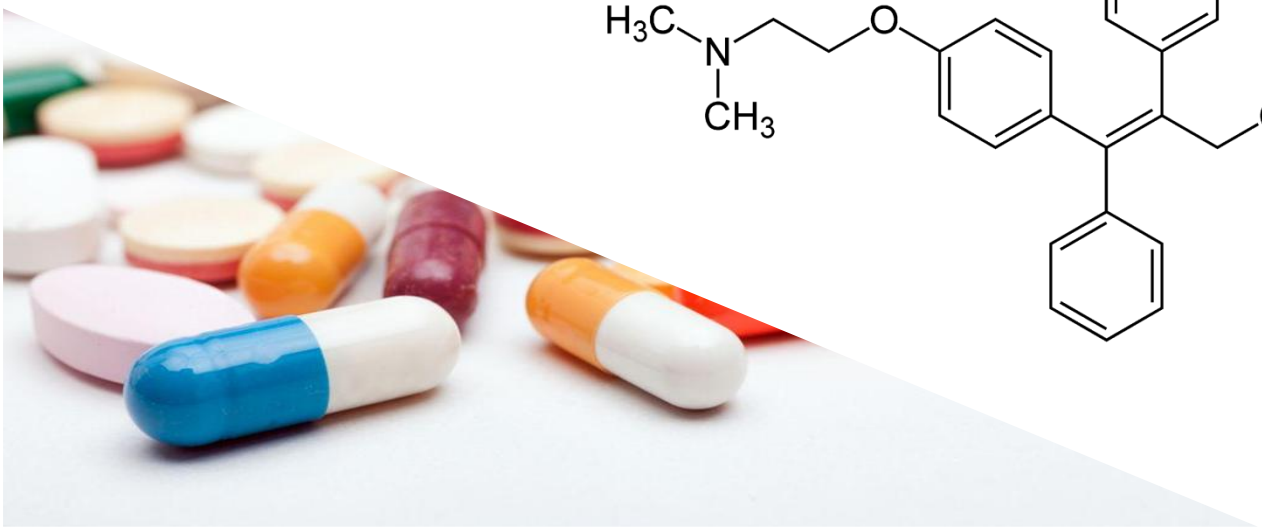

ONCOLOGY

Textbook for the Students of the Third Faculty of Medicine, Charles University

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et al.

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PREFACE

Dear students,

Oncology is a very wide field that deals with the complex treatment of solid malignant tumors. Over the past decade, oncology has seen tremendous development associated with new treatment options which have led to prolonged survival of our patients. It is why we have decided to write this up-to-date study material which reflects these new developments.

Oncology is a field that includes curative, palliative, symptomatic and supportive treatment. It also deals with post-treatment monitoring of patients. Both modern radiotherapy and systemic therapy are used for treatment.

Our textbook should introduce to you the basics of treatment of the most common malignant solid tumors. The entire text is divided into several chapters, the introductory chapters describe the principles and indications of radiation treatment and systemic treatment. We have also included chapters which deal with the notion of supportive treatment. The principles of surgical treatment, however, will be addressed in other subjects.

The general introductory chapters are followed by chapters dealing with specific diagnoses. These were written by doctors who specifically deal with these issues and are divided into a specific scheme:

- Epidemiology
- Etiology
- Symptomatology
- Diagnostics
- Differential Diagnostics
- Pathology
- Therapy
- Post treatment complications
- Follow Up Care

In the form of this text, we have tried to provide you with the latest information you will need not only for the exam in oncology, but also for further study and your eventual medical practice. Unfortunately, the statistics are harsh (more statistics can be found in the chapter on prevention and screening), and you are all more than likely to meet oncological patients in your practice.

Doc. MUDr. Renata Soumarová, Ph.D.

GENERAL ONCOLOGY

1 PREVENTION AND SCREENING IN ONCOLOGY

Renata Soumarová

Oncologic prevention is the most important point of National Oncological Programme (NOP) of Czech Republic, which is based on the conditions and needs of Czech Republic and in concordance with the conclusions of World Health Organization (WHO) adopted for cancer control.

The objectives of the National Cancer Program of the Czech Republic are aimed at reducing the incidence and mortality of cancer, improving the quality of life of cancer patients and rationalizing the costs of diagnosis and treatment of cancer in the Czech Republic. Under the guarantee of the Czech Society for Oncology (CSO), the program is distributed to a number of institutions that may have the slightest influence on the fulfillment of any point. Institutions are invited to sign the program and take responsibility for its implementation.

The basic objectives of NOP include:

- reducing incidence and mortality of cancer,
- improving quality of life of cancer patients,
- rationalization of costs of cancer diagnostics and treatment in the Czech Republic.

The main objectives of NOP are:

- Professional support for teaching cancer prevention in schools. Popularization of primary tumor prevention. In particular, reducing smoking in young people and women. Supporting positive changes in nutrition and lifestyle.
- Ensure long-term functioning and audits of breast cancer, cervical cancer, and colon cancer screening programs.
- Improve early diagnostics of malignant tumors, especially in cooperation with general practitioners. Innovating the content of preventive examinations integrating the detection of oncological, cardiovascular and metabolic diseases.
- Naming a network of complex diagnostic and therapeutic cancer care centers accredited by CSO on the basis of four competencies: qualification, equipment, self-evaluation and communication.
- Promoting equality of coverage of the population with comparable cancer services and access to information on cancer prevention, diagnosis and treatment.
- Ensure anchoring and stability of palliative and terminal care facilities. Support the development of home care. Monitoring the quality of life and pain treatment of patients with advanced malignancies.
- Support of continuity, stabilization, modernization and practical use of the database of the National Cancer Registry of the Czech Republic for controlled preventive and diagnostic-medical care in oncology.
- Support of applied cancer research and innovation. Introduction of principles of HTA (health technology assessment) in oncology. Support of education in oncology.

Only by concentrating highly specialized cancer care in relevant healthcare facilities can patients be provided with the highest quality care possible.

In 2005, the Czech Society for Oncology, ČSL JEP, institutionalized the establishment of **Comprehensive Cancer Centers** accredited by CSO on the basis of four competencies: qualification, equipment, self-

evaluation and communication. Comprehensive cancer centers co-create a network of cancer services in the regions in cooperation with other departments or outpatient departments involved in cancer care.

In general, the number of newly discovered cancer (**incidence**) is increasing, death rate (**mortality**) is slightly lower (graph), but prevalence is clearly increasing, i.e. number of surviving cancer patients. **Every third inhabitant of the Czech Republic gets cancer during its life and one in four dies of it.** Every year, more than **96,500** people in the Czech Republic suffer from malignant neoplasm (data for 2016), of which 49,302 cases in men and 47,198 cases in women. In 2016, there were almost **562,329 persons** living in the Czech Republic who were diagnosed with cancer in that year or earlier. In the Czech Republic, **27,261 people** died of cancer in 2016. Cancer mortality shows stagnation in absolute numbers! We are at the forefront in the number of oncological diseases in Europe.

Among the most common diagnoses, except skin tumors, are colon and rectal cancers, malignant prostate cancers in men, breast cancer in women and tumors of trachea, bronchi and lungs.

Main reasons of higher incidence of malignancies are:

- **aging of the population** – most tumors affect patients of middle and higher age, however growing incidence of tumors in people between twenty and thirty years of age is also alarming,
- **change in diet and lifestyle, higher occurrence of** physical and chemical carcinogens, which is caused, among other things, by **environmental pollution,**
- **but even improved diagnostics and quality of healthcare, which leads to extended lives.**

PRIMARY PREVENTION

Most of proven or probable risks leads to cancer only after some time. So, the sooner we will begin to avoid them, the higher will be our chances, that their effect on our lives will not be fatal. Only about 5% cancers are hereditary, at least third of tumors is preventable. Among those are for instance colorectal carcinoma, carcinoma of cervix, breast, lungs, skin and ENT tumors.

Therefore, the objectives of primary prevention in oncology are:

- reduction of incidence of malignant disease
- reduction of adverse effects of treatment
- reduction of mortality

Since smoking, alcohol and overweight are among the main causes of cancer, the primary prevention is primarily a change in lifestyle and eating habits.

SECONDARY PREVENTION

Secondary prevention, or **screening**, is aimed at detecting malignant tumors at an early stage, which is best treatable. The screening is nationwide but at the same time focused on a defined part of the population (e.g. regular recurrent mammography examinations in women over 45 years). Indicators of secondary prevention are the ratio of localized tumor stages to other more advanced stages and the development of cancer mortality. There are three basic screening programs in the Czech Republic: mammography screening started in 2002, cervical screening (cervical cancer) started in 2008 and

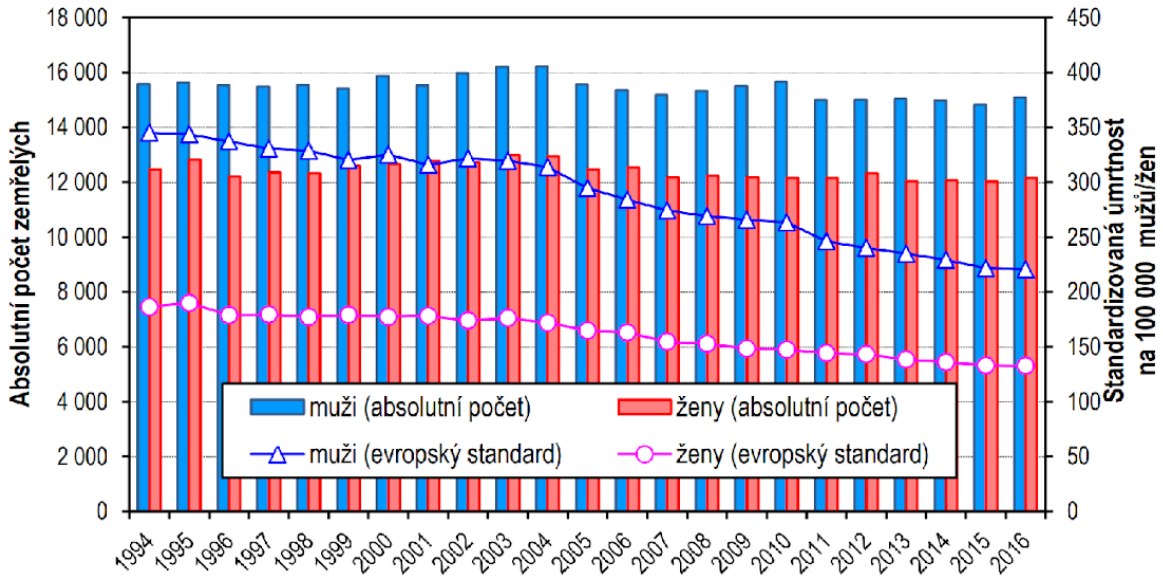
colorectal cancer screening started in 2009. You can read more about all types of screening on the website of the Czech Society for Oncology.

TERTIARY PREVENTION

The aim of tertiary prevention in oncology is to capture the possible return of cancer after primary treatment and asymptomatic interval in a timely and thus still curable form. Cancer patients are followed up for life (**dispensarized**). The way to improve tertiary prevention is primarily through better organization of dispensary care and better communication between specialists and practitioners. However, the problem of dispensary examinations is often the focus only on the original diagnosis or organ. In addition to relapse, patients with a cured tumor are at risk of developing **second primary** tumors. Secondary primary tumors have become the third most common tumor diagnosis. The incidence of multiple primary tumors in the Czech Republic is more than 11% and is still growing.

QUATERNARY PREVENTION

Quaternary prevention in oncology refers to anticipating and preventing the consequences of a progressive and incurable cancer that can shorten the rest of life or reduce its quality. These include, for example, keeping in mind the provision and availability of analgesic treatment and professional algesiological care before pain develops fully. It is also necessary to anticipate and timely address nutritional measures, psychological support and social background with limited self-sufficiency. The indicator of the quality of Quaternary prevention is mainly the continuous evaluation of quality of life questionnaires adapted to the given type of disease.



Graph 1 Development of mortality of malignant tumors in men and women in the Czech Republic between 1994 - 2016

2 BIOLOGY OF TUMORS

Marián Liberko

2.1 TUMOR GROWTH

Under normal conditions, cells of our body follow cyclical renewal, which allows for the replacement of old, damaged, or mutated cells of our body with new cells. This process is under the control of a series of different mechanisms. The control of these processes are hierarchical: mechanisms of cellular proliferation control, mechanisms of cell cycle control, and cell cycle. The main characteristic of malignant tumors is the failure of these control mechanisms (mutations), which leads to their uncontrolled growth, resistance to apoptosis, and eventually its local, regional and distant metastasis, which can be the main cause of death in patients. The cause of the mutation in genes related to the control of cellular proliferation and apoptosis are not only external factors (physical, chemical, and biological) but also internal factors as well (hormones).

2.2 MECHANISMS OF CONTROL OF CELLULAR PROLIFERATION

1. **Proto-oncogenes** – are genes, of which products are growth factors, receptors for growth factors, signal transducers, and transcription factors. The effect of mutations can cause a change of proto-oncogenes in oncogenes, which can have a final impact of excessive and uncontrollable stimulation of proliferation. An example can include excessive production of growth factors, activatable mutated receptors, intercellular signaling, chimeric (fused) genes and more. A mutated proto-oncogene has a dominant character, i.e, the mutation of one allele is manifested in the phenotype. For example:: k-ras, n-ras, b-raf, Her2-neu.
2. **Tumor-Suppressor Genes** – are genes, of which products have anti-proliferative effects, are involved in the repair of DNA and the induction of apoptosis. Their mutations have a recessive character, i.e, it is necessary to have a mutation of both alleles so that the mutation would be manifested in the phenotype. Heterozygotes with inborn mutations in some tumor-suppressor genes have a higher risk of inactivation of these genes (leading to development of tumors) due to it being sufficient to inactivate the only active allele of the gene. For example: p53, BRCA1, BRCA2, Rb, FAP.
3. **Mismatch Repair Genes** – are genes, of which products are involved in the reparation of miss-matched nucleotide bases, which occur during the replication of DNA, or due to environmental factors. Their mutations have a recessive character.

Isolated mutations of individual proto-oncogenes, tumor-suppressor genes, and mismatch repair genes do not lead to the development and transformation of malignant cells. It is necessary to obtain numerous mutations in different genes to lead to the malignant transformation of normal cells through a premalignant lesion. This process takes place over months, or years. Also, most of these mutations are repaired in a timely manner, hence they often do not manifest.

2.3 Control of the Cell Cycle

The cell cycle is a tightly controlled process, which is under the influence of internal and external factors. Regulation of the cell cycle includes - cyclins and cyclin-dependant protein kinases which are under the control of regulatory mechanisms of cellular proliferation (more above).

Cyclins are proteins, which do not have their own intrinsic enzymatic activity. Their concentration inside the cell during specific phases of the cell cycle increases and decreases.

Cyclin-dependent protein kinases are proteins, which have their own intrinsic enzymatic activity, however it is only active when combined in a complex with cyclin (cyclin/cyclin-dependent protein kinase). This complex regulates the progress of individual phases of the cell cycle.

There are many of these complexes, which to a certain level are specific to individual phases of the cell cycle. For example: cyclin D/CdK4,6 – in the G1 phase of the cycle, respectively the transition from G1/S. Their ongoing activation and inactivation is controlled by the changes in the individual phases of the cell cycle.

2.4 Cell Cycle

The cell cycle is the time between the formation of the cell until its division into two sister cells. It is under the control of regulatory mechanisms of cellular proliferation and mechanisms of regulation of the cell cycle (more above). The cell cycle is comprised of phases G0, G1, S, G2, M.

- G0 phase – most cells of an organism, resting phase.
- G1 phase – after mitogen stimulation, the growth of the cell commences, increasing the amount and size of cellular organelles. Preparation for replication of DNA in S phase and synthesis of needed proteins also occurs. G1 phase contains the main checkpoint of the cycle: G1/S checkpoint.
- S phase – takes up the longest time from the entire cell cycle. It is constant for each given cell. Every chromosome is copied exactly based on its template chromosome.
- G2 phase – the cell continues to grow, synthesizes structures, proteins for the daughter cell, synthesises proteins and structures for the mitotic apparatus. This phase contains the second main control point of the cycle: the G2/M checkpoint.
- M phase – contains the separation of chromosomes and the eventual division of the cell into two identical daughter cells.

2.5 Immunity Surveillance

An important role in the process of surveillance and control of malignant transformation and tumor growth is played by the cells of the immunity system. It is explained via the term immune surveillance, which is when tumor cells are eliminated from the organism in a timely manner just like it would happen to foreign cells. According to the theory of immune surveillance, there are three phases: elimination – equilibrium – escape. It is sometimes annotated as the 3E Theory. During the elimination phase, tumor cells are recognized and eliminated via the cells of the immune system, which in turn eliminates the chance of malignant transformation. After some time, tumor cells begin to defend themselves. Not only do they decrease the amount of surface antigens by which they are recognized but also produce cytokines, which inhibit the cells of the immunity system causing a period of equilibrium, when the

tumor is present in subclinical signs, where there is an equilibrium between the production and elimination of tumor cells. In the phase of escape, inhibitory mechanisms against host cells are commenced by the tumor cells, leading to the progression of the tumor and eventual clinical presentation/detection. This 3E Theory is the basis for successful application of immunotherapy in the treatment of oncological disease. The principle lies in the reactivation of the cells of the immune system in the fight against tumor cells. Possibilities include activation of activatable receptors and the inhibition of inhibitory receptors of immune cells.

2.6 APOPTOSIS

During normal conditions equilibrium exists between proliferative cells and apoptosis. Both of these processes are under tight control. In cancer we are met most often with dysregulation in both of these processes. The effect is accelerated and uncontrolled proliferation with a concomitant disruption in apoptosis. During early stages of tumor growth, growth is due to exponential proliferation of tumor cells, which during later clinical manifestation slows down. Even after, the size of the tumor continues to grow, but now more attributed to the development of resistance of tumor cells to apoptosis.

Apoptosis Is a physiological process, an active process, during which old, damaged, and mutated cells are eliminated with the goal of preserving homeostasis in the organism. A disorder of apoptosis is typical for cancer. Just like all other processes in the body, the process of apoptosis is highly controlled. The main role is played by proteins in the family BCL2. Some are inhibitors of apoptosis: BCL2, while others are activators of apoptosis: BAX, BAK, BOK. Two main paths for apoptosis exist, one being intrinsic while the other being extrinsic, which converge on a common pathway.

The external (extrinsic) pathway is involved in the interaction between death receptor ligands and receptors (Fas-FasL, TNF-TNFR, TRAIL-TRAILR). It is the main path towards apoptosis instigated by cells of the immune system. After the binding of the lignand on the death receptor, a signal is given to the cell which leads to the activation of the extrinsic pathway of apoptosis. Also activated is the chain reaction of Procaspase 8 to Caspase 8, which further activates Procaspase 3 to Caspase 3 which is a mutual pathway caspase.

The internal (intrinsic) pathway is launched by genotoxic stress, including damaged DNA mutation, chemotherapy, radiotherapy and other factors. This type of damage leads to the activation of p53, which furthermore stops cell cycle of a damaged cell. The effect of p53 further leads to increased expression of pro-apoptotic proteins. In the end leading to more signals which induce apoptosis. Initiation of this pathway occurs in mitochondria, which is why sometimes this pathway can also be named as the mitochondrial pathway. The pathway leads to increased permeability of the mitochondrial membrane and the release of cytochrome c into the cytoplasm, which in conjunction with proteins Apaf-1 and Procaspase 9 make the complex apoptosome, which activates Procaspase 9 on Caspase9. Caspase 9 further activates Procaspase 3 to Caspase 3 which is part of the mutual pathway of apoptosis.

The mutual pathway of apoptosis therefore begins with the activation of Procaspase 3 to Caspase 3, which can be activated by either the intrinsic or extrinsic pathways. The effector Caspase 3 further initiates the condensation of chromatin, fragmentation of DNA, degradation of organelles, reduction in size of the cell, and creation of apoptotic bodies, which are later phagocytosed by cells of the immune system without the development of inflammation.

2.7 Repair Mechanisms

Defects (mutations) in genes, which participate in the regulation of cellular proliferation, can be identified and repaired by the organism, occurring most of the time. The cell has a few methods of how to repair the mutation. Most of these repairs are instigated by the recognition of mutation by p53, which can further through cooperating proteins stop the cell cycle, which allow for repair mechanisms to repair the genetic defect. If the repair is not possible, apoptosis is incited. When repair mechanisms are faulty, the mutation is left, increasing the chance of malignant transformation of the cell.

Repair mechanisms of the cell are: base excision repair, nucleotide excision repair, mismatch repair for single strand break repair, and non homologous end joining and homologous recombination for double stranded break repair.

Base excision repair – is the recognition and excision of a damaged base and its exchange with correct complementary exchange. Nucleotide excision repair – is the recognition and excision of an entire nucleotide and its exchange. Mismatch repair system – repairs improperly paired bases during replication of DNA. Failure of this system leads to microsatellite instability. The repair system for single stranded breaks- the break is repaired by the complementary template, which is the other strand of DNA. The repair system for double stranded breaks - this system takes into account non homologous end joining and homologous recombination. Non homologous end joining is a repair process, which is fast, but prone to errors. During the repair of double stranded breaks, the break is repaired by random fill of the missing bases or nucleotides which can lead to faulty proto oncogenes, tumor suppressor genes when breaks occurred in the location of these specific genes.

Homologous recombination is another way of how to repair double stranded breaks it takes longer to complete, however it repairs double stranded breaks without error. The repair takes place according to a complementary template, which is copied from the identical chromosome during S phase, when the cell has 2x 46 chromosomes. Homologous recombination takes place during S phase and G2 phase of the cell cycle when every chromosome in the cell is duplicated. During G1 phase of the cycle, when the cell is not disposed to a copy of each chromosome, the repairs according to Non homologous end joining take place.

2.8 Resistance of Tumor Cells

Cancer is extremely difficult to treat when focused on the cause, which is mutations of many kinds of genes. During treatment, many different modalities are sought for with the goal of long term remission of the disease with bearable side effects of the oncological treatment. A common cause of the persistence or relapse of the diseases is the resistance of the tumor cells towards therapy.

In their early stages of development, tumors are a heterogeneous group of cells, with different sensitivity towards our therapy. The population of the tumor includes not only cells of the tumor itself but also tumor stroma, vasculature, and cells of the immune system. The effect of treatment leads to the reduction of the tumor population, ideally with complete remission seen with various imaging methods. Furthermore, as to the heterogeneous tumor population, a certain small amount of tumor cells exist which are resistant to treatment, i.e primary resistance. These cells are often named Tumor Stem Cells, which have wide array of mechanisms of how to defend against damage caused by chemotherapy, radiotherapy, and other modalities of oncological treatment. Even when imaging methods show

complete remission, these primary resistant cells are thought to be the cause of relapse in cancer. Primary resistance is therefore “in born.”

