandular cells present in lower third of the esophagus, often where they have already transformed to intestinal cell type (Barrett's esophagus). Rare types of esophageal cancer include lymphoma, neuroendocrine tumor, sarcoma or melanoma.
600 new cases of esophageal cancer and 1500 new cases of gastric cancer are diagnosed in the Czech Republic each year. It mostly affects men and patients aged 60 and more.
Causes of the squamous-cell type include tobacco, alcohol, very hot drinks, poor diet, and chewing betel nut. The most common causes of the adenocarcinoma type are smoking tobacco, obesity, Barrett's esophagus, reflux and Helicobacter pylori infection.
Symptoms are dysphagia, odynophagia, weight loss, dyspepsia (nausea, vomiting, regurgitation of food, coughing), anemization for ulcerating cancer. The disease is diagnosed by biopsy sampled during endoscopy. Endosonography (EUS) and other imaging techniques help set the stage of the disease. Examination of tumor markers CEA and CA 19-9 should support the definitive diagnose.
50% of esophageal and gastric cancers are diagnosed in metastatic or extensive stage with poor prognosis and median survival around 12 months.
Treatment is based on the cancer's stage and location and should always consider patient's general condition and individual preferences. Small localized cancers may be treated with radical surgery alone (esophagectomy, partial or total gastrectomy). But in most cases, chemotherapy (fluorouracil, cisplatin) or chemoradiotherapy is used along with surgery (neoadjuvant or adjuvant). Palliative care is often recommended for patients with poor performance status or extensive disease.
Prevention includes – healthy diet, stop smoking and cut down on alcohol.

- **Colorectal cancer – epidemiology, symptoms, diagnostics, prevention, screening**

The main (95%) histological type of colorectal cancer, is adenocarcinoma. There are 7 500 new cases diagnosed in the Czech Republic each year. 5-10% of colorectal cancer occurs due to inherited genetic alteration associated with soma hereditary syndrome (FAP – familial adenomatous polyposis, Lynch syndrome – hereditary non-polyposis colorectal cancer).
Risk factors: older age, male sex, high intake of fat, sugar, alcohol, red meat, processed meats, obesity, smoking, lack of exercise, inflammatory bowel disease (ulcerative colitis, Crohn's disease). Presented adenomas is a precancerous condition, so they should be excised during colonoscopy.
Main symptoms include changes in bowel habits and consistency (constipation, decrease in stool caliber, blood in the stool), loss of weight, nausea or vomiting, sideropenic anemia from chronic bleeding from the tumor, causing fatigue and faint. 50 % cases of colorectal cancer are asymptomatic.
Diagnostics - Screening program, colonoscopy, CT for staging of colon cancer and transrectal endosonography and MRI for staging of rectal cancer. Tumor markers CEA and CA 19-9.
Screening programs are conducted by general practitioners in cooperation with gynecologists.

- Colorectal cancer – fecal occult blood test - once a year in people aged 50-54, every two years in people older than 55 or colonoscopy every ten years

Prevention: Endoscopic radical resection of every polyp in the bowel. 50 % of colorectal cancer cases are due to lifestyle factors, 25 % are preventable. Increasing surveillance, engaging in physical activity, consuming a diet high in fiber, and reducing smoking and alcohol consumption decrease the risk of it.

- **Colorectal cancer – surgery, chemotherapy and targeted treatment, therapeutic options for metastatic stage**