During the treatment, we are often met with secondary resistance due to our treatment. The effect of selective pressure leads to the eradication of sensitive cells and the persistence of resistant cells. The surviving cells, under the effects of selective pressure of the therapy undergo more mutations, which increases its aggressivity and resistance towards therapy. Sooner or later, it leads to failure of the effect of previously effective therapy and the progression of the disease. With a change to a different line of therapy, another population of tumor cells is eradicated. The effect of the next line of therapy is reduced with the increase of resistant cells, thanks to these particular secondarily resistant cells, whose characteristic resistance is “gained”.

3 ASSESSMENT OF THE EXTENT OF THE DISEASE AND TREATMENT RESPONSE

Eva Kindlová, Martina Kubecová

3.1 ASSESSMENT OF THE EXTENT OF THE DISEASE – STAGING

An important factor determining not only the prognosis of the disease, but also the choice of treatment modalities is the **extent of the disease**. Its exact determination is also important for the creation of treatment standards, the possibility of comparing the treatment results of individual workplaces, for the evaluation of epidemiological data, etc.

On the basis of agreements of international and national oncological societies, a uniform classification was developed allowing a simple and relatively accurate description of the extent of the disease in most solid tumors. This classification, called **TNM system**, has been accepted worldwide and is binding for the Czech Republic. In addition to the TNM classification, there is also an "International Histological Classification of Tumors", but in practice the international classification of diseases for oncology "ICD-O-WHO" is increasingly used.

3.2 CLASSIFICATION SYSTEM TNM

TNM classification is based on - T (tumor), N (nodule) and M (metastasis) assays.

- **T-tumor** – determines the extent of the primary tumor. The digits 1-4 attached to the letter T indicate the range (size) of the primary tumor. It is determined by clinical and diagnostic examination. If the primary tumor cannot be detected by available examinations, the symbol T0 is used; if the tumor size cannot be determined, or if available tests have not been performed to identify the primary tumor, the TX symbol is used; to indicate carcinoma in situ – symbol TIS.
- **N–nodule** – status of the regional lymph nodes. It is precisely determined, which lymph nodes are regional for given tumor site. Numbers are used to describe their exact characteristics. N1-N3 marks growing damage of regional lymph nodes, N0 means negative finding, NX marks, that the finding on the lymph nodes cannot be accurately determined.
- **M – metastasis –** describes the presence or absence of distant metastases, including metastases in non-regional lymph nodes. Category of M1 can be specified according to localization (PUL - pulmonary, OSS - osseous, HEP - hepatic)

At this point, it should be emphasized that once a TNM classification has been established, it must not change! However, it can be supplemented – referred to as pathological classification – with p – pT pN pM on the basis of other surgical examinations or histology.

3.3 DETERMINING RESIDUAL TUMOROUS POPULATION

While determining the extent of the disease is important in determining the treatment procedure at the start of treatment, to stop or continue treatment we need information about the existence of a residual

disease. The residual cancer population may become the starting point for future recurrence or generalization of the disease. Until recently, the possibilities of determining residual disease have been very limited, and only methods of molecular biology and genetics make it possible in some cases to determine the residues of the tumor population.

3.4 Assessing the therapeutic response

Assessing the therapeutic response has the same value as determining staging. A committee of specialists from WHO has attempted to unify various suggestions for assessing therapeutic response.

Objective therapeutic response is assessed based on this proposal by 4 grades.

- **Complete response (CR)** is the disappearance of all measurable signs of disease, based on two observations during at least 4 weeks. Measurable tumors are, if possible, denoted by two dimensions, which are the longest diameter and its biggest perpendicular dimension.
- **Partial response (PR)** means 50 % and bigger shrinkage of measurable changes, again within 4 weeks. Also, there can be no new symptoms of tumor disease in other locations.
- **No change (NC)** or stable disease (SD) is marked for tumor shrinkage of less than 50 % or their enlargement by less than 25 %.
- **Progressive disease (PD)** means enlargement of the tumor or existing measurable pathological change by more than 25 % or discovering new, previously unknown lesion.

Currently most used system for rating therapeutic response in solid tumors is RECIST version 1.1 from 2009. The most essential changes compared to WHO are measurement of only one biggest diameter, definition of measurable lesions and specifications of their maximum quantity.

Subjective therapeutic response is judged with significant difficulty. A wide range of complementary aspects, such as pain relief and good appetite etc. exists, however these cannot be accurately evaluated and compared. Unified point of view is used only for assessing physical performance. The most commonly used score of physical performance is designed by WHO and evaluating performance by Karnofsky.

Evaluating physical performance according to the point scale of WHO compared to Karnofsky performance status scale.

Stage WHO	Corresponding status of physical activity	Karnofsky (%)
0	Capable of normal physical activity	90–100
1	Incapable of heavy physical exertion, but capable of doing lighter work	70–80
2	Self-sufficient, but unable to work. Spends more than 50 % of day time outside the bed	50–60
3	Limited self-sufficiency. Bedridden more than 50 % of day time	30–40
4	Dependent on assisting help. Permanently bedridden	20–30
-	Terminally ill. In last moments of life	0–20

3.5 DURATION OF TREATMENT EFFECT

Duration of treatment effect besides tumor response is a parameter, which is used to evaluate the therapeutic effect. Among the most important and most used in clinical oncology studies (usually used to compare new treatment plan to current one) are:

- **overall survival, OS** – time till death (all causes mortality)
- **cause-specific survival** – time till death caused by observed disease, other causes of death are not counted
- **disease free survival, DFS** – time period, during which the patient is alive and healthy and has no signs of disease after previous successful treatment of primary tumor (surgery, radiotherapy in some tumors)
- **progression free survival, PFS** – time period, during which the patient is alive and has no signs of tumor progression, is used for patients without surgical treatment and/or metastatic disease
- **time to progression, TTP** – is evaluated similarly to PFS, however without including patients who die from causes other than tumor progression.

4 BASICS OF RADIATION ONCOLOGY

Karel Odrážka, Tomáš Blažek

4.1 HISTORY

Radiotherapy is a medical field using biological effects of ionizing radiation for therapeutic purposes. It is mostly used to treat tumor disease - **radiation oncology**, and to a lesser extent to treat some **degenerative or inflammatory diseases**.

Radiotherapy is one of the youngest medical fields. It's growth was made possible by the discovery of X-ray by **Wilhelm Conrad Röntgen**. It was on October 8th of 1895 when, during his tests with cathode tube, which he from unknown motives wrapped in a black paper, he noticed, that luminescent shade with a layer of cyanide platinum-barium fluoresces even with a thick book placed between tube and shade. Only when he put a metal object in between, the fluorescing stopped. And when he put his hand in between the tube and shade, he saw a thin outline of his bones on the shade. He discovered, that the radiation will blacken a photographic plate and made the historically first X-ray photo, which was one of the hand of his wife, wearing a ring. He announced his discovery on January 23rd of 1896 on a meeting of scientific society in Würzburg. For this, he received his first Nobel Prize in Physics in 1901. He accepted the award and left the financial reward 50 000 Swedish crowns to the University of Würzburg.

It was soon discovered, that X-rays can be used even for therapeutic purposes. First attempts were happening several years after the discovery of X-rays in treatment of skin and breast cancers. In 1903, C. L. Leonard published a paper on tumor treatment using X-rays, in which he described, besides the palliative effect, cases of complete cure of cancer.

Next important milestones of radiotherapy development were the discovery of natural radioactivity by **Henri Becquerel** in 1896 and the discovery of radium and polonium by **Marie Curie-Sklodowska** in 1898.

Radiotherapy defined itself as a separate medical field in 1922, when Coutard and Hautant reported in International congress of oncology in Paris on completely curing advanced larynx cancer by radiation without developing any severe complications.

The first half of the 20th century was an era of orthovoltage X-ray machines (kV voltage), which produced radiation of low energy, which resulted in depositions of dosage in surface layers of namely skin and subcutis. For this reason, these machines were used in treatment of skin cancers and surface located tumors. Orthovoltage X-ray machines found their limits in deep tumors because of the physical aspects of radiation absorption described above. Treatment of deep tumors was only accessible after the development of high energy "mega-voltage" sources of radiation. Among the first machines of this kind were cobalt irradiators, which were installed in the early fifties. Further development took the path of linear **accelerators**. The first linear accelerator was used in England in 1953. In the present, linear accelerators belong among the standard sources of radiation for external radiotherapy.

4.2 RADIOLOGIC PHYSICS

4.2.1 Ionizing radiation

Ionizing radiation is a radiation, whose quantums have energy high enough to detach electrons out of the electron shell and thereby ionize the substance. For common types of radiation of photons (γ a X), electrons (β^-) and α, the standard energy limit of ionizing radiation is considered to be 5keV.

From the perspective of interaction of radiation with matter, ionizing radiation is divided into two groups:

- **directly ionizing radiation** – radiation, whose quantums carry an electrical charge, which is why they detach electrons out of atoms using Coulomb electric forces; radiation α, $\beta^-\beta^+$, proton radiation p^+ and others like heavy particles (carbon nucleus) belong in this group
- **indirectly ionizing radiation** – radiation, whose quantums are not electrically charged, they transfer their kinetic energy to charged particles, mostly electrones, and it is those particles that result in secondary ionization; X-rays, γ radiation and neutron radiation belong in this group

Radiotherapy uses mostly electromagnetic (photonic) radiation γ respectively X and electron radiation. This is why only interactions of these types of radiation will be discussed in the following text. Radiations γ and X have the exact physical properties (photonic radiation), however they differ in the manner in which they arise.

Photonic radiation emitted from atom nucleuses of radio-active elements is called γ radiation (even if the radiation has a low energy of several keV). Typical source of γ radiation is ^{60}Co. Radiation emerging via atomic electron transition in electron shell and braking radiation emerging during the impact of accelerated atoms on braking target made of heavy metal are called radiation X (X-rays).

4.2.2 Interaction of electron radiation (β -) with matter

During its flight near atoms, β^- particle, a negatively charged electron, gives away a part of his kinetic energy to other electrons via electric repulsive forces. If the energy of the electron is low, it is only enough for the electron to jump to a higher energy level = excitation. Excited state of an atom is unstable, electron will momentarily jump back to its original lower energy level and the energy difference is radiation in the form of quantum of electromagnetic radiation, respectively photon. Light is emitted during the excitation of electrons in the outer energy levels, UV light in the middle energy levels and characteristic radiation X in the inner energy levels. If the energy of the passing particle sufficient, enough energy can be transferred to fully release electron from its bind to mother atom – an **ionization** of an atom will occur. The now free electron will be subjected to the same interactions as the original, it can ionize other electrons along his path - **secondary ionization**. Besides excitation and ionization, **scattering** can happen - electric Coulombic and nuclear forces affect electron during its passing by and these forces can alter its direction. The scattering can be elastic, when there is only change in the direction of the path of the electron and kinetic energy remains the same. Opposite of that, inelastic scattering can happen in electron with high energy and is usually accompanied by excitation or ionization of atoms.

4.2.3 Interaction of γ and X radiations with matter

Photons of γ and X radiation do not carry an electric charge, however they are quantums of quickly oscillating electric and magnetic field, so they can transfer electromagnetic energy to other particles, which causes secondary ionization. Possible interactions are these:

Photoelectric effect – photon will hit and electron bound in electron shell of an atom, transfers all its energy to this electron and expires; the released electron will leave the electron shell with kinetic energy equal to the difference of energy of radiation and the binding energy needed to release that electron; it will now act as a β radiation, cause excitations and ionizations; an electron from a higher energy level will fill the void in the electron shell left by the electron that was knocked out of its place and the difference between the two energy levels will be emitted as a quantum of electromagnetic radiation - characteristic radiation X; photoelectric effect happens most commonly with γ radiation will lower levels of energy and in elements with high proton number Z, the chances of photoelectric effect happening with energies higher than 1-2MeV are minimal.

Compton scattering – a photon of γ radiation hits a free or weakly bound electron, transfers part of its energy to the electron, bounces elastically and continues in his movement on an altered path and with lower energy; the higher the angle of the scattering, the more energy photon loses (and the more electron receives); the accelerated electron will again cause secondary ionization; the chance of Compton scattering grows with proton number and decreases with higher energy of photons; Compton scattering is the most common interaction during radiotherapy using linear accelerator.

Creation of electron-positron pairs – if a γ radiation photon flies into a substance of high enough energy (above 1,022 MeV), then it can change into a pair electron + positron during its passing by the atom nucleus; out of this pair only the electron remains as a permanent particle, the positron will brake and annihilate with one of the other electrons and give rise to two γ radiation photons of 511 keV of energy each, flying in opposite directions from the place of the annihilation under the angle of 180° from each other; the process of creating electron-positron pairs happens mostly with high energy gamma radiation and elements of high proton number.

4.2.4 Physical values describing radiation

energy E – kinetic energy gained by a charge of one electron in electric field with acceleration by the potential difference of one volt is 1 eV (electronvolt), while 1 eV = 1,602 x 10^{-19} J; a radiation of 4-20 MeV of energy is used in radiotherapy of malignant tumors

activity A – expresses the number of radioactive transformations in a specific amount of radionuclide per unit of time; its unit is 1 Bq (becquerel), i.e. 1 transformation in 1 second.

dose D – energy of radiation absorbed in substance of certain mass; its unit is Gy (gray), while 1 Gy = 1 J/kg; *surface dose* is the dose on the surface of radiated volume; *maximum dose* is the highest dose in radiated volume, in high energy radiation is in a certain depth below surface according to the energy of radiation (effect of secondary electrons); *depth dose* – dose on the central beam in certain depth below the surface, most commonly expressed as percentage depth dose.

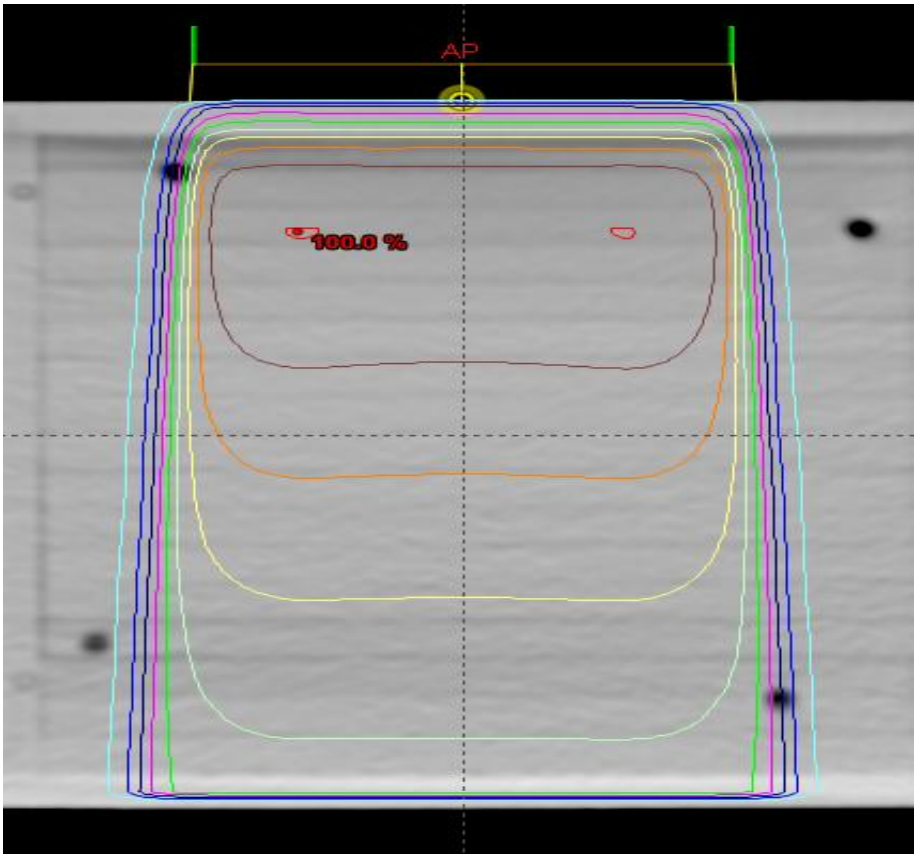
isodoses are curves connecting points with the same value of dose, they have typical layout according to the type and energy of the radiation (Fig. 1).

dose equivalent H – expresses biological impact of various kinds of ionizing radiation; it is the product of absorbed dose in tissue and quality factor (indicates how many times is a certain type of radiation

biologically more active than reference photonic radiation of energy level of 200 keV); its unit is 1 Sv (sievert), while 1 Sv = J/kg

linear energy transfer LET – energy transferred by ionizing radiation into absorbing surrounding on a certain path; its unit is 1 keV/µm.

Fig. 1 Isodose curves of photonic radiation of energy of 18 MeV



4.2.5 Sources of ionizing radiation in radiotherapy

It is necessary to use particles accelerated to a higher kinetic energy for therapeutic application of ionizing radiation and increase of depth dose (i.e. preventing absorption of the dose on the surface of the skin and subcutis). It is possible to accelerate only electrically charged particles - electrons, protons, helium nuclei and nuclei of heavier elements. Photons of electromagnetic radiation, which are incorporeal and carry no charge, are obtained secondarily – by interaction of accelerated particles (usually electrons) with suitable material (with high proton number). Particle accelerators work on the principle of electric field, magnetic field is used only to change the trajectory of charged particles (alternatively to induce electrical field for acceleration).

Therapeutic X-ray irradiators

Orthovoltage X-rays produce radiation X with energy of 10-300 keV and are used to treat surface skin tumors, in palliative therapy of surface metastases and for non-tumorous therapy. The irradiation distance is minimal (usually under 50 cm) and the dose delivered decreases sharply as the radiation moves into the body. The source of the radiation is an X-ray tube – vacuum tube placed in a circuit of high voltage. Hot cathode emits electrons, which are drawn towards the anode and accelerated by a strong electric field.

During the impact on the anode they brake sharply and part of their kinetic energy is transformed into a braking electromagnetic radiation – radiation X with continuous spectrum.

Cobalt irradiator

Cobalt bomb is used a source of radiation of **cobalt 60**. The overall activity of typical source of a diameter of 15-20 mm is approximately 5-10 thousand Ci. Half-life is 5,3 years; cobalt releases gamma radiation of energy of 1,17 and 1,33 MeV. The dose maximum is 5 mm below surface, 50 % of dose is 10 cm below surface. The source is shielded by depleted uranium. The radiation is started by moving the source from resting position to working position i.e above the outlet opening. A radiation beam from outlet opening is circumscribed (collimated) by two pairs of primary coverings. The cobalt irradiator is currently used primarily in palliative radiotherapy; however in selected tumor locations it is admissible to use it in curative radiotherapy (e.g. carcinoma of the vocal cords).

Linear accelerator

The basic machine for external radiotherapy is currently linear accelerator (Fig. 2). The modality used today are high frequency accelerators, where accelerating electrodes are connected to alternating current. Electrons are always accelerated in between the electrodes, whose polarities are reversed with the correct frequency. The acceleration happens in waveguide, separated into a series of resonating cavities, connected to a high frequency current generator (klystron or magnetron). A high frequency alternating electromagnetic field is created inside the waveguide in the form of transverse or longitudinal electromagnetic wave. If the charged particle is synchronized with the waves of the field, a permanent accelerating force defined by the electrical part of the electromagnetic wave will act on the particle.

Fig. 2 Linear accelerator

Particles (electrons) are injected from ionic source or electron nozzle (e.g. hot fiber in a lightbulb emits electrons) in a pulse sequence, in precise electronic synchronization with accelerating high frequency field. The accelerated electrons land on a wolfram target, giving rise to a high energy photon radiation X. A beam of photons exiting the head of the machine is formed by the covering of a **collimator**. It is also possible to gain and use accelerated electrons of various energies (usually between 6-20 MeV), besides the photon beam (usually 6 MeV and/or 18 MeV). The central axis of the beam of radiation will always target one point - **isocenter**, which is usually 100 cm from the source of the radiation (i.e. the gantry is moving along the surface of imaginary sphere of a radius of 100 cm). Isocenter is usually set to target the center of irradiated mass, so that we can position the patient and then move from one field to another without changing the position of the patient.

Work without accessories is unthinkable for the modern methods of radiotherapy – remotely controlled adjustable table, focusing lasers on the walls, wedge and compensatory filters, individual covering blocks, tubes for electron beam, dynamic wedges, multileaf collimator (MLC), fixation aids.

Linear accelerator has multitudes of advantages compared to the cobalt irradiator:

- smaller penumbra = higher accuracy of irradiation of the edge of the field, possibility of more accurate connection on the edges of irradiated fields,
- higher depth dose = possibility of irradiation in deeply located tumors while being gentle to surfacely located tissues, namely skin, reduction of risk of fibrosis and irradiation changes of the skin,
- possibility of use of both photons and electrons, possibility of modulation of fluence of photons, higher radiation security. Linear accelerator is the standard device for **curative radiotherapy**.

Modern linear accelerators can supply photons (X-rays) and electrons. **Photons** are not as harmful to the skin and have a maximum dose in 15-25 mm depth at energy of 6-18 MeV. We use them to irradiate tumors located deep in the body. While **electrons** have their maximum on the skin, their advantage is limited reach into the body (in order of centimetres depending on energy). They are used to irradiate tumors located on the skin or in subcutis, because they are gentle to deep tissues below the tumor.

4.3 RADIOBIOLOGY

The effects of radiation on living organisms is studied by **radiobiology**. As per its name, the main mechanism of ionizing radiation is ionization. In the case of irradiating complex organic compounds, it will induce the release of chemical bounds, dissociation of molecules and creation of highly reactive radicals, which further react with molecules of the substance, while giving rise to new compounds.

4.3.1 Effects of ionizing radiation on cells

The effect of ionizing radiation on living tissue takes place in four stages:

- **physical stage** – ionization and excitation, this process is very fast, virtually instantaneous (fractions of seconds),
- **physico-chemical stage** – secondary processes of interaction of ions with molecules, dissociation of molecules and formation of free radicals by water radiolysis; also a very fast process (fractions of seconds),
- **chemical stage** – reaction with important organic molecules, change of their composition and function; typical disorders are DNA strand breaks (single-strand, double-strand break), atypical binding bridges within the DNA double helix, local denaturation; lasts from thousandths of a second to several seconds,
- **biological stage** – development of functional and morphological changes; it can manifest itself after several tens of minutes at high doses of radiation, at medium doses within a few days – acute damage or radiation sickness, at low doses the latency is up to several years or even tens of years.

DNA is the key molecule in terms of the biological effect of radiation. It can be damaged by photons directly – the **direct effect** of radiation. These interactions are relatively rare but lead to significant DNA damage, including double-stranded breaks. More frequent (about 70%) is the **indirect effect** caused by free radicals, which are formed mainly from water molecules (hydroxyl radical, peroxides).

Critical lesions for further cell fate are double breaks. Some may be repaired; others will remain uncorrected due to a saturated repair process, insufficient repair time, or erroneous repair.

The cell response to radiation can be cell death, cell division arrest, or a change in genetic information passed on to the next generation of cells - a mutation. Cell death may be direct due to high radiation dose in interphase (**intermitotic death**). More common is **mitotic death**, which occurs during cell division. Cells are most sensitive to irradiation at the G2-M phase and G1-S phase transition. Relatively radioresistant cells are in the G0 and S phases. Therefore, cells that divide rapidly exhibit higher radiosensitivity.

4.3.2 Effect of ionizing radiation on tumors

Tumors differ by different sensitivity to radiation (**radiosensitivity**). In practice, all tumors are curable by irradiation, the limiting problem remains the presence of surrounding healthy tissues that prevent delivery of a sufficient lethal dose. Extremely sensitive to radiation (a relatively low total dose is sufficient to eradicate a tumor) are lymphomas, leukemias and germ cell tumors. Carcinomas are moderately sensitive, relatively radioresistant are especially gliomas and sarcomas. Tumor radiosensitivity is mainly influenced by the following factors.

- **hypoxia** – lack of oxygen in the tissues reduces the effect of radiation; because oxygen binds free electrons in the tissue and extends the duration of exposure to hydroxyl radicals.
- **the proportion of clonogenic cells** – proliferating cells are more sensitive to radiation because they are more likely to be in the process of cell division during the time of irradiation.
- **radiation damage repair** – the ability to repair DNA damage is different for different tumors and is virtually always limited compared to healthy tissues.

Radiosensitivity, however, does not mean radiocurability, for example lymphomas are very sensitive to radiation, but often relapse in non-irradiated areas. In contrast, cervical cancer, for example, is moderately radiosensitive but curable by irradiation.

The likelihood of curing a tumor correlates with the **total dose of radiation**, as each dose kills a fixed percentage of cells. Microscopic lesions may most likely be eradicated at 50 Gy, but for macroscopic tumors doses of 60 Gy or more are required.

To describe the effects of radiation on the organism (healthy tissue), the **linear-quadratic** (LQ) model is used. It is a physical calculation expressing the relationship (the dependency) of cell population survival on the dose administered. The biological nature of the tissue is not homogeneous, but consists of various cellular elements that differ in their growth activity, division and repair ability. While the mucosal epithelium, bone marrow, tumor tissue show relatively high growth fraction and cell division, connective tissue, muscle, glia are tissues with little cell turnover (cell division). These factors are taken into account in the LQ model using the **alpha / beta parameter**. The **alpha** parameter takes into account the cell population in the tissue that responds to the irradiation with lethal damage; the number of cells killed is proportional to the dose of radiation applied (decreases linearly). In the **beta** cell population, the decrease in elements is non-linear, that is, the cells are resistant to a certain dose of radiation and are able to repair changes after irradiation due to reparative mechanisms. Radiation causes sublethal damage. Only after a higher dose is the cell killed. The decrease in the cell population is quadratic; proportional to the square of the dose. The **alpha / beta** ratio is different for different tissues (healthy and tumor). Tissues with alpha / beta > 10 (most tumors, mucous membranes) react already during irradiation and are less sensitive to changing individual doses of radiation. The total dose administered is

important. Tissues with alpha / beta <5 (prostate cancer, nerve tissue) respond to irradiation with late changes, due to a greater proportion of the beta population and the ability to repair cell damage (see sublethal damage). Therefore, they are very dependent not only on the total applied dose, but above all on the amount of the single applied dose (fraction).

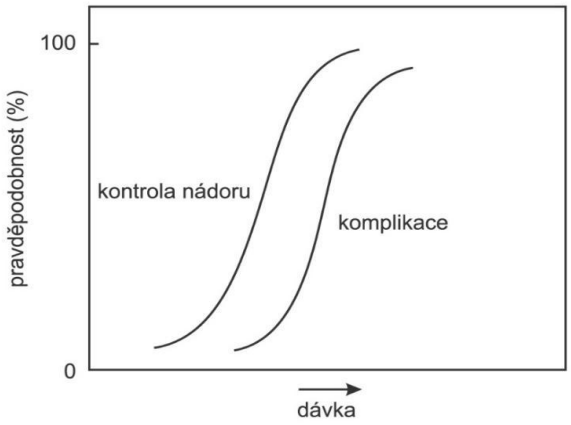
4.3.3 Effect of ionizing radiation on healthy tissues

Tumor irradiation always involves irradiation of healthy tissues in close proximity to the tumor. However, the degree of damage to healthy tissues does not correspond to the degree of tumor damage because the **ability to repair radiation damage is defective in tumor tissue**. Therapeutic use of ionizing radiation is based on this fact.

The aim of radiotherapy is to inject a dose of radiation into the tumor area that can destroy the tumor and at the same time minimally damage surrounding healthy tissues. The total dose administered to the tumor region is dependent on the tolerance of healthy tissues. It is necessary to choose the optimal form of radiation (external radiotherapy or brachytherapy), type of radiation (photons, electrons), radiation energy, fractionation (total dose and dose per fraction), number of fields, field shaping, healthy tissue coverage, patient position and fixation devices. All this to minimize the risk of radiation damage to healthy tissues and deliver the highest possible dose to the tumor area. The therapeutic options are documented by the **Paterson graph** (Fig. 3), which depicts the dose-dependency of the relative number of killed tumor cells (curve a) and the dose-dependency of the risk of irreversible damage to healthy tissue (curve b). If the tumor is radiosensitive, the curve is shifted further to the left, if it is radioresistant, the curve shifts to the right, closer to the tissue injury curve. The ratio of the lethal tumor dose and the tolerance dose of healthy tissue is called the **therapeutic ratio**. Tumor and healthy tissue response to radiation is influenced by a number of factors, collectively referred to as **radiation response modifiers**.

- **factors enhancing the effect of radiation** – radiation of high LET (Linear Energy Transfer – its effect is minimally influenced by tumor hypoxia), chemotherapy, hormonal therapy, hyperthermia; the resulting effect is usually additive, rarely potentiating,
- **radiation attenuating factors** (protecting healthy tissues) – conformal radiotherapy (advanced radiotherapy techniques – IMRT, IGRT enabling targeted tumor irradiation), radioprotectives (drugs protecting healthy tissues, not tumor, e.g. amifostine).

Fig.3 Paterson graph



left, tumor control probability (curve a),
right, probability of complications (curve b)

4.4 TOXICITY OF RADIOTHERAPY

4.4.1 Forms of radiation toxicity

Side effects of radiotherapy can be:

- **local** – they are limited to the irradiated area, they have typical exactly localizable manifestations depending on the irradiation site,
- **systemic** – tend to be non-specific, general fatigue, malaise, anorexia, nausea, vomiting; they occur mainly when irradiating large volumes, especially in the abdomen; hematological complications resulting from irradiation of the bone marrow can be included.

According to the time of onset of the reaction we distinguish 2 forms of radiation toxicity:

- **acute radiation toxicity** – is defined as the adverse effect of RT occurring within 90 days of the onset of RT. It typically manifests during the irradiation series; it mainly relates to rapidly proliferating tissues such as the skin, mucous membranes or the hematopoietic system; they are tissues with frequent cell division of stem cells – they respond to irradiation quickly, but also recover relatively quickly; morphologically it is various forms of acute inflammatory reaction; early toxicity is usually fully reversible, but very rarely transient to late toxicity
- **chronic radiation toxicity** – occurs after the end of the irradiation series at a distance usually with latency (months, years); affects slowly proliferating tissues, tissues with slow cell population variation such as liver, kidney, heart, lung, CNS, muscle, subcutaneous tissue; the late reaction has the characteristics of atrophy, fibrosis, the formation of teleangiectases, and in the case of parenchymatous organs decreased function; it is a chronic inflammatory reaction with typical collagen overproduction and radiation fibrosis, which is caused by microvascular damage; tissue changes are permanent, clinical manifestations may change over time (worsening and improvement).

Historically, when using orthopedic X-ray therapy, the skin was the main risk structure limiting the amount of total radiation dose administered. The reason was late toxicity in the form of fibrosis and chronic defects. With the use of high energy photons with a skin-saving effect, skin reactions are no longer so severe and the internal organs have become the limiting factor. Acute and chronic toxicity is evaluated according to different scales, the most commonly used is the RTOG / EORTC scale (Tables 1 and 2). Toxicity is evaluated in several stages (0–4 and 0–5, respectively), with the highest degree associated with fatal consequences. With proper indication and proper radiotherapy, severe toxicity occurs in less than 5% of patients, so many of the radiation side effects described below are no longer encountered in practice.

Table 1 Criteria for assessing acute toxicity according to RTOG / EORTC for selected tissues and organs

Degree	0	1	2	3	4
Skin	no changes	low erythema, epilation, dry desquamation, decreased sweating	clear erythema, non-merging wet desquamation, moderate edema	flowing wet desquamation, marked edema	ulceration, bleeding, necrosis
Mucous membranes	no changes	swelling, mild pain not requiring analgesics	confluent mucositis, seropurulent secretion, mild pain requiring analgesic	confluent fibrinous mucositis, severe pain requiring opiates	ulceration, bleeding, necrosis
pharynx, esophagus	no changes	mild dysphagia or odynophagia requiring a light diet, local anesthetics or non-opioid analgesics	moderate dysphagia or odynophagia requiring opiates, ground or liquid diet	severe dysphagia or odynophagia with dehydration or weight loss> 15%, requiring an NG probe, i.v. hydration or parenteral nutrition	complete obstruction, ulceration, perforation, fistula
CNS	no changes	normal functional state with mild neurological findings, without medication	Neurological findings requiring second person assistance, steroid medication or anticonvulsants	neurological finding requiring hospitalization	severe neurological deficit - paralysis, coma, seizures> 3 times a week even during medication
lower GIT	no changes	frequent stools or change in the nature of stools not requiring medication, rectal discomfort not requiring analgesics	diarrhea requiring parasympatholytics, mucus secretion not requiring inserts, rectal or abdominal pain requiring analgesics	diarrhea requiring parenteral hydration, mucus or blood flow requiring pads, air-fluid levels on X-ray	acute or subacute obstruction, fistula, perforation, bleeding requiring transfusion, pain or tenesma requiring stoma
leukocytes (x 1000)	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0
platelets (x 1000)	≥ 100	75 – < 100	50 – < 75	25 – < 50	<25 or spontaneous bleeding
hemoglobin (g/l)	≥ 110	95 – 110	75 – < 95	50 – < 75	-

Table 2 Criteria for assessing chronic toxicity by RTOG / EORTC for selected tissues and organs

Degree	0	1	2	3	4	5
skin	no changes	slight atrophy, pigmentation, partial hair loss	non-fitting atrophy, moderate telangiectasia, total hair loss	visible atrophy, major telangiectasia	ulceration	death directly related to chronic radiation toxicity
mucous membranes	no changes	slight atrophy and dryness	moderate atrophy and telangiectasia, dryness	visible atrophy with complete dryness of mucous membranes, severe telangiectasia	ulceration	
esophagus	no changes	moderate fibrosis, light difficulty swallowing a solid diet	inability to swallow solid food, necessity of semi-solid, possible dilatation	severe fibrosis, swallows only fluids, painful swallowing, necessary dilatation	necrosis, perforation, fistula	
CNS	no changes	slight headache, mild lethargy	moderate headache, pronounced lethargy	severe headache, severe dysfunction (partial loss of mobility, dyskinesia)	convulsions, paralysis, coma	
intestine	no changes	moderate diarrhea, convulsions, stools 5 times a day, slight rectal discomfort or bleeding	moderate diarrhea and colic, stools> 5 times a day, mucus leakage from the rectum or intermittent bleeding	obstruction or bleeding requiring surgery	necrosis, perforation, fistula	

4.4.2 Signs of radiation toxicity in tissues and organs

Skin

Early skin reaction is referred to as acute radiodermatitis. First, **erythema** occurs, then peeling begins (**dry desquamation**), after the loss of basal layer cells, **wet desquamation** occurs. The most serious is the development of an **early ulcer**, which is often secondarily infected and poorly healing. Late (**chronic**) **toxicity** is manifested months to years after the acute reactions have healed. The skin is atrophic, thin, dry, sometimes slightly scaly, with telangiectasia, hyperpigmentation, fibrosis to fibrosclerosis of the hypodermis, temporary or permanent alopecia and epilation. Hair grows again after 1-3 months, the dose for sustained alopecia is individual. The most severe form of late skin radiation toxicity is chronic non-healing ulcer with necrosis of the base.

Oral mucosa and mucosa of ENT area

Acute changes manifest as enanthem, edema, exudation, turning into epithelolysis with fibrin coatings, foci may coincide in confluent mucositis. Acute reactions greater than 2nd degree on mucous membranes have a typical appearance of so-called speckled reaction. Late changes affect the taste buds with a gradual loss of taste. Late toxicity in the salivary glands, which is manifested by xerostomy, is important and changing the quality of life. Due to technical advances, current radiotherapy options significantly reduce the risk of developing more severe xerostomia.

Gastrointestinal system

Acute esophageal reaction is similar to the reaction of mucous membranes of the oral cavity, manifested by pain in swallowing, pyrosis, esophagitis. Antimycotics, cool milk drinks, antacids, proton pump inhibitors, prokinetics increasing the tone of the lower esophageal sphincter, or local anesthetics in syrup form are used in therapy. Late toxicity in the form of stricture occurs rarely. The most sensitive section of GIT is the **small intestine**, where even after low doses there is congestion and edema of the mucosa, negatively affected resorption and acceleration of peristalsis in combination with dysmicrobia result in the development of diarrhea stools that respond well to Imodia, Reasec and Smectu. Irradiation with higher doses may cause mucosal ulcerations, which in extreme cases may cause perforation of the intestinal wall.

Late toxicity affects the mucosal ligaments and intestinal wall, resulting in the formation of stenosis, fistulae, intraperitoneal adhesions, which may cause a acute abdomen with impaired passage in the ileum (obstructive, strangulatory). The **colon** and **rectum** are organs with slightly higher tolerance to radiation doses. In the acute phase, toxicity may be manifested in the form of tenesmus, irritable bowel, more frequent stools and stool urges. A typical example of late toxicity is radiation proctitis usually manifested 1.5-2 years after termination of RT. The base is inflammatory mucosa, sanguineous, easily bleeding. The source of bleeding is telangiectasia and ulceration. These circumstances increase the risk of stenosis or fistula.

The liver is a relatively radiosensitive organ, especially when exposed to high doses, such as stereotactic radiotherapy, there is a risk of developing RILD (Radiation Induced Liver Disease). This is a manifestation of toxicity at the borderline of acute and late occurring in patients 3-4 months after termination of RT. Clinically manifested by weakness, weight gain, hepatomegaly, ascites with or without icterus, elevation of liver enzymes, especially ALP. In some cases, it can end fatally.

Lungs

Acute toxicity manifests itself in the form of radiation pneumonitis, usually 1-3 months after the end of irradiation, in the form of cough, fever and shortness of breath masquerading as bronchopneumonia. Physical finding is poor, only radiological findings will make the diagnosis accurate. X-ray describes multi-focal infiltrates or atelectasis or effusion, with changes localized in irradiated terrain. Corticoids, antibiotics and bed rest are used for treatment. The late consequence of irradiation is fibrosis in the irradiated volume, which occurs after 6–12 months.

Urogenital system

The radiosensitive tissues include **kidneys** in which acute toxicity manifests itself in the form of radiation nephritis. The clinical picture is dominated by anemia, hypertension, albuminuria, pain - lumbalgia and fatigue. Late radiation toxicity leads to atrophy of the renal parenchyma, glomerulosclerosis and the development of chronic renal insufficiency. The **bladder**, on the other hand, is relatively radioresistant. Acute toxicity is manifested after irradiating the entire volume of the bladder at lower doses, and / or irradiating smaller volume at higher doses. Patients report dysuric to stranguric problems, urgo-frequenct micturition.

Spasmolytics, spasmo-analgesics (Metamizol-Algifen, Novalgin) are usually sufficient in therapy. Acute toxicity to the mucous membranes of the lower urinary tract decreases resistance to pathogens, which may lead to a higher risk of developing uro-infect. Therefore, in clinically significant problems, urine culture examination should not be neglected and if examination is positive, uro-infect should be treated with appropriate antibiotics. Late radiation toxicity in the bladder region is significant and difficult to

manage. It develops especially after radical RT for bladder carcinoma or prostate carcinoma. Typical manifestations are reduced capacity and frequent or urgo-frequent micturition. Wall atrophy with formation of telangiectases, superficial mucosal erosions and chronic bleeding. The latter of these side effects may escalate to haematuria not responding to pharmacological therapy. There is usually no clear source of bleeding in the cystoscopic image that can be treated. Bleeding is capillary, diffuse from the area of telangiectases. The condition may result in refractory hematuria, causing severe anemization of the patient. In such cases, radical cystectomy is an effective treatment modality. Current intensity-modulated radiotherapy (IMRT) methods and precise targeting of image guided RT (IGRT) radiation have eliminated the late bladder toxicity in practice.

The testes are one of the most sensitive tissues, sterility can occur after irradiation with only 5 Gy. Supporting Leydig cells are relatively resistant and maintain testosterone production even after application of higher radiation doses (tens of Gy). In women, permanent sterility can occur after fractional irradiation of 6-8 Gy, a dose of 20 Gy eliminates even hormonal ovarian production, which has been widely used in the past for radiation castration (as part of hormone treatment for breast cancer). Currently, the so-called pharmacological castration by LHRH analogues is more frequently used.

Nervous system

Brain tissue is relatively radioresistant. Acute radiation toxicity may take the form of slight vasogenic edema, which may manifest in patients with headaches. In the field of postoperative changes, acute toxicity may increase the threshold of sensitivity to the development of epiparoxysms if they occurred before the operation. The late toxicity of RT of brain tissue takes the form of white matter radionecrosis, especially in stereotactic radiotherapy, when very high doses of radiation (> 60 Gy) are administered in a short time interval to a small, well-defined target of brain tissue. **Spinal cord** – compared to brain tissue, the tolerance dose related to the development of late toxicity, ie. myelopathy, is much lower (> 45 Gy).

A symptom of early myelopathy is the Lhermitt's syndrome – feelings of paresthesia (tingling) or discharges affecting the motorics of the upper limbs when bending the head. The highest degree of toxicity is incomplete or complete transverse spinal lesion.

Of the sensory organs, the most significant is **eye** involvement. Eye lenses are radiosensitive and even small doses of radiation initiate the development of cataracts even several years after irradiation. Higher doses of radiation (> 50–55 Gy) may cause changes in the retina, cornea or conjunctiva of the character of macular degeneration, retinopathy with the formation of telangiectases, corneal ulcerations or conjunctivitis.

Hematopoietic system

Bone marrow is one of the most radiosensitive tissues due to the rapid proliferation of the cellular population of blood elements. At any given moment, the cellular elements are caught in the different phases of the cell cycle of cell division, most importantly in the radiosensitive phases (G1-S and G2-M). This sensitivity to RT is used in the treatment of hemato-oncological malignancies in the so-called myeloablative whole-body irradiation, when total removal of the bone marrow of the patient before transplantation is necessary. The dose administered in this case is 12 Gy fractionated at 1.2-1.5 Gy / day. Toxicity (depletion) of blood elements increases with the volume of irradiated volume. The manifestation

is anemia, leucopenia, thrombocytopenia. After whole-body irradiation, the number of lymphocytes decreases several hours apart.

4.4.3 Possible ways to affect radiation toxicity

- **dose level and time factor** – the total dose level is related to the onset of early and late reactions; for early reactions, the duration of irradiation course is important, ie. total duration of treatment. In the case of late toxicity, meticulous documentation of the dose level and the development of late effects of RT must be maintained. Reparation of damage may occur over the years, but re-irradiation in previously irradiated volume is always risky.
- **size of irradiated volume** – affects early and late reactions; with large irradiated volumes, the accentation of acute reactions may limit overall treatment, therefore the effort is to minimize the volume, but not at the cost of insufficient irradiation (in the case of curative treatment).
- **irradiation technique** - number and configuration of fields, covering of healthy tissues,
- **fractionation – conventional fractionation** means 1.8-2.0 Gy per day, 5 days a week; **hyperfractionation** (lower dose more often e.g. twice a day at 1.2 Gy at intervals of 6-8 hours) worsens the development and degree of acute reaction, but does not increase late reactions; **hypofractionation** (larger doses less frequently) will reduce the acute reaction but will result in more chronic reactions; mathematically, this radiobiological fact is described by the LQ model, which makes it possible to determine equivalent biological doses of different fractionation schemes according to the alpha / beta ratio,
- **radiation response modifiers** - see above,
- **treatment regime and general condition of the patient** – care of irradiated skin (gentle washing with water, without cosmetics, airy cotton underwear, no sun exposure), sufficient diet, supportive treatment to reduce adverse effects so that radiotherapy can be continued (if radiotherapy is interrupted damaged healthy tissues will repair, but tumor cells will repopulate).

4.5 Clinical use of radiotherapy

4.5.1 Curative and palliative radiotherapy

Curative radiotherapy

The intention of curative (radical) radiotherapy is to completely eradicate the tumor and cure the patient. Therefore, a maximum dose of radiation is applied in order to eliminate it completely taking into account the radiobiology of the tumor population. The dose level, however, is limited by sensitivity (tolerance) of surrounding healthy tissues to radiation. A rate of serious complications due to radiation of **less than 5%** is acceptable. The curative dose of radiation in most solid tumors is $\geq$ 60 Gy in 6 weeks.

- **Primary (independent) radiotherapy** – eradicates macroscopic tumor, affected nodes and potential microscopic disease; it is used in a number of cancer sites with better therapeutic effect than surgery (lymphomas), better functional effect than surgery (larynx cancer), as an alternative to surgery (prostate cancer) or where locally advanced tumor is no longer operable (cervical cancer).

- **Postoperative (adjuvant) radiotherapy** – eradicates residual microscopic disease that surgery cannot remove. Adjuvant RT increases local control or reduces the risk of dissemination (breast cancer, rectum), the doses administered are lower than those of primary radiotherapy and are around 50 Gy in 5 weeks.
- **Preoperative (neoadjuvant) radiotherapy** – works on the same principle as adjuvant RT. It is indicated in preoperative treatment with the intention of tumor downsizing, circumscribing and enabling operability, elimination of microscopic disease and reducing the risk of tumor cell spreading during tumor manipulation during surgery. It finds its main application in the therapy of locally or locoregional advanced tumors (rectal cancer, soft tissue sarcomas), primarily inoperable. The chances of achieving radical operability increase after RT.
- **Radiotherapy with concomitant chemotherapy (chemoradiotherapy)** – the addition of chemotherapy to radiotherapy usually has a potentiating effect; shows a slightly higher effect than radiotherapy alone (but at the cost of higher toxicity).