Localized colorectal cancer (stage I-III) - Complete surgical removal with adequate margins is the preferred treatment (partial colectomy or proctocolectomy for rectal lesions) where the affected part of the **colon or rectum** is removed along with parts of its mesocolon and draining lymph nodes. The colon may then be reconnected or a person may have a colostomy. Sometimes radiotherapy with chemotherapy (capecitabine p.o.) is used before surgery (neoadjuvant) in locally advanced **rectal tumors** to shrink its size (downsizing) and to enable surgical resection, so that ultimately a colostomy is not required. It decreases a risk of a local relapse after surgery. Chemotherapy (5-fluorouracil i.v., oxaliplatin i.v.) in more advanced localized cancer (Stage III) is recommended in addition to surgery to reduce risk of a relapse.
Advanced, metastatic cancer (stage IV) - Surgery may be performed in patients with only few metastases in the liver or lungs, operability depends on the size, number and localization of the metastases. In some cases, cancer with few liver metastases may be treated with one of ablative techniques – radiofrequency ablation (RFA) or microwave ablation (MWA), or embolization technique (TACE, TARE). The main aim of treatment of stage IV cancer, is palliative –to prolong life with the best possible quality of life. Chemotherapy used in stage IV – 5-fluorouracil, oxaliplatin, irinotecan (i.v.). **Targeted treatment** include antiangiogenic bevacizumab and regorafenib - it slows the growth of new blood vessels in tumor by inhibiting vascular endothelial growth factor (anti-VEGF), or inhibitors of epidermal growth factor receptor (anti-EGFR) such as cetuximab and panitumumab.
Prognosis: 5-year survival drops with higher stages of the disease. I.stage 93%, IV.stage 8%. If the patient is able to receive intensive chemotherapy, the median survival for metastatic disease is between 24-30 months (complete resection of metastases carries a chance for long-term remission, even recovery).

- **Liver tumors – hepatocellular carcinoma – etiology, diagnostics and treatment options**

Hepatocellular carcinoma (**HCC**) is the most common (90%) type of primary liver cancer in adults and it usually occurs in cirrhotic liver tissue in patients with chronic alcohol abuse and patients with hepatitis B or C. Other risk factors include exposure to hepatotoxins (aflatoxins produced by certain molds found in food), metabolic syndrome and NASH (non-alcoholic steatohepatosis), hemochromatosis. Over 900 new cases of HCC is diagnosed in the Czech Republic each year. Incidence slowly decreases in time. Most cases of HCC occur in people who already have signs and symptoms of chronic liver disease. Main symptoms are loss of appetite, weight loss, abdominal pain, abdominal swelling due to ascites, hepatomegaly, belly discomfort, painless icterus, nausea/vomiting, tiredness, fatigue.
Ultrasound, CT scan, and MRI may be used to evaluate the liver for HCC. MRI is more sensitive and specific than CT. **A biopsy is not needed to confirm the diagnosis of HCC if certain CT or MRI imaging criteria in cirrhotic liver are met.** Tumor marker **AFP** can be used during follow-up controls, it is not used in diagnostics.
Treatment of HCC depends on the size and stage of the tumor and on patient's performance status including Child-Pugh score (used to assess the prognosis of chronic liver disease). Surgical treatment involves resection (hepatectomy), liver transplantation, radiofrequency ablation (RFA) or chemoembolization. **In stage IV (inoperable, metastatic)** HCC, targeted drugs (sorafenib, regorafenib) are used to prolong time to progression.
Prevention includes vaccination against hepatitis B, cut down on alcohol consumption (especially in patients with liver cirrhosis) and ultrasonography screening and AFP in patients with cirrhosis.

- **Liver tumors – metastases and possibilities if their treatment**

Secondary liver cancer (metastases) consist of malignant cells which spread there from an initial or primary site through blood vessels. **Secondary liver cancer is 20x more often than primary liver cancer.**
It is always preferred to remove all the metastases, if possible. It depends on their number, size and localization. Complete resection improves prognosis and even complete remission can be achieved. Resection of metastases include metastasectomy, segmenectomy or lobectomy.
In some cases, it is possible to use some of the ablative techniques – radiofrequency ablation (RFA) or microwave ablation (MWA), or embolization techniques (TACE, TARE).