  There are multiple schedules for concomitant chemotherapy, e.g. continuously, once a week, once every 3 weeks. It is used in a number of tumor sites, whether in the indication of curative – radical RT-CHT (tumors of ENT, cervix, lung carcinomas, bladder cancer) or neoadjuvant (carcinoma of the rectum, esophagus) or adjuvant (tumors of ENT, esophagus, rectum, stomach, pancreas, lung, primary brain tumors, biliary tract tumors)

Palliative radiotherapy

The aim of palliative radiotherapy is to alleviate the symptoms in a situation where the cure of the tumor is not realistic. Alleviating difficulties of cancer is associated with improved quality of life. In practice, this means several situations:

- Achieving an analgesic effect caused by, for example, tumor infiltration of nerve knitting, skeletal osteolysis in metastatic affection, tumor ingrowth into the thoracic wall.
- Alleviation of lymphedema of limbs caused by blockage of lymphatic drainage by the pathological packets of lymph nodes - typical localization in pelvis and inguinal, axillary and supraclavicular regions.
- Control of bleeding and anemization in bleeding tumors of the bladder, rectum, anus, endometrium, cervix, lung or ENT tumors.
- Alleviation of dyspnea related to airway obstruction by tumorous infiltration - RT can clear the main airways, aerate atelectatic segments or lobes of the lung.
- Treatment of neurological symptoms – epiparoxysms, cephalea, paresis in metastases affecting CNS or causing spinal compression.
- Treatment of symptoms related to locally advanced tumors in the head and neck area - swallowing problems, recurrent infections, bleeding, pain.

The total doses used are lower than for curative radiotherapy (usually up to 30 Gy / 10 fractions in 2 weeks or 20 Gy / 5 fractions in 1 week), but do not exceed tolerated doses of risk organs. Tumor regression is only a secondary effect, as well as affected survival.

4.5.2 Planning and performing radiotherapy

The planning and performing radiotherapy takes place in several successive steps, where the information about the patient, its location, target structures and radiation conditions are transferred in digital form into the planning software and subsequently into the control system of the accelerator. Radiotherapy is strictly individual, general conditions are always adjusted for a particular patient.

Immobilization, localization and planning CT

One of the most important factors at the very beginning of radiotherapy planning is the choice of the optimal patient position. It must be well and easily reproducible; it should not be a problem for the patient, it should be comfortable for the patient. Tumor localization and the appropriate RT technique at the irradiation site must be considered when selecting the optimal position. There must be no obstacle in the irradiated sites (e.g. preventing gantry collision with limbs when rotating around the patient). The position should also allow visual inspection of the irradiated area while preventing exposure of healthy tissues or other parts of the body beyond the target volume (e.g. the patient must not have his hands on his chest in the case of lung tumors or tumors of mediastinum. In such a case, the upper limbs must be elevated).

Various tumor **fixation aids** (thermoplastic masks for head and neck fixation, chest and hand pads for breast tumors, vacuum pads for abdominal and pelvic irradiation, vacuum or foam pads for lower limb fixation) are used to ensure reproducible positioning. The **CT simulator** is used to obtain a CT image of the part of the body that we will be irradiating. The device corresponds to the diagnostic CT, but it is also equipped with lasers for 3 planes (x, y, z). The patient is imaged in the same position as it will be irradiated, including immobilization aids. The default coordinates (zero point) for the CT scan are marked on the skin or fixation devices. The obtained CT image is transferred to the scheduling system. The **X-ray simulator** is a fluoroscopic diagnostic X-ray machine capable of imitating radiation conditions. Its mechanical and geometric parameters correspond to the irradiator. On the X-ray simulator it is possible to pre-locate the target volume according to bone structures. In addition, it is possible to directly set the field for simple palliative radiotherapy techniques (e.g. irradiation of the metastases of the skeleton of the vertebral bodies, pelvis, whole brain RT in metastatic problems). The X-ray simulator does not replace the planning CT. Therefore, we currently prefer the CT simulator for its versatility.

Radiotherapy planning

Radiotherapy planning is done in a planning system, which is software that can calculate 3D radiation dose distributions in the patient's body. The calculation is based on a three-dimensional reconstruction based on individual transversal CT scans. The planning system can take into account differences in radiation absorption depending on the density of tissues and organs according to the HU units from the planning CT.

The planning process begins with the **contouring** of the tumor area (target volume) and risk organs in individual CT scans. According to the International Commission on Radiation Units and Measurements (ICRU) recommendation number 50, three basic **target volumes** are defined.

- **GTV** *(gross tumor volume)* - macroscopic tumor (visible on planning CT in correlation with clinical findings, physical examinations and other assistive imaging (MR, PET / CT)). The planning system can fuse planning CT imaging with diagnostic MR or PET / CT. The definitions of tumor properties are then very precise.

- **CTV** *(clinical target volume)* - GTV plus margin for potential microscopic tumor spread (we do not see microscopic disease on CT, but we have evidence that the microscopic tumor spread varies from a few mm to a few cm depending on histology)
- **PTV** ***(****planning target volume)* - CTV plus internal margin and setup margin.
    - **Internal margin** = margin compensating target volume movements in response to physiological movements, e.g. lung tumor movements during breathing excursions, peristaltic waves, different fillings of bladder and rectum during irradiation.
    - **Setup margin** = patient movements during RT and inaccurate settings during irradiation series. In practice, the first case may occur in the indication of palliative RT, where it is more difficult for the patient to tolerate the radiation position because of pain, lymphedema, dyspnoea. In these cases we are talking about so-called intrafraction movements. The second case is setup errors, where the accuracy with which the patient is placed in the irradiated position by the attending staff (radiological assistant) and how the patient's placement is reproduced every day plays a major role.

  It is essential to correct the deviations in the misalignment using the display device on the accelerator, where X-rays or con beam CT are taken before irradiation and the final position of the patient is corrected with maximum accuracy. (Note the IGRT principle - see below for image-guided radiotherapy.)

The margin size ranges from approximately 5 mm to a few cm.

The planning process continues by choosing the appropriate **radiation technique** (see – irradiation techniques) to try to irradiate the entire volume of PTV with the required dose and to avoid risk organs. A suitable arrangement and number of fields is selected which can be shaped using a multi-leaf collimator (MLC) or individual lead blocks. Wedge or compensation filters may be used to modify the radiation beam. The scheduling software is able to calculate the dose at individual points of the body according to the density of tissues (HU units) on CT scans (data entered into the program). Therefore, CT must always be used to calculate the dose. Other imaging examinations such as MRI or PET-CT provide, in some situations, more accurate information about the tumor and its spread and are thus used to identify target volumes, see GTV definition above. By fusing MR, PET / CT images with planning CT, the resulting tumor size is identified with maximum accuracy. The radiation dose is usually specified in the isocentre, which is approximately in the middle of the irradiated volume. It is normalized to 100% with a recommended dose variation in PTV of 95-107%. The assessment of the plan is performed using the **dose-volume histogram** (DVH), whose curves show the parameters of the irradiated plan - dose dependence and the volume of irradiated risk organs and, in particular, coverage of the target volume with the prescribed dose.

Simulation

Simulation means **transferring the radiation schedule** to the patient. It is performed on a CT simulator (virtual simulation) or on an X-ray simulator (conventional simulation). The radiation plan created in the planning system contains the coordinates (x, y, z) of the isocentre. The patient is first set up on the simulator according to the markings on the skin / fixation devices drawn at the zero point location. This is usually a cross or lead shot placed on the skin / fixation aid when locating and planning CT.

Then, the shift in the x, y and z axes (according to the data in the radiation plan) to zero will focus the isocentre, ie. the table moves with the patient to the exact irradiated position. The position of the isocentre is drawn on the patient's skin or fixation devices by new simulation marks, lines that intersect in individual planes - (lateral, longitudinal, vertical). The position of the coordinate table is stored in the verification system and shared electronically to the control systems in the treatment rooms. The accuracy of the isocentre survey is verified by comparing the simulation CT slices with the reference CT from the planning system. When working on an X-ray simulator, we compare fluoroscopic images of fields with reference images from a planning system (digitally reconstructed DRR X-rays created from a planning CT).

Irradiation and verification

At the irradiation facility, the patient is set by laser sights on the skin marks (or fixation aids) to the desired position. The Linear Accelerator automatically sets radiation parameters for this particular patient based on data from the verification system. Irradiation will only be triggered when all indicators match. The images obtained on the irradiator (**verification images**) are used to verify that the settings are correct. The images are taken using a small diagnostic dose of braking radiation from the accelerator head captured on a detector under the patient – so-called portal. The resulting image corresponds to the X-ray image, however, of much worse quality due to the energy of the radiation used. The skeleton contours in the thus made image are compared with reference skeletal contours on the so-called DRR image (digital reconstructed radiograph) of the reconstruction from the planning CT. A newer method is the OBI (on board imaging) system, which allows to obtain X-ray or CT images in digital form directly from the accelerator, which are compared with reference images. Any position deviation is corrected by moving the table to obtain the correct position. The more accurate the patient's settings for each fraction of the radiation, the less safety margin for PTV we can choose (further saving healthy tissues around). Radical radiotherapy also includes regular dosimetric control, which provides reliable data on the delivered radiation dose.

4.5.3 Irradiation techniques

Conventional radiotherapy

Conventional radiotherapy uses a simple configuration of irradiation fields where the irradiated volume is perceived in one plane, not as a three-dimensional object. The fields can be shaped simply by covering blocks.

Three-dimensional conformal radiotherapy (3D-CRT)

Irradiation technique where the target volume boundaries correspond to a three-dimensional representation of tumor shape and volume. It appeared along with the introduction of CT into clinical practice in the 1970s. It allows to irradiate the target volume with minimal safety margin, thereby reducing the exposure of surrounding tissues and reducing toxicity. This results in the possibility of dose increase with the aim of higher local control.

Stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS)

The principle of stereotaxis is to deliver a radiobiologically very high dose of radiation in a short time horizon in a very small number of fractions. The target volume is usually smaller in size, precisely defined. In the case of SRS it is the application of 1 fraction. In the case of SRT, usually 3-5 fractions. The

efficiency of these modalities is highly local, ie. it can be compared to surgery. It is widely used in the treatment of acoustic neurinomas, eye melanomas, metastatic lesions, AV malformations, skeletal or liver metastases. Among the new indications in arrhythmology was the stereotactic ablation of accessory pathways.

Instruments that perform SRS or SRT are Leksell's gamma knife and Cyber knife. The radiation dose is delivered to the target volume from several different directions and planes. The positions of the radiation source are located on the hemispherical or spherical surface. In the Czech Republic, SRS and SRT are performed in the Na Homolce Hospital, which has a Leksell gamma knife (source of radiation ^{60}Co) and in the University Hospital Ostrava - Cyber knife (braking radiation X linear accelerator) (Fig. 4).

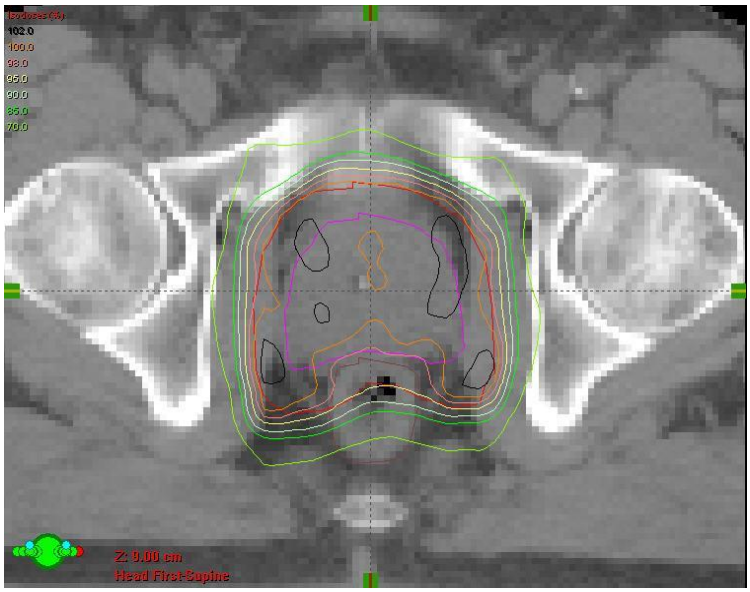
Fig. 4 Cyber knife

Intensity Modulated Radiotherapy (IMRT)

As with 3D-CRT, the beam is shaped, but the intensity of the beam changes across the sagittal line. IMRT is associated with inverse planning, where the minimum and maximum dose requirements in target volumes and maximum doses in risk organs are first defined. Priorities are assigned to individual structures, and the planning system looks for the way and delivery of the dose to the target volumes accordingly.

It uses individual settings of the optimum beam intensity profile of individual fields. Compared to 3D-CRT, IMRT allows for better dose distribution in the required volume with a steep decrease in the dose delivered into the environment and thus less stress on risk structures. (Fig. 5).

Fig. 5 IMRT technique in prostate cancer



significant saving of rectum - isodosis 100% and 98% completely avoid the rectum

Image-guided radiotherapy (IGRT)

It is an essential part of modern radiotherapy and is part of IMRT or 3D-CRT techniques. The technical capabilities of today's linear accelerators make it possible to deliver a very high dose to the target volume with maximum screening of healthy tissues – especially using IMRT techniques. However, with increasing complexity of irradiated fields, modulated beams, "dose bending" and the resulting dose distribution shapes, high accuracy of dose delivery to target volumes is essential. Even slight deviations can have serious consequences if the target volume is missed – risk of local relapse or irradiation of healthy tissues with the development of acute or late toxicity. It is IGRT that allows accurate delivery of the dose to the target volume. The basic principle of this method is a perfect imaging of the actual tumor position or target volume just before or during the irradiation and precise correction of deviations in the patient position. The OBI (on board imager), which is an X-ray tube or a low-dose CT mounted on a linear accelerator gantry, is used for this imaging. After placing the patient on the table of the linear accelerator and adjusting it for the marks on the skin, X-ray images of the skeleton are made in 2 perpendicular projections (AP and side). In the best case, it is possible to carry out a low dose CT called con beam CT (CB-CT). These OBI images are evaluated in the control room and in case of deviations, the patient's position is corrected to match the reference position from the planning CT. This minimizes the risk of erroneous exposure. IGRT is used in conjunction with IMRT and 3D-CRT.

A special variant of IGRT is *tumor tracking* – irradiation of a moving target. A typical representative is Cyber Knife, which uses online imaging of the position of X-ray contrast markers inside the tumor during stereotactic irradiation. Another possibility of IGRT is *gating* – irradiation only in a certain position of the tumor. E.g. gating respirators in lung carcinomas located in the lower lobe, where, with respiratory excursions, large tumor movements occur in the cranio-caudal direction. Irradiation is only performed at a certain stage of the breath cycle, usually in inhalation.

The same applies to irradiation of the breast only during deep breaths, which can significantly reduce the dose delivered to the heart and prevent late cardiac toxicity (CHD, AIM, cardiomyopathy).

4.6 BRACHYTHERAPY

While in external radiotherapy the radiation source is at a certain fixed distance from the patient, brachytherapy is the opposite. It is a technique in which the **ionizing radiation source** is placed directly in the tumor region, into **close contact with the tumor**, or is placed in the **tumor bed**. Brachytherapy fully utilizes the physical aspects of radiation dose absorption in the tissue depending on the distance from the radiation source. As the distance from the source increases, the radiation dose decreases steeply with the **square of the distance (m2)**. (For example, if the distance between the source and the irradiation volume increases twofold, the dose will fall fourfold.) In practice, this means that a very high dose of radiation can be delivered to the tumor in a short span of time while saving surrounding healthy tissues. Compared to external RT, there is a clear benefit of dose escalation in the target volume and the saving of surrounding healthy tissues. In the indication of radical treatment of prostate cancer or cervix cancer, the dose delivered by brachytherapy is several times higher compared to external RT.

4.6.1 Physical aspects of brachytherapy

Brachytherapy apparatus

Previously, radioactive needles were used directly or applicators were introduced near the tumor and radioisotopes were manually inserted into them (manual afterloading). Radium ^{226}Ra was used as the isotope. The method entailed a certain radiation load for the personnel when handling radiation sources. From the second half of the 1960s onwards, a method called **automatic afterloading** began to develop and is now practically exclusively used. The iridium ^{192}Ir radiation source is usually placed in a special shielded mobile container, which is located in the brachytherapy hall (Fig. 6). The hall is constructed similarly to the irradiation room. Shielding, dosimetric inspection and closable doors must meet the radiation protection criteria. The afterloader functions can be controlled from the remote desktop in the control room to ensure radiation protection for the personnel.

Fig. 6 Automatic afterloading for brachytherapy

Brachytherapy is an invasive method, therefore it is necessary to insert proximal applicators (needles, probes, vaginal cylinders and ovoids, endoluminal catheters) near the tumor in the first phase. The reconstruction of their positions in space (orthogonal X-ray, CT, MRI) follows, and in the planning system, similarly to external radiotherapy, the irradiation plan is prepared and calculated.

After approval of the plan by a physician and radiological physicist, the afterloader is connected to the applicators using special plastic connecting tubes. Through these tubes, the radiation source will then enter the applicators (needles, probes, vaginal cylinders, ovoids, endoluminal catheters) and irradiate the target volume at given positions calculated in the planning system in accordance with the irradiation plan. After the wiring and the final check, the patient is left in the brachytherapy room under continuous monitoring (camera system, visual supervision, vital signs monitor, ...). As soon as the screened door of the hall is closed, radiation can be started. In the control room, the afterloader is activated via the control console, and the radiator (^{192}Ir) automatically enters the applicators through the connecting tubes without the need for staff to be present. At the end of the treatment, the device automatically ejects the radiation source from the patient's body and places it back in the shielded mobile container. The radiation load of personnel is thus reduced to a minimum. Brachytherapy with automatic afterloading means **temporary application**. The radiation source in the patient never stays permanently, but only for a certain period of irradiation. It is then retrieved back into the instrument.

However, there is also an indication when the application of radiation sources is permanent. We are talking about **permanent brachytherapy**. This indication has found its place in the treatment of localized

prostate cancer, where it achieves excellent results and minimal side effects. Compared to radical surgery, continence and erectile function are maintained in a high percentage of patients. Local control and overall survival are the same as in radical surgery. This procedure is more demanding technically and requires manual dexterity, as the radiation sources (^{125}I radioactive seeds) are placed under precise sonographic control in the prostate position using special application needles. Due to the manipulation of the radiation source in needles, medical personnel are exposed, but only to a small extent. When upholding all radiation protection rules, the exposure values usually do not exceed the limits for the personnel.

Classification of brachytherapy according to dose rate

- **Low-dose rate (LDR) brachytherapy** – dose rate 0.4–2.0 Gy / h, treatment lasts several tens of hours, usually given in a single fraction. *(Permanent BRT prostate cancer ^{125}I.)*
- **High-dose rate (HDR) brachytherapy** – dose rate higher than 12 Gy / h, treatment lasts in minutes. Due to the great strength, it is necessary to administer the dose fractionated to avoid the development of necrosis or complications in the form of late toxicity. The patient can be treated on an outpatient basis.

In the present, mainly HDR brachytherapy is used in clinical practice. A short application time is associated with a high number of advantages (outpatient treatment, better fixation of applicators). LDR brachytherapy is used especially in the treatment of localized prostate cancer.

Sources of radiation for brachytherapy

Cesium 137 is the most used element for LDR, while HDR uses mainly iridium 192. Permanent implantation of prostate cancer is performed with sources of iodine 125 or palladium 103. The therapeutic effect of radioisotopes used for brachytherapy is mediated by γ radiation. Some isotopes also emit other types of radiation (α, β^-, β^+), which is filtered out.

4.6.2 Clinical aspects of brachytherapy

Methods of application of brachytherapy

- **Intracavitary** brachytherapy – the applicators are inserted into the body cavities (uterus, vaginal stump, rectal cylinder),
- **Intraluminal** brachytherapy – applicators are inserted into the lumen of organs (esophagus, bronchus, biliary tract),
- **Interstitial** brachytherapy (implantation) – insertion of applicators directly into the tumor area (oral cavity, lip, tongue, breast, soft limb tissue after sarcoma resection, prostate),
- **Superficial** brachytherapy – placement of applicators on the surface of the tumor (skin in the area of curved surfaces - orofacial area, calva, vertex, auricles).

Clinical use of brachytherapy

Curative treatment

- Oral and oropharyngeal tumors – interstitial brachytherapy in early tumors at the edge and tip of the tongue, lip, oral cavity, used in combination with surgery or independently,
- Breast cancer – interstitial brachytherapy in combination with surgery and external radiotherapy to increase radiation dose to the tumor bed area. APB – accelerated partial radiation in a selected group of patients,
- Cervical cancer – intracavitary brachytherapy in combination with external radiotherapy, cures 70% of patients in stage II and 40% of patients in stage III,
- Endometrial cancer - intracavitary brachytherapy in combination with surgery or surgery and external radiotherapy,
- Skin cancer - superficial brachytherapy in sites unfavorable for surgical treatment,
- Prostate cancer - localized disease has excellent results in median follow-up > 10 years.

Palliative treatment

- Lung cancer – intraluminal brachytherapy in bronchial obstruction,
- Esophageal cancer – intraluminal brachytherapy in obstruction,
- Bile cancer – intraluminal brachytherapy in obstruction.

List of abbreviations

LET	linear energy transfer
MLC	multileaf collimator
LQ model	linear-quadratic model
RTOG	radiation therapy oncology group
EORTC	European Organization for Research and Treatment of Cancer
ICRU	International Commission on Radiation Units and Measurements
GTV	gross tumor volume
CTV	clinical target volume
PTV	planning target volume
DVH	dose-volume histogram
DRR	digitally reconstructed radiograph
OBI	on board imaging
3D-CRT	three-dimensional conformal radiotherapy
IMRT	intensity-modulated radiotherapy
IGRT	image-guided radiotherapy
LDR	low-dose rate
HDR	high-dose rate

5 SYSTEMIC THERAPY OF SOLID TUMORS

Milan Brychta

The treatment of cancer can be divided into local/locoregional and systemic. Surgical and radiotherapeutic methods belong to the locoregional approaches while chemotherapy, hormonal therapy, immunotherapy, biologic treatment, radiotherapy in the form of full body radiation, and supportive treatment belongs to systemic therapy.

5.1 CHEMOTHERAPY

Chemotherapy is one of the basic modalities in the treatment of malignant cancers. In conjunction with surgical methods, radiotherapy, and hormonal therapy, they form the basic pillars for treatment of malignant cancers.

The history of chemotherapy, with regards to the usage of chemical substances with cytotoxic effects, were first written about during the first half of the last century. A breakthrough occurred in the development of anti-tumor chemotherapy during the 40s of the last century. Paradoxically the development of chemotherapy can be attributed to the usage of the chemical bis(2-chlorethyl)sulfide during the First World War in the town of Ypres, when the world first saw the use of the blister causing chemical weapon called Yperit (mustard gas). As research in chemical warfare continued, the Americans replaced sulfur in Yperit with nitrogen, which created the chemical chlor alkylamine, still today known as Nitrogen Mustard (mustargen). Soon after, it was discovered mustargen had the ability to inhibit proliferation of rapidly proliferating tissues - therefore the potential to inhibit tumor growth. This chemical soon became the first known agent to be used in the treatment of malignant tumors (as the preparation Mustargen under the name TS-160). These compounds were still used 20 years ago in the treatment of Hodgkin's Disease.

The success of chemicals in the destruction of tumor cells led to breakthrough research and development of novel compounds. This development however is very complicated, as both a timely and costly process. From tens of thousands of molecules which are tested in research laboratories, it takes seven to ten years for on to be held in clinical practice.

The difficulty and complexity of research and development of cytostatics with individual phases of preclinical and clinical stages is shown below in Figure 1. The cost of development of a new compound is difficult to say, however, one can assume that it is as expensive as the cost of sending a rocket into space.

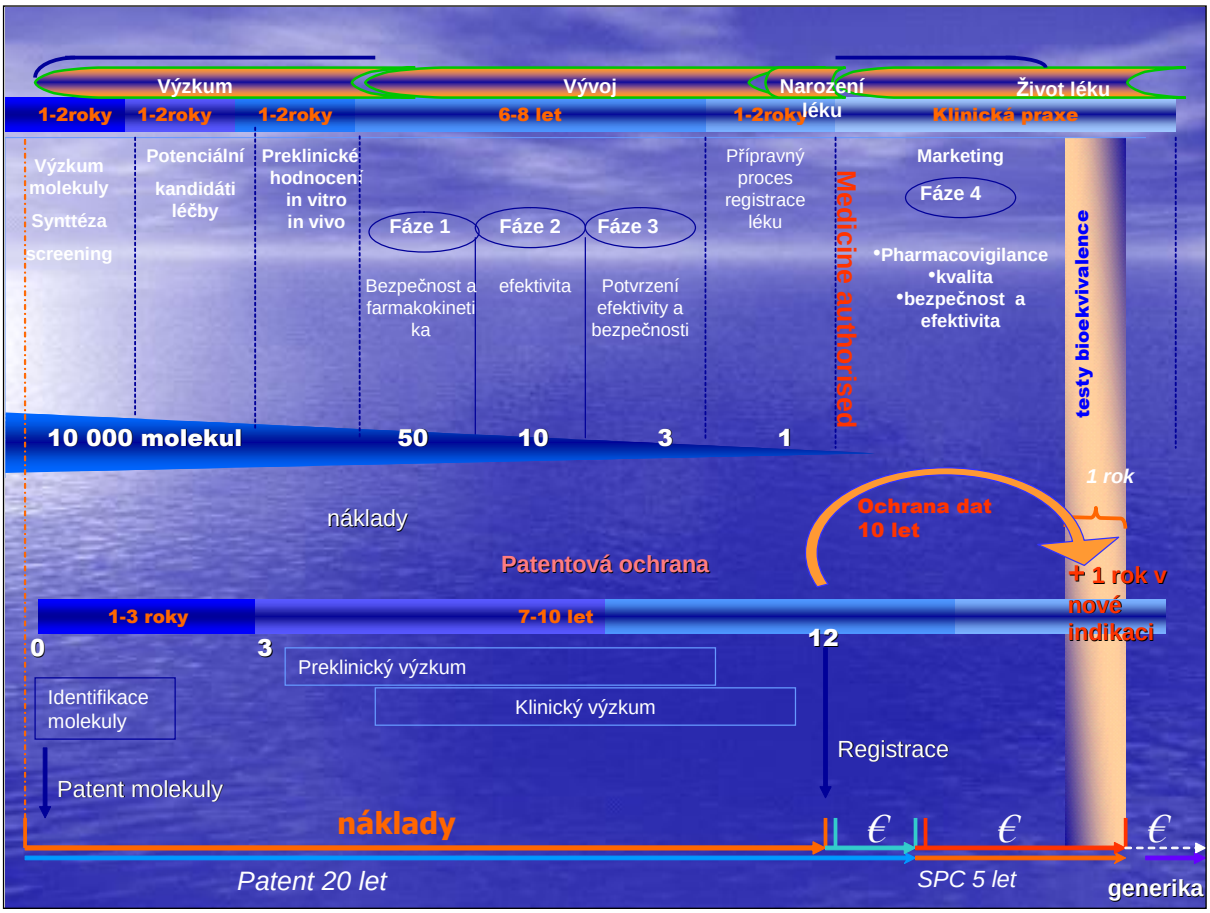


Figure 1 Phases of Development of Cytostatics

Chemotherapy has its own irreplaceable spot in the treatment of cancer, it is important however to use it in the correct circumstances in conjunction with other treatment modalities.

Breakthrough points occurred not too long ago - the discovery of new molecules - which helped to expand therapeutic potential. This individual milestones are shown in Table 1 below.

Table. 1 Milestones in Chemotherapy

Decade of Last Century	Drug
40s	Nitrogen Mustard, Actinomycin
60s	Antimetabolites
70s	Anthracyclines, Platin derivatives,
90s	Taxanes
Present	Biologic therapy
Future	Gene therapy, Immunotherapy

Cytostatics unfortunately do not have selective effectiveness. From the general point of view, cytostatics do not differentiate between a healthy cell and a tumor cell. This leads to a limitation of use due to a number of accompanying unwanted side effects.

From the point of view of the mechanism of action, we can divide cytostatics into a few different groups:

1. **Compounds leading to inhibition of synthesis of nucleic acids** – antimetabolite: purine analogues – fludarabine, cladribine, pyrimidine analogues – 5 fluorouracil, capecitabine, analogues of cytidine-cytarabine, gemcitabine, analogues of folic acid – methotrexate, raltitrexed
2. **Compounds leading to the disruption of the structure of already created nucleic acids**
    a) alkylating compounds: cyclophosphamide, cisplatin, Carboplatin, Carmustin, lomustin,
    b) intercalating compounds: anthracycline – doxorubicin, epirubicin, actinomycin,
    c) inhibitors of topoisomerase I: irinotecan, topotecan,
    d) inhibitors of topoisomerase II: etoposide, teniposide,
    e) radiomimetic: compounds cleaving molecules of DNA – bleomycin.
3. **Compounds altering microtubule structure during mitosis**
    a) inhibitors of polymerase: vincristine, vinblastine, vindesine,
    b) inhibitors depolymerase: paclitaxel, docetaxel.
4. **Compounds disrupting the synthesis of proteins**: asparaginase,
5. **Compounds with combined effects**: procarbazine, dacarbazine, temozolomide, thalidomide.

Chemotherapy is sometimes used as the only (**single**) treatment choice against cancer, however often it is used in **combination** with other treatment modalities (surgical, radiotherapy, hormonotherapy). In regards to the tolerability of oncological treatment and its side effects, supportive treatment is an integral part of correctly administered oncological therapy. Most often combined with surgical methods, chemotherapy is administered in a **neoadjuvant** (**preoperational)** setting - for example in carcinoma of the breast, where after administration of chemotherapy we watch not only systemic effects but also the reduction of the primary tumor, which leads to easier surgical resection and allows for a breast sparring operations to occur.

Postoperative chemotherapy, is given after surgical treatment, it can be applied from two treatment ideologies. It can given be as **adjuvant** treatment- after successful surgical treatment or as a **palliative** treatment, where surgical intervention could not be radical (i.e after discovery of liver metastasis, lymph or intraperitoneal dissemination). Generalized cancer is incurable, and even after all the breakthroughs in treatment, it is still not possible to cure this kind of a patient completely. On the other side, there are diagnoses such as a tumor of the mammary glands, colorectal carcinoma, malignant tumors of the ovary or testicular tumors, which are possible to treat successfully repeatedly and long term even in stage 4 of the disease, leading to a phase of complete remission or long term stabilization of the disease. This kind of stabilization can last for years, but in the end unfortunately, surviving aggressive clones of tumor cells win the battle against the patient and physician.

Postoperative application of chemotherapy in regards to adjuvant chemotherapy gives patients the highest chance of survival, or at least a considerable amount of time until the return of the disease. This type of treatment is used in patients after radical surgical interventions where there is a high risk of relapse. A high risk of recurrence of a tumor or the possibility of existence of subclinical dissemination, depends on the accompanying **risk factors.** These factors are different in each specific disease, however generally they include the size of the tumor, affection of regional lymph nodes, histological type of the tumor, and its detailed examination (grading, angio invasiveness, specific histologic markers seen with immunohistochemistry, for example receptor types, and others). The optimal goal of adjuvant therapy is

the survival of the patient without signs of relapse of the disease. In this type of treatment plan, we do not have any type of clinical correlation to our disposal, which could help us score our effectivity of treatment because we cannot correctly measure the size of the existing tumor lesion.

Combined chemotherapy, together with **radiotherapy** is another possibility of how to combine both treatment modalities. We can utilize sequential or concomitant treatment. **Sequential** administration is used in cases where there is a need for both targeting of locoregional (carried out by radiotherapy) and systemic locals (carried out by chemotherapy). Both methods are carried out individually, with chemotherapy application being applied first, and radiotherapy applied at the end.

Concomitant treatment, is the application of chemotherapy and radiotherapy at the same time, and is very difficult to tolerate for the patient. This method is prone to high occurrence of many unwanted side effects, which are summed up from both treatment modalities. It is often used with regards to preoperative radiochemotherapy in tumors of rectum or in tumors of the head and neck.

In some cases chemotherapy is applied as **single** (independent) method, in either goals of total cure/remission or palliative care.

Curative chemotherapy is used only in highly chemosensitive disease, which include childhood tumors, hematological malignancies (Hodgkin's disease, non Hodgkin's lymphoma, and other forms of leukemias) and solid tumors of adult age including choriocarcinoma, testicular tumors, and some ovarian tumors. During the administration of radical chemotherapy, even severe unwanted side effects are sometimes tolerated, which can severely decrease the quality of life of the patient in the meantime, because there is a real chance of complete curative treatment.

Palliative treatment is used in progressed stages of disease where the goal of treatment is not cure/remission because that goal is not attainable. The goal of palliative treatment is the stabilization of the disease, push back the commencement of progression, and increase life expectancy. The side effects of the treatment are acceptable in proportion to the expected effectiveness of the treatment.

Symptomatic treatment (chemotherapy) does not follow the effect of treatment on the size of the tumor. The goal is the liquidation, and reduction of symptoms which are produced the tumor itself. The side effects of treatment must be minimal and must not impair the quality of life of the disease during treatment.

Effectivity of applied chemotherapy is due to three limiting factors :

1. the number of tumor cells and their heterogeneity,
2. chemosensitivity and chemoresistance,
3. general condition of the patient, comorbid diseases.

The number of tumor cells is estimated by the size of the tumor itself. A tumor on the border of diagnostic capabilities, with a size of 1 cm, is estimated to contain 10^9 cells. This kind of tumor already doubled more than thirty times. It is important to note that a tumor with 10^6 cells can already form distant metastases. With the increased number of cells, also increases the number of different clones and their heterogeneity. Heterogeneity of a tumor is most likely the most important factor in the failure

of chemotherapy, the existence of only one resistant clone allows for the survival of tumor cells, and the future progression of the disease.

Chemosensitivity and chemoresistance can be divided as primary and secondary. Primarily, tumor cells are sensitive to chemotherapy. This sensitivity can change secondarily to a loss of sensitivity (resistance) during the lifespan of the tumor and therapy (due to activity of the tumor, effect of gained resistance - multidrug resistance and the effect of applied treatment, when the liquidation of sensitive clonal cells increases the activity of stem cells changing the sensitivity and resistance).

Chemosensitivity of tumor cells for a given type of tumor.

- the **1st group** contains highly sensitive cancers including all childhood tumors, hematological malignancies and solid tumors like choriocarcinoma and testicular tumors.
- the **2nd group** contains tumors with lower sensitivity to chemotherapy include carcinomas of the ovary, breast tumors and small cell lung carcinomas.
- the **3rd group** contains tumors with even lower chemosensitivity including tumors of the gastrointestinal tract and ENT tumors.
- the **4th group** contains tumors with the lowest chemosensitivity including tumors of the thyroid, pancreas, and large cell carcinoma of the lung.

The general state of the patient, age, and comorbidities, direct the intensity of possible oncological treatment.

Pharmacological knowledge of individual cytostatics is a prerequisite for proper chemotherapy. The classification of cytostatics according to their mechanism of action is discussed above. Of course, other knowledge is also necessary, such as the resorption of a cytostatics, its possible binding to proteins and distribution in the body, its biotransformation, whether anabolic - conversion to active substance, the active substance, or catabolic - its inactivation. Also it is important to know about excretion of cytostatics (hepatic, renal routes), because when one of these routes is slowed, the effectivity of treatment would increase, but sometimes at the cost of toxicity. More details about this information are provided in every pharmacology textbook and oncology monograph..

The mechanism of action of individual cytostatics suggests that they act on tumor cells only in certain phases of their dividing cycles (always only in the G1, M phase, never in the G0 resting phase). Tumor cells are found at different stages of the cell cycle, and so cytostatics are only capable of destroying some of the cells during its limited activity in the body. For example: antimetabolites act in phase S lasting 2–6 hours, while antibiotics (anthracyclines) act on the G1 - S - G2 phase transition, which is a little longer. Mitotic poisons (vinca alkaloids and taxanes) act only during certain moments of M phase, which last around 0,5–2 hours. The longest acting drugs on tumor cells are alkylating compounds which act on practically the entire duration of G_1, which guarantees that the drug acts longest on the tumor cells, however at the same time it also acts longest on the healthy cells. Thus, they cause the greatest chronic toxicity in particular, because the greatest number of sensitive hematopoietic stem cells is damaged permanently. The mechanism of action of cytostatics is shown in Figures 2a and 2b.

Figure 2a Mechanism of action of cytostatics from the point of view of cellular division.

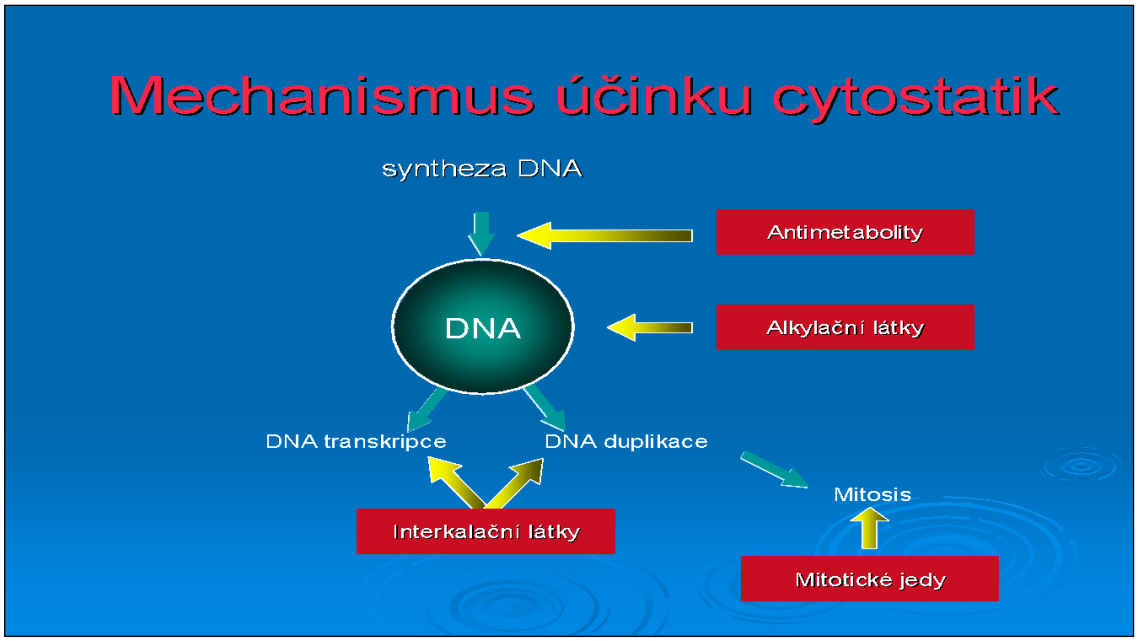
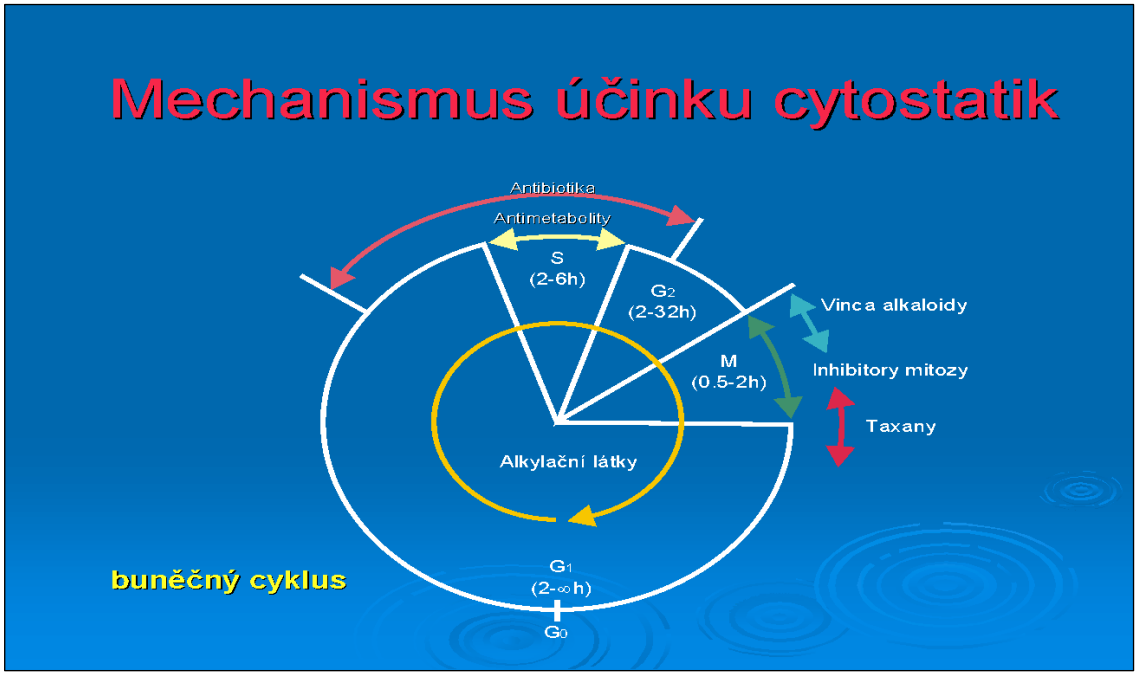


Figure 2b Mechanism of action of cytostatics from the point of view of the cell cycle



Prolonging the duration of cytostatic activity in the body increases the number of cancer cells killed, but it is dangerous in terms of long-term damage to the body. How is it possible to therefore increase the effectiveness of chemotherapy?

There is a possibility to increase the dose, assuming a higher dose = more cells killed. This is not absolutely true. The limit however is the time of action of the cytostatic on the phase of the cell and the percentage of cells in this phase. Another limit is the potential capacity of transport mechanisms and anabolic activation of the cytostatic. Nevertheless, the efficacy of chemotherapy can be increased by using different dosage schedules in conjunction with cytostatic dose, more specifically called cytostatic dose intensity (drug dose / time of action). Dosing of cytostatic regimens is usually monotherapy (one

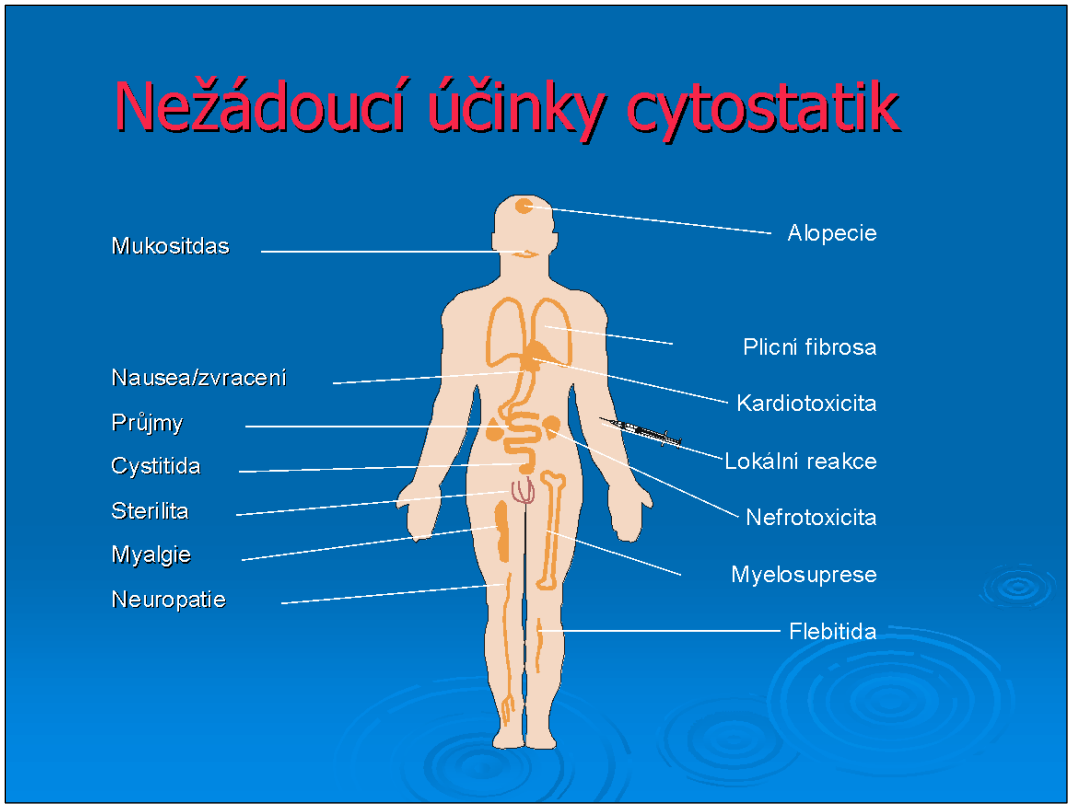
cytostatic used) or polychemotherapy (multiple cytostatics used), and calculated as the drug dose per m2 of body surface area. The second principle of the chemotherapeutic regimen is the time at which the next dose is to be administered, ie, repetition of the cycle. Dosage intensity can be increased by simply increasing the dose, or by reducing the interval between each administration or both. In the latter case particularly, haematological toxicity increases markedly and careful and active supportive therapy is required.

Individual possibilities of does intensities are shown below:

Standard Dose	50mg/ m^2	Interval of administration of 3 weeks
Escalation Dose	75mg/ m^2	Interval of administration of 3 weeks
Dose Dense Schedule	50mg/ m^2	Interval of administration of 3 weeks
Dose-Intensive Schedule	75mg/ m^2	Interval of administration of 3 weeks

Non selective effect of cytostatic chemotherapy causes a host of unwanted **side effects,** which is due to the fact that cytostatics kill not only tumor cells but also healthy cells, affecting rapidly dividing cells the most. Rapidly dividing cells include hematological stem cells of the bone marrow, and dividing cells of surface mucosal epithelium - most often side effects of cytostatics are hematologic, gastrointestinal, and infectious. Individual cytostatics have their own specific unwanted side effects, which are common for each individual compound, and need to be taken into account when utilized. The Figure 3 shows typical examples of cytotoxic toxicity.