TACE: transarterial chemoembolization using microparticles with cytostatics applied to the metastase

TARE: transarterial radioembolization using microparticles with radionuclide Yttrium-90

- **Bile duct tumors – symptoms, diagnostics, treatment options**

Gallbladder and bile duct cancer (cholangiocarcinoma) may rise from intra- or extrahepatal bile ducts and are more common in women. It is a rare Incidence is slowly decreasing. Gallbladder cancer is often diagnosed coincidentally in a sample from cholecystectomy. Main risk factors are cholecystolithiasis, cholecystitis, gallbladder polyps and calcifications, Crohn's disease, ulcerative colitis, primary sclerosing cholangitis.
Symptoms include loss of appetite, weight loss, abdominal pain, abdominal swelling due to ascites, hepatomegaly, belly discomfort, painless icterus, Courvoisier sign (enlarged, palpable and painless gallbladder), tiredness, fatigue.
Diagnostics. ERCP is used to get a biopsy from a suspect lesion, insert a stent in case of obstructive icterus. Second way to treat obstruction is to make a drainage during percutaneous transhepatic cholangiography (PTC). CT scan is used for staging.
Only possible curative treatment is a radical resection, followed by adjuvant chemotherapy (5-fluorouracil). Chemotherapy (5-fluorouracil, cisplatin, gemcitabine) is also used for metastatic or inoperable stages with palliative aim to prolong time to progression. Strictures of bile ducts, that are not suitable for resection, can be treated with intraluminal brachytherapy to prevent local growth of the tumor around the inserted stent.

- **Pancreatic cancer – manifestation, diagnostics, treatment options**

95 % of all cases are pancreatic adenocarcinomas, which start within the exocrine part of the pancreas, usually in the head of the pancreas (70-80%). Neuroendocrine tumors make up to 5% of all pancreatic malignancies and are less aggressive than adenocarcinomas.
It is more common in men and the incidence slowly increases in time, along with the mortality. There are around 2,200 new cases in the Czech Republic every year. Pancreatic cancer rarely occurs before the age of 40, and more than half of cases occur in those over 70. Risk factors for pancreatic cancer include tobacco smoking, obesity, diabetes, chronic pancreatitis (usually induces by alcohol), 5-10% are linked to inherited genes. Protective effect has physical activity and a healthy diet rich in fruit and vegetables.
Pancreatic cancer usually starts in the head of the pancreas (70-80%) and may have early symptoms (obstructive icterus). On the other hand, cancer localized in the body or the tail is usually asymptomatic for a long time and first symptoms may occur in highly advanced stages. **Common symptoms are obstructive icterus, pain,** ascites, hepatomegaly, thrombophlebitis or phlebothrombosis (Trousseau sign), cholangitis, cancer cachexia.

Endoscopic retrograde cholangiopancreatography (ERCP) with biopsy sampling is the best way to diagnose pancreatic cancer. Computed tomography (CT), ultrasonography or PET/CT is used for staging. **The only curative treatment is Whipple procedure (pancreaticoduodenectomy) followed by adjuvant chemotherapy, in early operable stages (only in 15-20% patients).** In other cases, palliative chemotherapy (5-fluorouracil, oxaliplatin, gemcitabine) is used to prolong survival for several months.

- **Renal cancer – symptoms, diagnostics, treatment options for localized and metastatic disease**

Every year, around 3,000 new cases of **renal cell carcinoma (RCC)** are diagnosed **in the Czech Republic, and the highest incident in the world. The most common histological type in adults is the clear cell carcinoma** (75%) that originates from in the lining of the proximal convoluted tubule. The most frequent renal cancer in children is nephroblastoma (Wilms' tumor).
The greatest risk factors are lifestyle-related - smoking, obesity and hypertension.
The initial symptoms include hematuria (in 40 %), flank pain (40%), weight loss (33%), a mass in the abdomen or flank (25%), hypertension and night sweats. Advanced disease usually spreads to the lymph nodes, lungs, liver, adrenal glands, brain or bones. **Best imaging technique for diagnostics of RCC is CT scan with several typical signs (i.e. saturation, enhancement). Biopsy sampling is needed when the diagnose is uncertain or to verify distant metastases.**
Treatment of localized stages of RCC is partial or radical nephrectomy. In some cases, cryoablation, radiofrequency ablation or chemoembolization can be the best way of treatment, preferentially for polymorbid patients. Adjuvant therapy has no benefit in RCC.
Due to general resistance to radiation and chemotherapy, **metastatic RCC is treated with systemic immunotherapy** (checkpoint inhibitors – nivolumab) **or targeted therapy** - multi-targeted tyrosine kinase and vascular endothelial receptor inhibitors (pazopanib, sunitinib), m-TOR inhibitors (temsirolimus, everolimus).

- **Bladder cancer – symptoms, diagnostics, treatment options**

Most cases 90% of bladder cancer is urothelial carcinoma, other types are rare (i.e. squamous cell carcinoma, adenocarcinoma). Every year, around 2,200 new cases of bladder cancer are diagnosed in the Czech Republic, mostly diagnosed in non-invasive stage. Incidence is 3x higher in men population. **Risk factors** include smoking, prior radiation therapy, frequent bladder infections and exposure to certain chemicals.
Bladder cancer may be asymptomatic for a long time. **Symptoms include hematuria (90%),** dysuria, and low back pain. Even unrepeated hematuria should be a reason for complete examination including cystoscopy. Diagnosis is typically by cystoscopy with tissue biopsies or by cytology from urine. Staging of the cancer is determined by transurethral resection and medical imaging. Staging follows the first **transurethral resection of tumor (TURT), which is also the main treatment of non-muscle invasive cancer** (Ta/T1 – tumors confined to the mucosa or which invade the lamina propria, Tis - flat lesion). Instillation of chemotherapy or BCG vaccine into the bladder (intravesical) after primary TURT has shown benefit in decreasing recurrence.
Treatment depends on the stage of the cancer and performance status of the patient. It may include surgery, radiation therapy, chemotherapy or immunotherapy. Surgical options are transurethral resection, partial or complete removal of the bladder, or urinary diversion.
Majority of non-invasive carcinomas (60%) tend to relapse – periodical surveillance with cystoscopy is recommended. Invasive and poorly differentiated carcinomas bring higher risk of spreading throughout the body – to lymph nodes, lung, liver and bones.

Invasive disease (T2-T4) is treated with radical cystectomy (RACE). There are several options to create new way to drain away urine (i.e. ureteroileostomy, neovesica). Cisplatin - containing combination chemotherapy is the standard of care for metastatic bladder care, or checkpoint inhibitors immunotherapy. Median survival is around 15 months.

- **Prostate cancer – symptoms, diagnostics and treatment options for localized stages, monitoring of the effect**