Figure 3 Toxicity of Cytostatics



Toxicity of chemotherapy can be viewed from two points of view - one looking from time, while the other looking at the organ affected.

When looking from the time of onset of side effects we can divide them into **immediate onset** (hours to days after applications, i.e, allergic reactions, gastrointestinal problems: nausea, vomiting, diarrhea), **early onset** (days to weeks after application: hematological and gastrointestinal ailments, i.e. stomatitis), **delayed onset** (weeks to months after application: cardiotoxicity, lung fibrosis, nephrotoxicity, hematotoxicity, neurotoxicity), and finally, **late onset** (months to years after application: including liver cirrhosis, cataracts, and secondary malignancies).

When looking from the point of view of organs affected, the most common side effects are **hematological** toxicity (leukopenia, thrombocytopenia, and anemia), toxicty of **skin and skin adnexa** (alopecia, changes of nails and nail beds, erythema of palms of hands and soles of feet called hand-foot syndrome), **gastrointestinal** toxicity (diarrhea, nausea, vomiting, stomatitis), **pulmonary** toxicity (interstitial pulmonary fibrosis after bleomycin, **cardiotoxicity** (anthracycline cardiomyopathy, biologic therapy – trastuzumab, lapatinib), **nephrotoxicity** typical after administration of platin derivatives – cisplatin, cystitis (after application of alkylating agents – cyclophosphamide, ifosfamide), **neurotoxicity** (damage to especially sensitive functions – paresthesia with treatment by taxanes, vinca alkaloids, kapecitabinem and platin derivatives – cis-platin and oxaliplatin), **damage to gonads** (secondary sterility after treatment by alkylating compunds) and lastly **infectious complications** caused by an altered immune system, hematologic toxicity - neutropenia and gastrointestinal toxicity - stomatitis - disruption of mucoso-epithelial barrier.

Non Selectivity and toxicity of cytostatic treatment leads to effort to identify new, and safer molecules, and to an effort to selectively target treatment for a select few of patients, also known as **tailoring.** This type of approach or selection of specific treatment is used in a group of patients with the same diagnosis, who will most profit from the chosen therapy, after which it is further adjusted by dose, this is the usual second step in modern oncological treatment, which individualizes the therapeutic approach. In order to select the proper group of patients, we utilize prognostic and predictive factors, which are different in individual diagnoses. Today, these factors are most often decided on the basis of histological examination (for example, grading hormonal and growth receptors, angio invasiveness, mitotic index, and histological subtypes) and biochemical parameters (for example levels of LDH, hemoglobin, tumor markers). An integral part of such a scoring process is also understandably the biologic age and state of the patient, previous treatments and their courses, interval from the previous therapy and any existing comorbidities. It looks like, a large help in the future of tailored treatment will be gene analysis of these predictive factors, as evidenced by the results of the first studies– analysis of 21 genes (Rotterdam research group) and analysis of 70 genes (Amsterdams group). The use of gene analysis is currently the only possible alternative to the involvement of gene "manipulation" in the treatment of cancer. What the future will hold in regards to genes and genomes is not easy to predict at this time.

Currently we must however use current, and proven knowledge so that we provide chemotherapy according to recommended principles, which include:

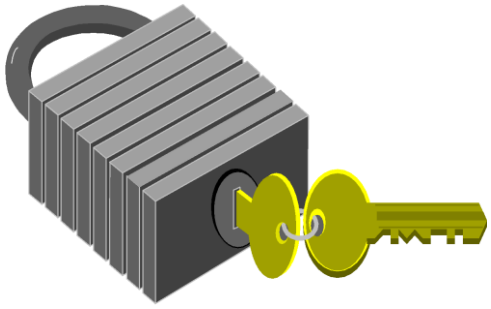
1. assessing the suitability and effectiveness of chemotherapy,
2. performing chemotherapy in multimodal therapy in combination with other treatment modalities (radiotherapy, surgery, hormone therapy),

3. selecting suitable cytostatics or combinations there of,
4. initiate treatment as soon as possible and follow the recommended timing (dosing interval) and dosing schedules,
5. close monitoring of the patient during therapy for effectiveness and toxicity of treatment,
6. active use of supportive therapy,
7. the choice of alternative chemotherapeutic regimens in the absence of efficacy.

5.2 Hormonal Therapy

Hormone Therapy is another of systemic treatment modality used in oncology which acts on a similar principle as biologic therapy - relying on the presence of specific receptors on the tumor cell (receptor - lock) and it interaction with a ligand (hormone - key). The interaction of the lock and key (ligand - hormone or pharmacological compound with the receptor) initiates a cascade of information transmission, whose final result is the proliferation of tumor cells and growth of the tumor. A schematic of the basic principles of hormone therapy is shown in figure 4 below.

Figure 4 Basic mechanical principle of hormone therapy



Hormone therapy as a method of treatment was first used in the treatment of breast carcinoma in 1896 (the removal of ovaries in a patient with a generalized breast tumor).

The basic condition of successful hormone therapy is the presence of the receptor on the tumor cell and the basic principle of its effectiveness is either occupation, blocking of the receptor site or causing the disappearance of a ligand (key) that would stimulate the receptor.

Hormone therapy can only be successfully used in tumor cells with positive presence of the hormonal receptor. The presence of hormonal receptors in tumor cells is shown below in Table 2.

Tab. 2 Type of Tumor – Hormonal receptors

Type of Tumor	Ligand – hormone	Clinical Use
Endometrial Carcinoma	gestagens	yes
Prostate Carcinoma	androgens	yes
Lobular Breast Carcinoma	estrogens	yes
Grawitz tumor	estrogens	no
Hepatocellular Carcinoma	estrogens	no
Endometrioid Carcinoma of Ovary	FSH, LH	no
Non Hodgkin's lymphoma	corticoids	no

Clinical data has shown the effectivity of hormonal therapy only in tumors of endometrium, prostate carcinoma, and lobular breast carcinoma. In other tumors, the effectivity of hormonal therapy and its therapeutic use has been abandoned.

The principle is to reduce the receptor activity or prevent ligand contact with the receptor. Most often we use pharmacological compounds, however, to a lesser extent we use surgical procedures and radiotherapy. An overview is shown in Table 3.

Table 3 Methods of Hormone Therapy

Pharmacotherapy	Surgical Procedure	Radiotherapy
estrogens	castration	castration
antiestrogens	adrenalectomy	hypophysectomy
androgens	hypophysectomy	
antiandrogens		
gestagens		
inhibitors of aromatase		
LHRH analogue		
glucocorticoids		

The pharmacotherapeutic effect of hormone therapy is:

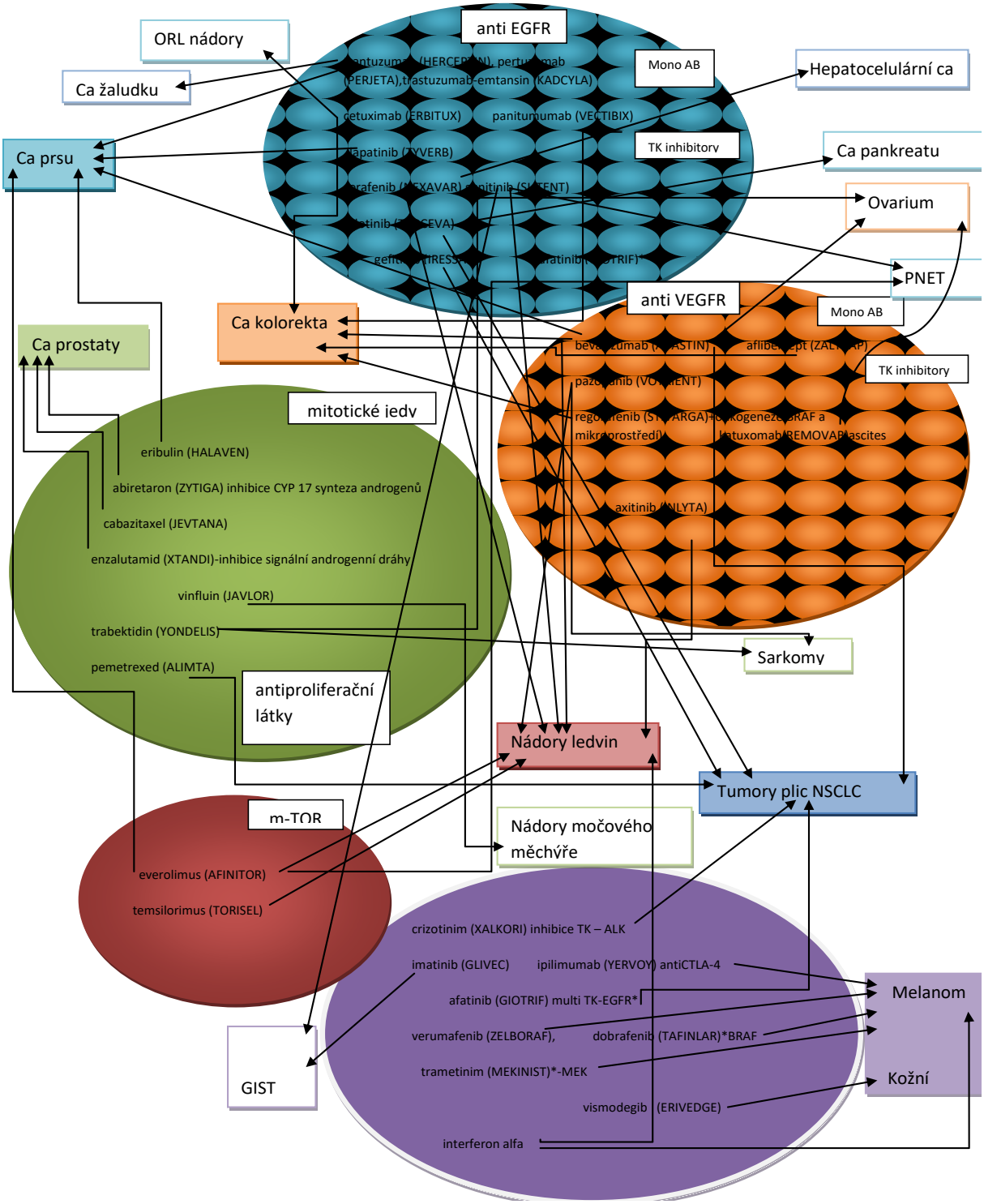
- **Ablative – elimination** of function of an organ producing a ligand- hormone, i.e chemical castration using LHRH analogue,
- **Competitive – administration** of a competitor with a ligand for receptor contact, i.e., antiestrogens or antiandrogens,
- **Inhibitory – reducing** the levels of ligand by blocking its formation, i.e reducing the formation of strogens with the help of aromatase inhibitors,
- **Additive – administering** high doses of hormones, ligands, leading to blocking of the receptors, i.e. gestagens, androgens, estrogens.

Hormonal therapy is able to be administered as neoadjuvant, adjuvant, or palliative treatment.

5.3 Biological Therapy

Biological therapy is synonyms with “targeted therapy” which represents an effort to maximize the selectivity of cancer treatment, with maximum effort to diversify the intervention – to utilize characteristics between healthy and tumor cells, eventually identifying different targets in tumor and healthy cells, so that the maximum effect of was on tumor cells and minimal effect on healthy cells. Its motto”without a visible target it's not possible to lock on to a goal”. This type of treatment is used in a large host of malignancies and the number of possible diagnoses and drugs is on the rise. Even though there are many new possibilities in a number of cancers, where earlier our therapeutic possibilities were minimal, it is important to note, that the most common indication for biological therapy is in the field of palliative treatment, where the goal of therapy is not on curing the patient but rather on pausing or slowing the progression of the disease. The current situation of biological therapies in cancer is shown below in Figure 5.

Figure 5 Schematic of use of biological therapy in malignant tumors



The main current targets of biological therapy are receptors and their complexes on tumor cells - epidermal growth factor receptor (EGFR) and vascular endothelial grow factor receptor (VEGFR), but the number of "targets" is constantly expanding (mTOR, CDK 4/6, PARP, PI3K/Akt BRAF, MEK, ALK).

The principle of targeted biological therapy is to block the transmission of information mediated by the intracellular pathways, which usually begins with the binding of a ligand to the extracellular portion of a specific receptor. By this contact, a signal is transmitted to the intracellular portion of the receptor where, through activation of tyrosine kinase (one of the key enzymes for intracellular transmissions), a

cascade of information is transferred, leading to cell proliferation, differentiation, alteration of apoptosis, angiogenesis, metastasis and chemoresistance is triggered.

Our therapeutic goal are these most targeted receptors – EGFR and VEGFR and their respective pathways. Our aim is focused at the extracellular domain of the receptor - replacement of the ligand with a monoclonal antibody, or evening focusing on the intracellular domain of the receptor - blocking tyrosine kinase activity (TK). Receptor malfunction and activation of alternative intracellular pathways are the reasons why biological treatments are not absolutely successful. In recent research, the effort to shift the intervention deeper into intracellular processes in the cell is becoming more promising.

Efforts in selective oncological therapy continues. Currently, at our disposal is the first drug, which combines biologic and chemotherapeutic modalities- conjugate antiHER2 preparation trastuzumab and the cytostatic emtansine (mitotic toxin) – preparation Kadcyla used in the treatment of metastatic breast cancer. More detailed and concrete used of biologic therapy is shown the secretion of specific oncological malignancies.

5.4 Supportive Therapy

Does not directly affect the survival of the tumor cell. Nevertheless, supportive therapy has its place in the complex of treatment cancer. The side effects of treatment, particularly chemotherapy, can be so severe that they can directly endanger the well being and life of the patient, or even influence the intensity and radicality of the concrete oncological treatment, which can lead to the failure of the treatment goal, i.e curing of the patient. Supportive therapy aims to prevent, reduce the intensity and remedy the side effects of the treatment as quickly as possible.

The goal of supportive therapy is to eliminate side effects. The most frequent complications are haematological, gastrointestinal, infectious and organ complications (pulmonary, cardiac and urinary).

The treatment of **hematological** complications – decrease of white cells is a typical side effect of chemotherapy. The appropriate therapy is chosen according to its severity. This can be either prophylactic, which works by the preventative administration of growth factors for hematopoietic stem cells G-CSF (filgrastim – Neupogen® and its pegylated form pegfilgrastim Neulasta®) or acute treatment - which is aimed at neutropenia, where we administer either G-CSF or corticoids, usually 20–30 mg of Prednisone daily. After application of corticoids, leukocytes are released into the circulation from the marrow to the periphery, which quickly solves the acute lack of leukocytes in the blood. However, this is less gentle compared to physiological stimulation of stem cells with G-CSF and may lead to depletion of the leukocyte reserve pool in the bone marrow. The application of B-group vitamins is rather a symbolic act on the border with the placebo effect.

Treatment of **gastrointestinal** complications is represented by a wide range of measures. Most poorly controlled is stomatitis after chemotherapy. Stomatitis in the oral cavity can be treated by careful oral hygiene, application of calming solutions or antimycotics. Therapy of mucositis in the lower parts of the GIT is even more complicated. Diarrhea is treated with the help of local disinfectants, drugs reducing intestinal motility, and even control of water and mineral metabolism. Easiest to treat are side effects including nausea and vomiting - which until recently were the most common side effects of chemotherapy. The era of setron antiemetics (ondansetron, granisetron, tropisetron and others) completely changed the course of a number of chemotherapeutic regimens. Prophylactic and curative

setron antiemetics in conjunction with corticoids and metoclopramide significantly improved the quality of life of patients undergoing chemotherapy. A separate chapter is focused on the treatment of nausea and vomiting.

Leukopenia and neutropenia result in a deterioration of an already poorly functioning immune system, and when added to the open mucosal barriers in mucositis, a certain amount of **infectious** complications during oncological treatment is increased. Further, these infectious complications are often atypical with minimal contributing symptoms. Consistent prophylaxis and early deployment of broad-spectrum antibiotics and antivirals is an integral part of supportive cancer therapy.

It is necessary to prevent **organ involvement and damage** during cancer treatment, as definitive damage tends to be irreversible and can lead to permanent consequences. To prevent organ damage :

- strict monitoring of the functions of organ systems (liver and kidney tests, echocardiography),
- not to exceed the cumulative toxic doses known about individual cytostatics and organs (eg Bleomycin and pulmonary parenchyma, anthracyclines and myocardium),
- administration of antidotes (eg application of uromitexan to protect the bladder in holoxan and high dose cyclophosphamide therapy or calcium folinate in high dose methotrexate therapy, administration of amifostine to reduce the side effects of actinotherapy and cis-platinum)
- administration of protective agents - the only known protective agent in oncology is the cardioprotective dexrazoxane, reducing the toxic load of anthracyclines on the myocardium without affecting the cytotoxic efficacy of anthracyclines. Unfortunately, the significance of clinical use is uncertain and therefore relative.

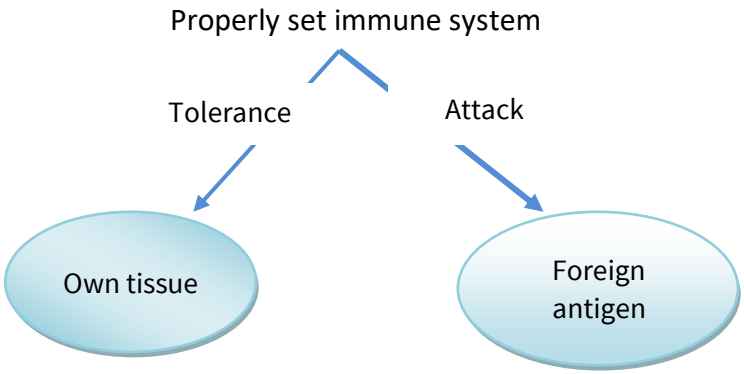
Correct and consistent use of supportive therapy is important in other treatment modalities as well.

6 IMMUNOLOGICAL TREATMENT IN ONCOLOGY

Jan Dvořák

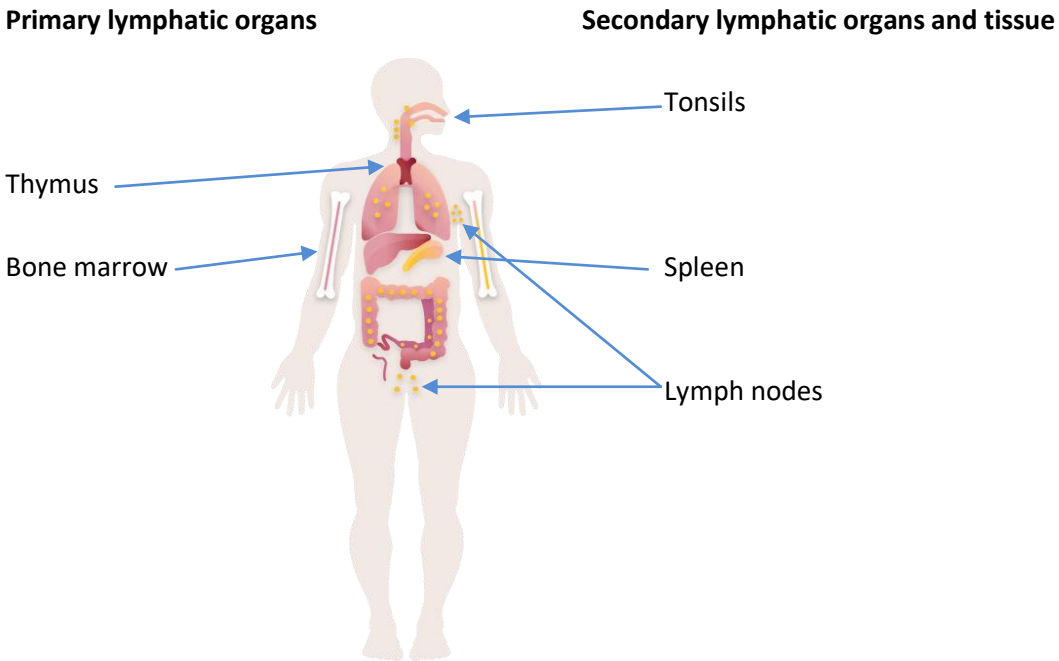
The role of the body's immune system is to protect the host from pathogens and tumors. Properly configured immune system identifies and removes threats by recognizing foreign antigens while avoiding damage to its own tissues.

Foreign antigens are molecules recognized as "non-self" derived from pathogens such as bacteria, viruses and fungi, as well as from tumors. Genetic and cellular changes that characterize cancer cells can also be recognized as “foreign” by the immune system, resulting in the ability of the immune system to eliminate cancer cells. The ability to differentiate between normal and abnormal host cells and thereby detect and destroy abnormal cells can help to prevent cancer.



6.1 ANATOMY OF THE IMMUNE SYSTEM

The immune system consists of various immune organs, cells and tissues.



Modified from Abbas A.K et al. Basic immunology: Functions and disorders of the immune system 2012; Neyt K. et al. Trends Immunol 2012

6.1.1 Primary (central) lymphatic organs

- tissues where lymphocytes are formed and mature.

Thymus: a glandular organ located behind the sternum. T-lymphocytes develop in the thymus from bone marrow progenitors prior to migration to the body.

Bone marrow: tissue located in the center of long bones. B-lymphocytes develop in the bone marrow and then migrate from the bone marrow to the body circulation.

6.1.2 Secondary lymphatic organs

- tissues where lymphocytes are activated.

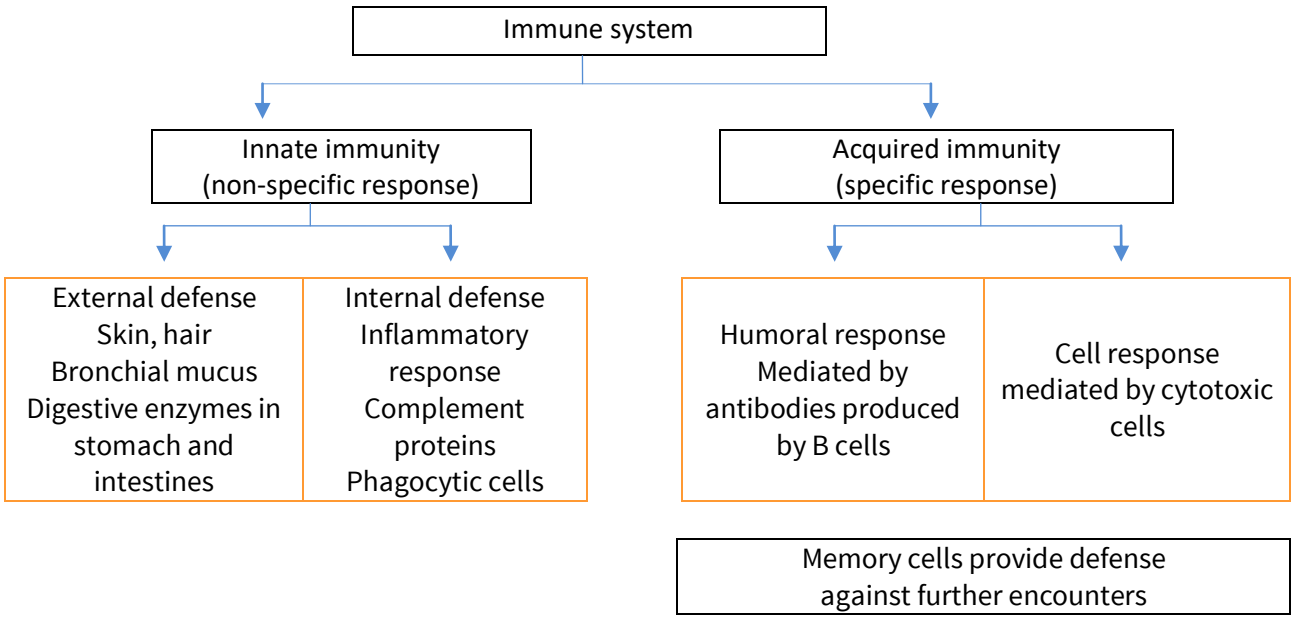
Tonsils: they are exposed to pathogens such as viruses and bacteria and then activate the immune system.

Spleen: stores cells used in immune defense, such as macrophages and white blood cells, which are then released into the bloodstream.

Lymph nodes: found throughout the body, more numerous in the neck, axilla and groin. Extracellular fluid from organs and tissues moves into the lymph nodes through the lymph vessels. In lymph nodes, the lymphatic fluid is filtered, all detected antigens lead to activation of the immune system.

6.2 CONGENITAL AND ADAPTIVE (ACQUIRED IMMUNITY)

The immune system includes two types of immunity, congenital and acquired.



Adapted and modified from Murphy K. et al. Janeway's Immunobiology 2012; Abbas A.K. et al. Basic immunology: Functions and disorders of the immune system 2012; Chen D.S. et al. Immunity 2013; O'Donnell-Tormey et al. Cancer and the immune system: the vital connection 2016

6.2.1 Innate immunity

- First line of defense, present in all individuals from birth.

Basic characteristics:

Rapid response: occurs within 0-12 hours after antigen challenge.
Limited specificity: the same reaction is applied to a wide range of antigens.
Limited diversity: detects a limited number of germline-encoded antigens.
No memory: next exposures generate the same response.

Basic components: Physical (e.g. skin and mucous membranes) and chemical barriers (e.g. stomach acids and lysozymes)

Inflammatory mediators and complement

Cells of innate immunity such as macrophages, neutrophils, dendritic cells, and natural killer cells (NK cells).

Macrophages: present in all tissues, they can move between blood vessels and tissues. Their key role is phagocytosis. They are activated by the binding of pathogen-associated molecular patterns (PAMP) to the Pattern Recognition Receptor (PRR) on the macrophage.

NK cells (natural killer cell) develop in the bone marrow and circulate in the blood. They can induce apoptosis and cell lysis using perforin. They are called "natural killer" because they do not require activation, only recognize and destroy cells infected with a virus or tumor cells. These infected or tumor cells have altered class I major histocompatibility complex (MHC) on the cell surface. NK cells recognize and kill cells that do not express MHC Class I.

Dendritic cells: develop in the bone marrow. We distinguish two types of dendritic cells, immature and mature DC. Immature DCs are found in tissues and blood and mature DCs in lymph nodes. The role of dendritic cells is phagocytosis and presentation of antigens. Then, when the PRR (Pattern recognition receptor) on immature DC recognizes PAMP, the antigen is phagocytosed. After maturation, the antigen is presented on the cell surface by MHC complexes. Dendritic cells play a key role in the interaction between innate and adaptive immunity.

6.2.2 Acquired (adaptive) immunity

Usually leads to permanent immunity. It occurs only in vertebrates and develops from time of birth when an individual is exposed to new antigens.

Basic characteristics of acquired immunity:

Slower response than innate immunity: the time required for the onset of an immune response is usually 4 to 7 days. Specific: targeted to specific antigens that induced it.
Diverse: the ability to detect a wide range of antigens, virtually any foreign molecule.
Memory: Subsequent exposure to the same antigen induces faster and more enhanced reactions.

Basic components

Lymphocytes are a key component of adaptive response.

Humoral immunity is mediated by **antibodies produced by B lymphocytes (B cells)**. It is the primary protection against extracellular pathogens (eg bacteria and circulating viral particles). The mechanism of elimination works through circulating antibodies that bind and neutralize antigens and enhance foreign antigens phagocytosis.

Cell-mediated immunity is mediated by **T lymphocytes (T cells).** It is the primary protection against intracellular pathogens (eg viruses and fungi) and cancer. The mechanism of elimination involves the activation of cytotoxic T lymphocytes which, after direct contact with the cells having the target antigen, cause targeted cell lysis and death.

T cells: develop in the thymus and are activated in secondary lymphatic organs such as the spleen and lymph nodes. T cells differentiate into a number of effector T cell types that have three main functions: killing (cytotoxic T cells), activation (helper T cells), and regulation (regulatory T cells). The T-cell receptor (TCR) recognizes an antigen in the form of a peptide bound to a major histocompatibility complex (MHC) molecule on the surface of antigen-presenting cells (APC). APCs express three signals for T cell activation: 1) peptides: MHC complex -TCR, 2) costimulatory molecules (B7.1 and B7.2), and 3) cytokines. Activated T cells proliferate and differentiate into effector T cells: cytotoxic T cells (CD8 + T cells) that kill target cells, helper T cells and regulatory T cells (CD4 + T cells), which play a key function in activation and regulation of the immune system.

B cells: Develop in the bone marrow and are activated in secondary lymphatic organs such as the spleen and lymph nodes. They produce antigen-specific antibodies that neutralize antigens and label antigens for phagocytosis. B-cell receptors (BCRs) are membrane-bound antibodies that recognize different antigens. BCR internalizes and degrades the antigen and provides the first signal for B cell activation. The antigen then returns to the surface of B cells bound to MHC class II molecules, where it is recognized by antigen-specific CD4 + T cells that supply a second activation signal. Activated B cells undergo mutations and selection for cells with a higher affinity antibodies resulting in plasma cells secreting high affinity antibodies and memory B cells.

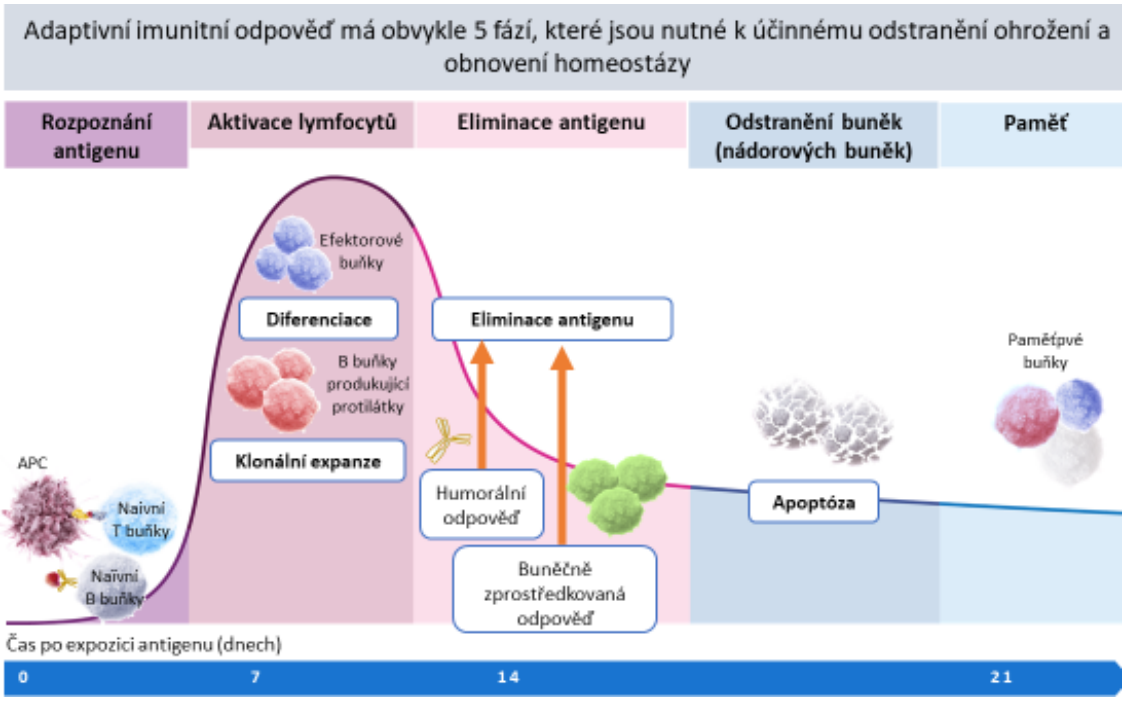
6.3 PHASES OF IMMUNE RESPONSE

Table 1 shows type-phase of the immune response and the duration of the response, and Table 2 contains in detail phases of adaptive response.

Tab. 1 Typ phases of immune response

Phases of immune response		**Duration of response**
Innate immune response	PRR receptors on cells of the innate immune system recognize common features of foreign pathogens and damaged or mutated tumor cells: Result: inflammation, complement activation and phagocytosis	First answer: It starts minutes after exposure to the antigen and lasts for several days
APCs of the innate immune system, particularly dendritic cells, interact with cells of the adaptive immune system, leading to their proliferation and differentiation		
Acquired-adaptive immune	It involves two major types of	Secondary response is

Phases of immune response		Duration of response
response	lymphocytes having cell surface receptors capable of recognizing a single specific antigen	initiated when the innate immune system is unable to eliminate the foreign antigen or pathogen
Immunological memory	Memory B and T cells provide protection against reinfection as a result of an adaptive immune response	Lifetime response It starts days to weeks after the initial identification of the foreign antigen



Tab 2 Phases of adaptive immune response

In the first phase, antigen presentation is initiated. The most important antigen-presenting cells are macrophages, dendritic cells and B lymphocytes.

In the second phase, lymphocytes are activated by stimulating factors produced mainly by antigen-presenting cells (APCs). These factors include MHC - TCR complex, costimulatory molecules and cytokines. T cell clonal expansion and differentiation occur. CD4 + T cells differentiate into different types of effector cells (Th1, Th2, Th17, Tfhelp, Threg). Activated B cells undergo mutations with development to plasma cells and highly specific memory B cells.

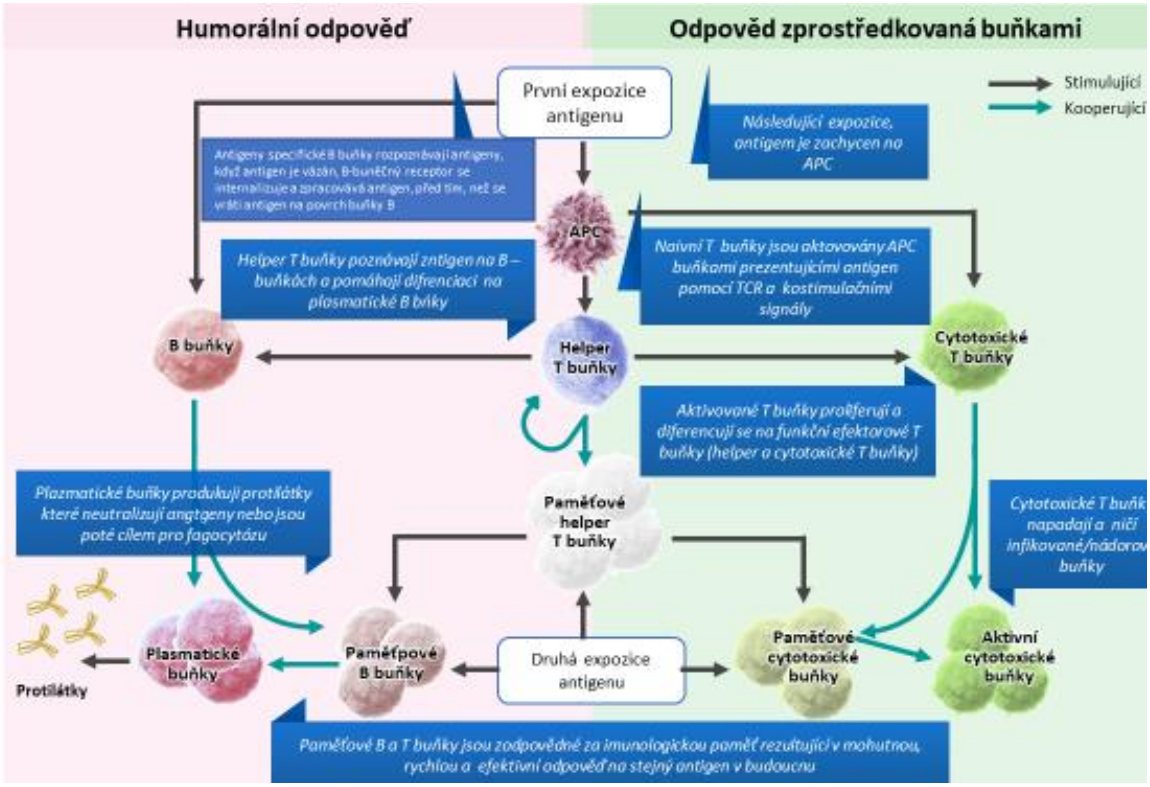
In the third phase, there is a cell-mediated immune response against intracellular pathogens such as viruses and tumor cells that exhibit tumor-specific antigens. CD8 + cytotoxic T cells, which interact with MHC class 1, release cytotoxic granules with effector molecules (perforin, granzymin, granylsin). The humoral immune response results in secretion of antigen-specific antibodies by plasma cells and destruction of extracellular pathogens found in the blood.

In the fourth phase, apoptosis occurs. Once target antigen is eliminated, there are several mechanisms for inhibiting the immune response to protect healthy cells. Immune checkpoints ensure a reduction in the regulation of the immune response to protect its own healthy tissue. Regulatory T cells (Treg cells) suppress T cell response to reduce the immune response and prevent autoimmunity. Treg

cells express CTLA-4 on their surface, that compete with B7, expressed on the surface of APC, thus preventing adequate stimulation of naive T cells by CD28. Inactivated T cells are removed by programmed cell death (apoptosis). Immune checkpoints are pathways in the immune system that are critical for modulating immune response and prevent autoimmunity and minimize collateral damage. Immune control sites ensure an appropriate magnitude of the immune response. Nowadays the influence of these checkpoints is used in immunological treatment of tumors.

In the fifth phase, "immunological memory" occurs. After the immune response, most antigens of specific T cells and B cells die. However, a small number of cells are converted to memory cells. This is a key characteristic of adaptive immunity. Memory cells exist in a state of readiness and have the ability to proliferate rapidly. Memory T cells are found in peripheral tissues and non-lymphoid tissue. Memory B cells are found in the spleen, lymph nodes, and circulate in the blood. Thanks to their increased affinity, memory cells have the ability to respond to lower doses of antigens compared to naive T and B lymphocytes.

Acquired - adaptive response - summary



6.4 ANTI-TUMOR IMMUNE RESPONSE

Genetic and cellular changes in tumor cells are recognized by the immune system as if it was a foreign cell organism:

- **Tumor-associated antigens -** shared antigens, overexpressed in cancer.
- **Neoantigens-** tumor-specific immunogens arising from genetic mutations during oncogenesis.

T cells directed against the tumor are capable of killing tumor cells.

The anti-tumor immunity cycle consists of 7 consecutive steps providing an anti-tumor immune response. For the anti-tumor immune response to kill tumor cells, all steps of the cycle must be completed.

Interruption of the cycle at any step leads to inhibition of T-cell activity and contributes to tumorigenesis.

Activation of tumor-directed T cells requires several processes:

1. **Release of tumor antigens.** Tumor antigens are released during oncogenesis and captured by dendritic cells.
2. **Presentation of tumor antigen.** Antigens are transported to the lymph nodes where they are presented to T lymphocytes.
3. **Preparation and activation**. Presentation of antigen by dendritic cells to T-lymphocytes, activation of T-cells. Activation is regulated by a number of anti-tumor immune response checkpoints.
4. **Transport of T cells to tumor.** Activated T cells travel through the blood vessels from the lymph nodes to the tumor site.
5. **T cell penetration into the tumor.** Activated T cells penetrate the tumor microenvironment through blood vessels - the process involves rolling and adhesion to the endothelium.
6. **T-cell recognition of tumor cells.** Activated T lymphocytes recognize tumor cells - binding of TCR to the antigen-MHC-I complex.
7. **Killing of tumor cells.** The killing of tumor cells leads to the release of additional antigens → re-initiating the anti-tumor immune response cycle

Failure in the anti-tumor immune response cycle results in a tumor hiding from the immune surveillance

1. By preventing tumor cells from being killed by T cells,
2. By blocking the penetration of T cells into the tumor and subsequent killing of the tumor cells,
3. By blocking the formation and activation of T cells, their penetration into the tumor and the killing of tumor cells.

There are 3 immunological tumor phenotypes, which can cause an error in the anti-tumor immune response cycle: a phenotype "without inflammatory infiltration", a phenotype "with infiltration of tumor periphery" and a phenotype "with inflammatory infiltration". Each immune phenotype requires specific T-cell activity to restore the anti-tumor immune response. The individual phenotypes can overlap each other.

6.5 TREATMENT

Currently, several mechanisms - groups of substances - are used in clinical practice:

1. **Interferons** – Interferon α2a-.It is used for melanoma treatment, renal tumor treatment.

2. **CTL4 A (cytotoxic T-lymphocyte-associated protein 4) inhibitory checkpoint inhibitors.** These are antibodies against the receptor (anti CTL4 A). In practice, ipilimumab and tremelimumab are used in the treatment of melanomas.
3. **Inhibitors of inhibitory checkpoint PD** (program death). These are antibodies against the receptor (anti PD) or against the ligand (anti PD-L1). Represented by nivolumab and pembrolizumab (anti PD), atezolizumab, avelumab, durvalumab (anti PD L1). Used in malignant melanoma, lung cancer, renal cancer, bladder cancer, head and neck cancer, Merkel cell cancer, and others. In the Czech Republic, these drugs are now being reimbursed by a state health insurance in indications: renal cancer, melanoma and some lung cancer.
4. **Dendritic cell vaccines**– (sipuleucel T, rarely in prostate cancer).
5. **CAR-T lymphocytes** – T cells modified by the chimeric antigen receptor (used in hematological tumors).

2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for discovering cancer treatment by "inhibiting negative immune regulation".

6.6 Conclusion

The role of the immune system is to protect the host from pathogens and cancer by identifying and eliminating *“non-self”* antigens while avoiding affecting damage to healthy *"self"* tissue.

The immune system provides two types of immunity: innate and acquired.

Innate is rapid but non-specific reaction. Acquired - adaptive reaction is slower but highly specific. It is mediated by lymphocytes that provide two types of response: cell-mediated immunity (T-cells), antibody-mediated or humoral immunity (B-cells). Adaptive immunity results in immunological memory, important for a faster and more efficient response to the same antigen in the future.

7 NAUSEA, VOMITING

Lenka Rušínová

Nausea and vomiting are relatively common and severe symptoms in cancer patients, which in most cases are accompanying anticancer treatment or arise in connection with the tumor itself. Chemotherapy-induced nausea and vomiting are among the most common adverse effects of cytostatics and may significantly affect patient´s quality of life and compliance with other cancer treatments. The aim of modern anti-cancer therapy is to prevent nausea and vomiting, not to treat these adverse effects after they appear.

7.1 PATHOPHYSIOLOGY

Nausea is defined as a subjective discomfort accompanied by vegetative manifestations such as paleness, sweating and salivation. Vomiting is a sudden, nerve-controlled oral excretion of the chyme from the stomach or duodenum, caused by convulsive contractions of the abdominal and diaphragm muscles.

The vomiting center is located in the medulla oblongata, which receives stimuli from:

- upper digestive tract,
- chemoreception trigger zones in area postrema at the bottom IV. cerebral ventricles,
- vestibular apparatus,
- higher levels of the brain, including the cortex.

Cytostatics and their metabolites induce vomiting by stimulating the chemoreceptor zone in the central nervous system, but also by stimulating peripheral receptors. The chemoreceptor trigger zone is rich in dopamine D2 receptors and serotonin 5-HT3 receptors, which are also found at high concentrations in the afferent nerve endings of the vagal nerve in the intestine. Other emesis-affecting receptors include neurokinin, histamine, cannabioid, and opioid receptors, which are located in the vomiting center and also in the vestibular apparatus.

Various causes may contribute to the onset of nausea and vomiting in cancer patients, not just the adverse effects of cancer therapy plays its role. Often more than one cause of discomfort can be identified in one patient. Causes of nausea and vomiting in cancer patients:

- gastrointestinal: gastrointestinal obstruction, gastric evacuation disorder, hepatomegaly,
- metabolic: hypercalcaemia, hyperglycaemia, hyponatraemia, infection, uraemia, hepatic failure,
- drugs: cytostatics, opioids,
- radiotherapy,
- central causes: increase in intracranial pressure when the central nervous system is affected (morning vomiting without nausea),
- psychogenic: anticipatory before the next cycle of chemotherapy,
- chronic in advanced cancers.

Repeated vomiting can have serious consequences for the patient, leading to fluid loss, hypochloraemia, hypochloraemic alkalosis, hypokalaemia, dehydration, reduced food intake.

7.2 NAUSEA AND VOMITING INDUCED BY CHEMOTHERAPY

7.2.1 Types of nausea and vomiting

Regarding the time when chemotherapy started, we distinguish several types of nausea and vomiting.

Acute vomiting occurs within 24 hours of chemotherapy start, may occur soo- right after initiation of cytostatic therapy or later – with several hours delay. Is mediated by sudden release of serotonin due to cytotoxic drugs and its binding to serotonin receptors both in the gastrointestinal periphery and in the chemoreceptor trigger zone.

Delayed vomiting occurs 2 to 5 days after the administration of cytostatics, especially after cisplatin, carboplatin, doxorubicin treatment. The efficacy of serotonin receptor blockers in delayed vomiting is substantially lower, with corticosteroids, neurokinin receptor blockers or dopamine receptor blockers being more effective for prevention and treatment.

Anticipatory nausea and vomiting develop before the cytostatic administration in connection with previous negative experience with chemotherapy, and the incidence increases with continued cycles of chemotherapy. Benzodiazepines are used in therapy of anticipatory nausea and vomiting for its effects of causing amnesia for cytostatic administration**. Breakthrough vomiting** occurs despite optimal anti-emetic prophylaxis. **Refractory nausea and vomiting** persists even after „rescue“ antiemetic treatment.

7.2.2 Emetogenicity of cytostatics

The emetogenicity of anticancer treatment depends on the emetogenic potential of the individual drug and its dose, and on the individual risk factors of the patient. The high risk group are considered cytostatics inducing vomiting in more than 90% of patients without anti-emetic prophylaxis, moderately emetogenic cytostatics are leading to vomiting in 30% to 90% of patients, while low emetogenic cytostatics in only 10% of patients. Combined chemotherapy is more emetogenic than administration of a single cytostatic.