Every year in the Czech Republic about 7000 new prostate cancers are diagnosed. **The main risk factors include** age, hormonal effects (androgens - dihydroandrosterone and testosterone) and genetics (BRCA mutation). The tumour is usually hidden for a long time, and symptoms may manifest after about 15 years. Symptoms start to manifest only when the central zone of prostate is affected - difficult urination with poor starting urination or weak urine flow, frequent nycturias, occasionally even haematuria or retention. A part of the patients is diagnosed in the metastatic stage (pain from sceletal metastases).
The basic examination is digital rectal examination. The tumour marker is **serum PSA** (prostate specific antigen), but is not specific, because it could be increased in elderly men, after prostate massage, during inflammation, after prolonged cycling. Among the imaging methods, **transrectal ultrasound (TRUS)** of the prostate and magnetic resonance imaging are important. Furthermore, the performing of the prostate biopsy is essential. The skeletal scintigraphy, more precisely PET/CT or PET/ MR, is added to determine the extent and possible dissemination (most often into the skeleton). The result of the prostate biopsy is essential for further treatment.
The effect of the treatment is mainly monitored by controlling the development of PSA at regular intervals after treatment.
In localized disease, radical prostatectomy or radiotherapy are available, but in low-risk patients (low PSA, low grade) or with multiple co-morbidities or shorter life expectancy, simple monitoring with repeated follow-up examinations may be selected (active surveillance, watchful waiting).
Radical prostatectomy: in localized tumour, the prostate removal. The risk of urinary incontinence and erectile dysfunction is reported to be around 11 % and 43 %.
Radical radiotherapy: its efficacy in comparison with radical prostatectomy is fully comparable, survival parameters are consistent, and there is lower risk of generalization, as well as sexual dysfunction and urination problems. High doses to 74-80 Gy are applied in standard fractionation (i.e. 5 fractions in a week á 2 Gy, for 7-8 weeks). Alternatively, brachytherapy - permanent (very low dose rate) with implantation of palladium (Pd^{103}) or iodine grains (I^{125}) or temporary (high dose rate) using iridium sources (Ir^{192}). **In patients with more aggressive, more extensive tumor, the radiotherapy is complemented by hormone therapy aiming to reduce testosterone level (androgen deprivation)** - injection LH-RH (luteotropin releasing hormone) agonists or antagonists, that induce the blockage of LH (luteotropic) and FSH (follicle-stimulating hormone) and, by this mechanism, there is decrease in testosterone secretion in the testicles. Antiandrogens (e.g. flutamide, bicalutamide) are used very rarely, they have their role in the introduction of treatment before administration of the LH-RH analogue by short-term bridging of the flare phenomenon (the initial increase in testosterone levels before its decline associated with worsening of the disease).

- **Prostate cancer – symptoms, diagnostics and treatment of metastatic stage, importance of hormonal and targeted therapies, chemotherapy, castration resistance**

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difficult urination with poor starting urination or weak urine flow, frequent nycturias, occasionally even haematuria or retention. A part of the patients is diagnosed in the metastatic stage (pain from sceletal metastases).
The basic examination is digital rectal examination. The tumour marker is **serum PSA** (prostate specific antigen), but is not specific, because it could be increased in elderly men, after prostate massage, during inflammation, after prolonged cycling. Among the imaging methods, **transrectal ultrasound (TRUS)** of the prostate and magnetic resonance imaging are important. Furthermore, the performing of the prostate biopsy is essential. The skeletal scintigraphy, more precisely PET/CT or PET/ MR, is added to determine the extent and possible dissemination (most often into the skeleton). The result of the prostate biopsy is essential for further treatment.
In advanced (metastatic) diseases, the basis of the therapy is the hormonal therapy aimed at reducing testosterone levels (androgen deprivation - castration), the disease initially responds well and usually long-term to hormonal treatment. However, there is a failure of treatment and **transition to a status so-called castration-resistant disease**. In very advanced findings with massive dissemination and organ involvement, therapy combined with chemotherapy (e.g. docetaxel) or targeted ARTA therapy is also recommended.
Hormonal therapy (endocrine therapy), androgen deprivation: The simplest solution leading to a rapid decrease in testosterone levels is to perform bilateral orchiectomy (surgical castration). However, this is no longer preferred. A comparable castration effect have injection LH-RH (luteotropin releasing hormone) agonists or antagonists, that induce the blockage of LH (luteotropic) and FSH (follicle-stimulating hormone) and, by this mechanism, there is decrease in testosterone secretion in the testicles.
Targeted therapy - ARTA: A group of drugs targeted to androgen receptors in advanced diseases. The main representatives are: abiraterone - blocks the enzyme (CYP17A1), which participates in the synthesis of testosterone and thus induces its decrease, and enzalutamide - a strong androgen receptor blocker.
Chemotherapy: limited possibilities of some cytostatics (eg. docetaxel, cabazitaxel, mitoxantrone).
Radium^{223}: Radioisotope, an alpha emitter that is after i.v. application primarily captured in the skeleton and acts on metastatic bone involvement. It is used in patients with symptomatic skeletal metastases.

The overall survival of patients with already generalized prostate cancer is limited and ranges in 2-5 years with active treatment.

- **Testicular tumours – types, characteristics, diagnostics and treatment options**

Malignant testicular tumours can be divided into germinal and non-germinal tumors, with germinal tumors accounting for 92-96 %. **Germinal tumours are histologically seminomas** (55 %) **and nonseminomas** (45 %; main types: embryonal carcinoma, teratocarcinoma, choriocarcinoma, yolk sac tumour, mixed tumours). The most common non-germinal testicular tumours are lymphomas, Leydig and Sertoli cell tumours and sarcomas.
Germinal tumours occur mainly in younger men, annually newly diagnosed in the Czech Republic in about 500 patients. Extragonadal germinal tumours are rare and most often arise in mediastinum and retroperitoneum.
Cryptorchism is **one of the strongest risk factors** for the subsequent development of a testicular tumour. The risk decreases if orchidopexy is performed early. Another important risk factor is the family history of testicular tumour.
Initial symptoms are local in about 90 % of patients. These include testicular pain, testicular enlargement or testicle lump. High levels of choriogonadotropin (HCG) in some non-seminoma tumours can cause mastalgia, swelling of the nipples and gynecomasty. In about 10 % of patients,

symptoms of metastatic disease such as back and abdominal pain (due to retroperitoneal lymph node involvement), dyspnoea and hemoptysis (metastatic lung involvement) are already present at the diagnosis. The tumour usually spreads lymphogenically to the retroperitoneal lymph nodes, later hematogenously most often to the lungs.
The primary treatment is inguinal orchiectomy. Depending on the extent of the disease, subsequent **postoperative adjuvant therapy is added - most commonly combined and intensified BEP chemotherapy** (bleomycin, etoposide, cisplatin). **The prognosis of the disease is generally very good, with a very high chance of complete recovery after intensive treatment.**

- **Uterine tumours – symptoms, diagnostics and treatment options, screening, prevention**

The most common uterine cancer is endometrioid adenocarcinoma from the endometrium, as well as leiomyosarcoma from the myometrium. **In the cervix**, there is squamous cell carcinoma from the exocervix, and less often adenocarcinoma from the cervical canal (endocervix). **The main etiological factor of cervical cancer is infection** with high-risk HPV (human papillomavirus), most often types 16 and 18, and a higher number of sexual partners. **In endometrial cancer, there are estrogens**, late menopause, obesity, Lynch syndrome.
Most pre-cancerous and non-advanced cervical tumours are asymptomatic (screening required), sometimes there is bleeding after sexual intercourse. More advanced stages with bloody or purulent discharge, spontaneous bleeding or abdominal pain or pressure on the rectum. Most tumours of the uterine body are manifested by vaginal bleeding - hypermenorrhea in premenopausal women, or more often by so-called metrorrhagia in postmenopausal women.
The basic diagnostic method is a comprehensive gynecological examination. Transvaginal ultrasonography is a compulsory imaging method for vaginal bleeding.
Precancerous lesions of the cervix are diagnosed by so-called oncological cytology and histological diagnosis can be made by probatory excision. **In case of endometrial involvement, curettage or biopsy of the endometrium is performed under hysteroscopic control**.
As part of the staging of the disease it is recommended to perform X-ray examination of the lungs and CT examination of the abdomen and pelvis. **The extent of uterine tumors is classified according to either the FIGO classification of gynecological malignancies or the TNM classification (stages I-IV).**
The basic treatment method of uterine cancer is **surgical treatment**. The radicality of the procedure varies depending on the disease extent. **Adjuvant (postoperative) radiotherapy** has been shown to reduce the incidence of local and regional relapses and is more commonly used in locally advanced stages. It can be performed either by external beam radiotherapy alone for the pelvic lymph nodes or in combination with brachytherapy. In more advanced stages, concomitantly with chemotherapy
The most reliable method of primary prevention of cervical cancer is HPV vaccination. Vaccination is recommended before initiation of sexual life. **Hormonal contraceptives and increased physical activity reduce the risk of endometrial cancer**.
Screening programs for cervical cancer: organized in collaboration with general practitioners and gynecologists - the first gynecological examination at the age of 15 and once a year with a cytology examination of the cervical smear.

- **Ovarian and Fallopian tube tumours - symptoms, diagnostics and treatment options, ascites and GIT obstruction, surgery, chemotherapy, possibilities of targeted treatment, genetics**

The most common (90%) ovarian malignancy is adenocarcinoma, which includes several specific subtypes. In addition, **germinal** or **lymphoma** or **metastasis of the gastrointestinal carcinoma (the so-called Krukenberg tumor)** may occur more rarely. Approximately 1,000 women a year suffer from ovarian carcinoma in the Czech Republic. **One of the important causes in a minority of cases (approximately 10%) is the mutation of BRCA oncogenes,** which pose a risk of developing ovarian cancer in up to 60% and 30% of carriers (mutation also plays a role in breast cancer). Otherwise, the cancer is sporadic, where risk factors include early onset menarche, late menopause.
At the begining, the cancer develops mostly without symptoms, and the first manifestations occur after its progression, especially because of implant metastases on peritoneum and also pleurally leading to the development of ascites and hydrothorax. In most cases, there are recurrent disorders of intestinal passage, cachectization. Otherwise pelvic and abdominal pain, abdominal volume increase, shortness of breath can be observed.
Diagnostics: Basic gynecological examination including transvaginal sonography is essential. CA-125 and HE-4 may be elevated when examining tumor markers. Among imaging methods, besides USG, CT is particularly beneficial. Histological examination from a tru-cut biopsy or directly from a surgical resection is essential to accurately classify the cancer.
The basic therapy is surgical radical resection, which usually includes radical hysterectomy with bilateral adnexectomy, appendectomy, omentectomy, pelvic and paraaortal lymphadenectomy. **Very often adjuvant (postoperative) chemotherapy (paclitaxel and carboplatin) is given in several repeated cycles.** In cases of more advanced diseases, preoperative (neoadjuvant) chemotherapy may be applied, where possible regression of malignancy after chemotherapy may allow resectionm usually followed by adjuvant (postoperative) chemotherapy again. **For inoperable or metastatic diseases,** systemic treatment in the form of palliative chemotherapy (eg. pactlitaxel, carboplatin) is often used. **Targeted treatment molecules,** such as the anti-VEGF bevacizumab or the PARP (poly-ADP-ribozo polymerase) inhibitor olaparib in BRCA mutation patients, are also important and they contribute to prolonging the time to cancer recurrence. **Hormonal therapy (antiestrogen, progesterone, megestrol) can be used in less frequent hormone receptor expressing tumors.**
Prevention - presumably protective effect of hormonal contraception; counseling in BRCA carriers - prophylactic adnexectomy, mastectomy.

- **Sarcomas - basic characteristics and general treatment options**

It is a very heterogeneous group of connective tissue tumors with different prognosis - more than 100 different subtypes has been described, which may differ completely in their biological behavior and therapeutic approach. **Soft tissue and bone sarcomas are rare diseases,** in the Czech Republic about 400 new cases are diagnosed annually. They are more common in children and adolescents. The causes of most sarcomas are unknown.
Palpable resistance is the most common symptom, especially in limb sarcomas. In the case of deeply localized sarcomas, the first symptoms may be caused by local oppression, may include shortness of breath in the case of intra-thoracic localization, enlarged abdomen. Metastasis is very often in the lungs.
Magnetic resonance imaging is a basic examination method for soft tissue tumors. A simple X-ray image is suitable to exclude the presence of primary bone tumors, CT, PET / CT. **In tumors of unclear etiology larger than 5 cm, a high-needle biopsy from multiple tumor sites is**

indicated to minimize the risk of insufficient material for pathologists to capture the diagnosis. For minor superficial lesions (<5 cm), primary excision is acceptable as a final surgical solution. Thin needle biopsy is not recommended. Biopsy is performed by an experienced surgeon or radiologist.
The basis of sarcoma treatment is surgical treatment. The aim is a radical extirpation with negative 2 cm margins. Neoadjuvant chemotherapy or radiotherapy in borderline operable tumors (especially in limb sarcomas, osteosarcomas, Ewing's sarcomas) is indicated to enable radical and limb-saving resection. Alternatively, radiotherapy can be supplemented postoperatively (adjuvantly) to reduce local recurrence. Advanced generalized disease is treated by combined chemotherapy, treatment of child sarcomas is performed according to international standardized protocols.

- **Basic malignant haemato-oncological diseases and their main manifestations, importance of autologous and allogeneic haematopoietic stem cell / bone marrow transplantation**

Acute leukemia **AML (acute myeloid leukemia)** and **ALL (acute lymphoblastic leukemia)** are malignant neoplasms resulting from the uncontrolled growth of immature hematopoietic cells (blasts) of the bone marrow. In the case of **chronic lymphocytic leukemia (CLL)**, the essence is malignant transformation and uncontrolled proliferation of lymphocytes with their accumulation in bone marrow, blood, spleen, liver and nodules. In **chronic myeloid leukemia (CML)**, the hematopoietic stem cell that multiplies uncontrollably but retains the ability to mature, and cells of the whole myeloid hematopoietic developmental line (from blasts, through promyelocytes, to mature granulocytes) accumulate in the bone marrow, blood and spleen, **Lymphomas** are based on malignant reversal of lymphatic cells with typical occurrence in nodules, often in bone marrow, spleen and other organs. In terms of morphological and immunohistological characteristics they are divided into **Hodgkin's lymphoma** (contains typical Reed-Sternberg and Hodgkin cells) and **Non-Hodgkin's lymphomas** group. **Multiple myeloma** is a malignant tumor disease resulting from malignant reversal of plasmocytes - cells of the immune system primarily in the bone marrow and responsible for the production of immunoglobulins. A typical manifestation is the production of monoclonal paraprotein and osteolytic bone lesions.
The most common general symptoms in haemato-oncological diseases are:

Anemic syndrome: tiredness, weakness, paleness, palpitations, vertigo, shortness of breath.
Bleeding manifestations: gingivitis, nasal bleeding (epistaxis), petechiae and haematomas in thrombocytopenia.
Fevers and infections: angina, inflammations of the airways, lungs, dental infections, fevers of unclear origin.
Laboratory and Imaging - peripheral blood testing with differential leukocyte count is always the basic test in case of abnormal blood count finding.

The choice of treatment depends primarily on the patient's age and general condition, leukemia subtype or lymphoma. **All systemic treatment modalities (chemotherapy, targeted therapy, corticotherapy) and radiotherapy can be practically applied,** only surgery is not essential with regard to the systemic character of diseases. **High-dose chemotherapy followed by autologous haematopoietic stem cell transplantation** is an important part of the treatment of relapsing lymphomas and highly malignant lymphomas - enabling high-dose chemotherapy to treat malignancy while ensuring rapid and reliable repair of hematopoiesis. **Allogeneic hematopoietic stem cell transplantation** is reserved for diseases resistant to routine treatment and recurrent, it is very useful in acute leukemias after initial intensive chemotherapy - donated hematopoiesis and transplant lymphopoiesis provide new anti-tumor immunity able to eliminate tumor cells indestructible by previous chemotherapy.

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V Plzni 31.8.2020