Emetogenicity of routinely used intravenous anticancer drugs:

- **high** (risk of emesis 90%): cisplatin, high-dose cyclophosphamide,
- **moderate** (30-90% risk of emesis): anthracyclines, ifosfamide, irinotecan, carboplatin, oxaliplatin,
- **low** (risk of emesis 10–30%): docetaxel, etoposide, flourouracil, gemcitabine, paclitaxel.

Individual risk factors affecting the emetogenicity of cytostatics include gender, age, psychological condition, previous drug induced vomiting, kinetosis, abusus of any kind. Vomiting after chemotherapy is more common in younger patients, especially women or patients with anxiety. On the other hand, there is a lower incidence of vomiting in the elderly and in those who regularly consume alcohol.

7.3 TREATMENT OF NAUSEA AND VOMITING

Nausea and vomiting can be treated or prevented by drugs called antiemetics that block the brain centers responsible for controlling vomiting and involved receptors in the gastrointestinal tract. Antiemetics have the highest effect when given preventively, therefore, from the beginning of the first cycle, strong antiemetic prophylaxis based on the emetogenicity of chemotherapy is recommended. There are several types of antiemetics that differ in their mechanism of action and spectrum of adverse effects.

7.3.1 Setrons

Setrons are antagonists of 5-HT_3 receptors in the central nervous system in the chemoreceptor trigger zone and in the gastrointestinal tract at the nerve endings of the vagus nerve. They play a dominant role in the prevention and treatment of acute vomiting. Oral administration of the recommended dose is equivalent to intravenous form in efficacy and toxicity. The addition of corticoids improves the effectiveness of the antiemetic treatment regime containing setrons. They do not have a greater effect than corticoids or prokinetics against delayed vomiting. The most common adverse effects are headache, constipation, QT prolongation and induction of arrhythmia.

The 1st generation of setrons include ondansetron and granisetron, the more modern setrons of 2nd generations (palonosetron) have a high affinity for 5-HT_3 receptors with an effect lasting up to 5 days and a lower risk of QT prolongation.

7.3.2 Antagonists of neurokinin receptors NK_1

Neurokinin receptor antagonists NK1 are inhibitors of the action of substance P on NK1 receptors (neurokinin receptors 1), which are abundantly expressed in the area postrema at the bottom of IV. cerebral ventricles and medulla oblongata. Unlike setron antiemetics, they significantly reduce the incidence of delayed vomiting and nausea. Because of their different mechanism of action, they desirably complement the antiemetic combination of 5-HT_3 receptor blockers with corticosteroids. Neurokinin receptor inhibitors are moderate inhibitors of CYP3A4 - thus have the potential to interact with drugs that are metabolised by this enzyme. They are administered orally (aprepitant, netupitant) and have a long half-life. In fixed combination with palonosetron, one tablet is given for the entire chemotherapy cycle.

7.3.3 Corticosteroids

The mechanism of antiemetic action of corticosteroids is not well known, their anti-oedematous effect or inhibition of prostaglandin production might be exerted. In antiemetic prophylaxis, corticosteroids increase the effect of setrons, but they also have a significant effect in preventing delayed nausea and vomiting. Hyperglycaemia is a typical adverse effect that occurs even in short-term use of corticosteroids as antiemetics. Dexamethasone is often used orally or intravenously in antiemetic prophylaxis and therapy.

7.3.4 Dopamine D2 receptor antagonists

Dopamine D2 receptor antagonists affect peripheral dopamine receptors in the intestine and central receptors in the CNS, and therefore may induce extrapyramidal symptoms, especially in geriatric patients or when co-administered with neuroleptics. The most commonly used drug is metoclopramide, belonging to the group of prokinetics, which, besides inhibition of dopamine receptors, boost the motility of the upper part of the digestive tube, including gastric emptying. In addition to antipsychotic and sedative effects, neuroleptics, which mainly affect central dopamine receptors, have an antiemetic effect. The most important substances of this group are thiethylperazine, haloperidol.

7.3.5 Benzodiazepines

Benzodiazepines do not directly have an anti-emetic effect, but affect the patient's anxiety and potentiate the effect of setrons. They may cause amnesia for the administration of cytostatics, which is favorably used to prevent anticipatory vomiting - Alprazolam.

7.4 NAUSEA AND VOMITING IN RADIOTHERAPY

Adverse effects of radiotherapy also include nausea and vomiting, especially in the case of irradiation of the head and the upper abdomen, but also in the case of irradiation of larger areas of body. Emetogenicity is also strong when higher single dose of radiation therapy is applied. Prophylactically, the antiemetic treatment is administered before each dose of radiation therapy.

When irradiating the upper abdomen and craniospinal axis, the risk of emetogenicity is in the range of 60-90%. In such high risk of emetogenicity antiemetic prophylaxis in the form of setrons is indicated possibly in combination with dexamethasone. Radiotherapy in areas of the chest, pelvis, cranium or head and neck is associated with a 30-60% risk of nausea and vomiting. Ondansetron or a dopamine receptor antagonist is administered in such case.

8 PAIN MANAGEMENT

Marie Fischerová

8.1 DEFINITION AND CLASSIFICATION OF PAIN

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or is described by the terms of such damage. Pain is always subjective. Adequate pain management has an key effect on patient comfort and mood, quality of his life and improves treatment adherence. Untreated pain can lead to reduced mobility or even immobility, anorexia, malnutrition, cachexia, social dysfunction and isolation.

A classification of pain based on the prevailing pathophysiological mechanism

- **Nociceptive somatic pain**

Is caused by an irritation of nerve endings (nociceptors) at the site of tissue damage. Usually well localized at the site of injury (bone pain, soft tissue tumors, exulcerated skin tumors).

- **Nociceptive visceral pain**

Is pain caused by an infiltration, compression, constriction or distension in abdominal and lesser pelvis organs. It is usually not specifically localized, sometimes also called transmitted pain (tumor affecting pancreas, intestines, liver, urinary tract).

- **Neuropathic pain**

Is caused by a damage to the peripheral or central nervous system. Other sensomotory disorders (compression or infiltration of nerve roots, nerve plexuses, spinal cord, axonal damage after chemotherapy - polyneuropathy) are also common.

- **Mixed pain**

Has the properties of nociceptive and neuropathic pain (a tumor in a lesser pelvis growing into bones, muscles and destroying nerve plexuses).

A classification of pain based on the duration

- **Acute pain**

Lasts less than 3 months and usually resolves completely after injured tissue heals (postoperative pain, mucositis after chemoradiotherapy).

- **Chronic pain**

Pain lasting more than three months, in prolonged pain vegetative and psychological changes occur.

- **Episodic (breakthrough) pain**

Pain exacerbation episodes in a patient with otherwise moderate pain.

Namely:

- pain at the end of a drug dose interval - occurs in the last hours before the next dose administration. Is considered a manifestation of an inadequate drug dosage - insufficient dose or insufficient length of a dose interval,
- incidental pain - caused by a specific factor - eg. cough, movement,
- breakthrough pain without any known cause.

8.2 Assessment of pain

Major requirement for a successful treatment of pain is a clarification of the cause of pain and its relationship to an ongoing cancer.

Components of the pain examination are:

- detailed clinical examination,
- complex history taking with focus on type of pain, time course of pain, intensity of pain,
- physical and neurological examination,
- in some cases also laboratory testing and imaging testing.

8.3 Pain evaluation

The principle is to express complex experiencing of pain in an aggregate value.

Tools used:

- visual analogue scale (VAS) - a line from 0 to 10, where zero is the pain-free state and the 10 most severe pain the patient can imagine,
- numerical pain scale (NRS) - a patient assigns a number to the pain intensity, usually 0-10,
- verbal pain scale - a patient evaluates pain and selects from offered categories, usually- none, mild, moderate, strong, intolerable,
- pain diary - a patient regularly records the current state of pain during the day,
- Brief Pain Inventory - multidimensional tool for research purposes.

In hospitalized patients, a daily record of pain is established in the nursing documentation as well as in the doctor's rounds records.

8.4 General principles in cancer pain management

Pain management is a part of complex cancer treatment.

- **causal treatment**, which is based on the use of anticancer treatment procedures to remove or reduce the tumor size (surgery, chemotherapy, biological therapy, radiotherapy),
- **symptomatic treatment** - influencing the formation, management and processing of painful stimuli (pharmacological treatment)

8.5 PHARMACOTHERAPY OF PAIN

Choice of the right approach is based primarily on a patient's pain intensity data and the character of his pain.

Determining tool is a three-step WHO analgesic ladder for cancer pain relief.

I. step – mild pain	II. step – moderate pain	III. step – severe pain
NSAIDs	Weak opioids	Strong opioid
+ / - co-analgesics	+/- non-opioid analgesic	+ / - non-opioid analgesic

In intense acute pain, parenteral analgesics should be used, otherwise non-invasive analgesics are preferred. In acute pain, we apply the step down procedure.

- Combination of non-opioid analgesics with opioids has an additive effect.
- Combination of analgesics with co-analgesics depending on the character of pain has an additive effect (paracetamol with NSAIDs)
- We do not combine different NSAIDs for the increased risk of adverse effects.
- We individualize analgesic treatment, monitor the effectiveness of treatment and check for adverse effects.
- An occurrence of adverse effects is not a reason for discontinuation of analgesic therapy, but a reason for treatment and addressing of these reactions.

NSAIDs

Indicated in the treatment of nociceptive somatic and visceral pain in monotherapy or in combination with opioids. NSAID have defined maximum daily dose, its exceeding does not lead to an enhanced analgesic effect but increases the risk of adverse effects.

NSAIDs are very effective and well tolerated. CAVE risk of NSAID caused gastropathy, GIT bleeding - the risk is increased in the presence of peptic ulcer disease, in patients over 65 years of age, when co-administered with corticosteroids, anticoagulants, other NSAIDs and in higher NSAID doses. The risk can be reduced by concomitant administration of proton pump inhibitors (always indicated when NSAIDs with high risk of GIT bleeding are used). Renal and cardiac toxicity of NSAIDs more common in cardiac and dehydrated patients.

Substance (brand name)	Onset of action, routes of administration	Max. daily dose	Note
Analgesics – antipyretics			
Paracetamol (Panadol, Paracetamol, Paralen, Paramax...)	30 min p.o, p.r	4x 1 000 mg	At higher doses and in patients with chronic hepatopathies, the risk of hepatotoxicity. Usually safe in patients with liver metastases. At doses above 2 g / day affects INR in patients treated with warfarin.
Metamizol (Metamizol, Algifen, Novalgin, Analgin)	30 min p.o, i.v	6x 1 000 mg	Spasmolytic effect Contraindicated in patients with leukopenia or in risk of agranulocytosis. When used regularly, INR affects patients treated with warfarin.

Substance (brand name)	Onset of action, routes of administration	Max. daily dose	Note
COX -2 nonselective NSAIDs			
Ibuprofen (Apo–Ibuprofen, Dolgit, Ibalgin, Ibumax...)	15-20 min p.o	4x 600 mg	GIT sparing
Diclofenac (Almiral, Apo–Diclo, Dolmina, Veral, Voltaren...)	30 min p.o, p.r, i.m, i.v	3x 50 mg	Dose of 50 mg comparable to Ibuprofen 400 mg, moderate risk of GIT bleeding, high cardiovasc. risk
Naproxen (Etrixenal, Nalgesin, Naproxen)	2 h p.o	2x 500 mg	
Indometacin	60 min p.r	2x 100 mg	High risk of GIT bleeding, relatively frequent also other CNS A.E. (vertigo, ceflea, nausea)
Ketoprofen (Ketonal)	p.o	3x 100 mg	High risk of GIT bleeding
COX -2 selective NSAID			
Nimesulid (Aulin, Nimesil, Mesulid, Nimed)	60 min p.o	2x 100 mg	Wel tolerated by patients

Opioid analgesics

Weak opioids

A common feature is the presence of a clinically significant ceiling effect. Starting from a certain dose, a further increase in the dose results in a very small increase in the analgesic effect. Adverse effects include constipation, sedation and respiratory depression may be intensified by further increasing of the dose.

- Combination with non-opioid analgesics is preferred. Tramadol + Paracetamol (Doreta, Zaldiar, Tramylpa, Palgotal) Tramadol + Ibuprofen, Codeine + Paracetamol (Korylan, Ultracod)
- In long-term therapy neither combining various weak opioids nor combining weak opioids with the strong ones is recommended.

Drug (brand name)	Onset of action, routes of administration	Max. daily dose	Note
Codein	30-60 min p.o	4x 60 mg	Relatively weak analgesic effect. Antitussive effect, frequent AE is constipation. In approximately 10% of the European population ineffective due to enzyme deficiency.
Dihydrocodein (DHC Continuus)	2-3 h p.o	2-3x 120 mg	Higher analgesic effect compared to codein
Tramadol (Mabron, Tralgitt,	20-30 min p.o, p.r, i.v, i.m, s.c	2x 200 mg	Many dosage forms. AE - nausea, dizziness. Adhere to slow

Drug (brand name)	Onset of action, routes of administration	Max. daily dose	Note
Tramal...)			increase in doses, especially when drops are used. In combination with SSRI can cause serotonin syndrome - relative CI.

Strong opioids

Drug group of choice in the treatment of severe cancer pain.

- Opioid receptor agonists, one of the safest analgesics. (Buprenorphine partial agonist at μ-receptors and antagonist of κ-receptors)
- Non-toxic to parenchymatous organs, hematopoiesis and do not interfere with the function of the coagulation system.
- If pain of high intensity is respected as the only indication for opioid administration, the risk of developing a psychological dependence in patients without a previous history of abuse is low.
- Every patient receiving long-term opioid treatment must be considered physically dependent - there is a risk of withdrawal symptoms from sudden abstinence.
- The analgesic effect depends on the dose, doses with comparable analgesic effect (equianalgesic) have comparable adverse effects.
- Oficially, there is no maximum daily dose (ceiling dose). For example, max. dose of transdermal buprenorphine as given in summary of product characteristics of 140 μg / h is only a recommendation, new clinical data suggest that higher doses can be safely administered.

Drug (brand name)	Onset of action, routes of administration	Max. daily dose	Note
Fast release morphine	20–30 min p.o, pr., s.c, i.v (i.v 5 min, s.c 15 min)	4–6 h	Golden standard in a treatment of severe cancer pain. Various dosage forms. Tablets must not be halved, crushed, must be administered whole, temporarily also p.r Analgesically active and toxic metabolites accumulate in renal insufficiency
Controlled release morphine	3–5 h	12 h	
Fentanyl TTS (Durogesic, Fentalis, Dolforin)	8–12 h	72 h	Stable plasma concentrations of fentanyl Lower occurrence of constipation compared to p.o. Morphin. There is no significant accumulation in renal or hepatic insufficiency.
Fentanyl transmucous (Breakyl, Effentora, Lunaldin, Instanyl, Vellofent)	5–15 min buc. flm, slg. tbl, nas. spray,		Therapy of breakthrough pain In forms of nasal spray, buccal tablets, sublingual tablets, buccal film.

Drug (brand name)	Onset of action, routes of administration	Max. daily dose	Note
Controlled release Oxykodon (Targin, Oxycontin)	1-3 h p.o, p.r	8–12 h	Analgesic efficacy in neuropathic pain Also useful in renal insufficiency Better AE profile (especially lower incidence of constipation) in combination with naloxone.
Buprenorfin TDS (Noprex, Transtec)	10–12 h	72–84 h	Good tolerability in seniors, useful in renal and hepatic insufficiency. It accumulates in biliary tract obstruction.
Controlled release Hydromorfon (Palladone, Jurnista)	3–5 h p.o	12 h, 24 h	Can be used in renal insufficiency
Tapentadol (Palexia)			Use in neuropathic pain Low potential for undesirable drug interactions, favorable AE profile

Breakthrough pain therapy

The aim is a rapid onset of action and a short duration of activity.

- In the case of pain at the end of the dose interval, we shorten the interval or increase the dose of the basic analgesic.
- For episodic pain with a causative cause, we treat these causes.
- In breakthrough pain without a causative cause, we administer the so-called rescue dose, increase the daily dose - in opioids by 30%.
- In mild to moderately painful episodes of breakthrough pain - non-opioid analgesics, combination of paracetamol with weak opioids.
- Severe pain episodes of breakthrough pain - weak opioids - tramadol (possibly also in patients chronically treated with strong opioids), rapid release morphine, transmucosal fentanyls.

Indications for increasing the basic (regular) analgesic medication:

- In sudden and very short episodes of breakthrough pain, where oral, transmucosal, parenteral dosage forms are not effective, because their effect only occurs after the pain episode subsides. Except for a brief episode of pain associated with rehabilitation or medical procedures in which patient can be premedicated.
- In the worsening of pain or a higher incidence of breakthrough pain episodes.
- If the patient needs more than 4 rescue doses per day.

Opioid rotation

A change in the type of opioid administered. We assume that each patient has an individual susceptibility to analgesic effect, but also to adverse effects.

Indications for opioid rotation:

- it is not possible to relieve pain by the opioid chosen, increasing the dose is not possible due to adverse events occurrence (we reduce equianalgesic dose by 10–20%).

- treatment causes serious adverse effects (in the new opioid we reduce equianalgesic dose by 50%).

Morfin s.c, i.m	10	20	30	40	50	60	80	100	200
Morfin p.o	30	60	90	120	150	180	240	300	600
Morfin i.v	7,5	15	20	25	35	40	55	70	140
TTS Fentanyl ug/h	12,5	25		50		75	100	250	
Oxycodon p.o mg	20	40	60	80	100	120	160	200	400
TDS Buprenorfin ug/h		35	52,5	70	87,5	105	140		
Hydromorfon p.o mg	4	8	12	16	20	24	32	40	80
Tramadol p.o mg	150	300	450	600					
Tramadol i.m, i.v	100	200	300	400					
Dihydrocodein p.o	120	240	320						

Side effects of opioid analgesics

- Very common (> 10%) constipation, nausea, sedation, fatigue, drowsiness, dry mouth
- Common (1-10%) vomiting pruritus, urinary retention, sweating
- Uncommon (0.1 - 1%) confusion, hallucinations, hypotension
- Rare (<0.1%)

Adjuvant analgesics (coanalgesics)

- Conditions other than pain are the primary indications, in neuropathic pain these drugs are the first choice.

Multipurpose coanalgetics

Have an adjuvant effect on most types of pain.

- **Antidepressants** - eg. in dysesthesia, neuropathic pain,
- **α 2 agonists** - clonidine - neuropathic pain, tizanidine (Sirdalud) - muscle relaxant, in pain with a pronounced myofascial component,
- **Corticosteroids**
  There is no standard dosage recommendation, an effective dose is individual for every patient. The analgesic effect occurs quickly, if it does not occur within 5-7 days, then it is usually advisable to discontinue administration. Indications for corticosteroids use: bone metastasis pain, neuropathic pain due to infiltration or compression of nerve structures, muscle and joint pain, hollow organ obstruction pain (ureter, intestine), capsule tightening (liver, kidney), headache in intracranial hypertension, spinal cord comppression.

Coanalgesics in a treatment of neuropathic pain

- **Anticonvulsants and gabapentinoids**

First-line anticonvulsants - Gabapentin (Gabanox, Neurontin) 300–1200 mg / day in 3 daily doses, Pregabalin (Lyrica, Pragiola) 150–600 mg / day in 2 daily doses, carbamazepine for trigeminal neuralgia, valproic acid clonazepam.

- **Local anesthetics**

antiarrhythmics mexiletine, trimecain (slow infusion), lidocaine,

- **Antidepressants**

TCA, SSRI, NSRI, NaSSA

Coanalgesics in a treatment of musculoskeletal pain

- **Myorelaxants**

Tolperisone (mydocalm) 100–150 mg three times a day, Mephenoxalon (Dorsiflex) 200 mg three times a day, followed by Baclofen 10–20 mg three times a day

- **Benzodiazepines**

diazepam, clonazepam, tetrazepam

- **Tizanidin (Sirdalud)**

starting dose 2 mg per night, individual dosing

Coanalgesics in a treatment of bone metastases pain

Zoledronate 4 mg IV for 4 weeks, Ibandronate - 6 mg IV for 4 weeks or 50 mg p.o daily, Denosumab 120 mg s.c for 4 weeks, Pamidronate 60 - 90 mg IV for 3-4 weeks, Clodronate 800 mg p.o 2 times a day

- **Corticoids**

Prednisone, Dexamethasone, Methylprednisolone - individual dosing

Coanalgesics in a treatment of pain caused by a malignant intestinal obstruction

- **Corticoids**

reduction of intestinal wall edema, reduction of intestinal secretion

- **Scopolamine buthybromide (Buscopan)**

in colic pain 20 mg inj. s.c. / i.v. bolus after 4-6 h or 80 mg / 24 h by continuous s.c infusion

Other coanalgesics

- **Psychostimulants**

Methylphenidate 10-20 mg twice a day (starting dose 5 mg twice a day, gradually increase the dose), reduce sedation and fatigue induced by higher doses of opioids

- **Cannabinoids**

Main active ingredients are tetrahydrocannabinol (THC) and canabidiol (CBD). Have been shown to be effective in cancer pain and neuropathic pain (HIV), antiemetic effect, improves appetite and affects sleep. In CZ available as medical cannabis - use in vaporizers or p.o in the form of capsules.

8.6 RADIOTHERAPEUTIC TREATMENT OF CANCER PAIN

The indication is based on severity of a patient's symptoms, thus not only based on the results of imaging methods.

Examples of indications for palliative analgesic therapy:

- bone metastasis pain, prevention of pathological fractures, spinal cord compression, dysphagia and odynophagia in esophageal tumors, affection of intracraial hypertension in brain metastases, pleural pain and chest wall pain in lung tumors, alleviation of pain in liver, spleen, pancreas, small biliary tract or lesser pelvis infiltration. Reduction of vascular compression edema, lymphedema in malignant lymphadenopathy. Skin infiltration, multiple myeloma.

8.7 USE OF UNSEALED SOURCES IN THE TREATMENT OF CANCER PAIN

After i.v. application of radionuclide (Strontium, Samarium) it is selectively taken up in the osteoblastic zone surrounding the bone metastasis. Local absorption results in inhibition of nerve endings and reduced production of pain mediators.

Indication:

- multifocal painful bone involvement where external radiotherapy is difficult or impossible to perform, osteoplastic or mixed type bone metastases.

9 VENOUS THROMBOEMBOLIC DISEASE IN CANCER PATIENTS

Jiří Švec

Venous thromboembolic disease (VTE - Venous thromboembolism) is a frequent, potentially life-threatening disease and is one of the major causes of morbidity and mortality in cancer patients. Approximately 20% of all cases of VTE are associated with cancer and malignant cancer patients are in 4-7 fold higher risk of developing VTE compared to normal population. The presence of VTE complicates and delays cancer therapy, is associated with worse prognosis (increases mortality 2–8 times) and is the second most common cause of death after cancer itself in cancer patients.

9.1 CLASSIFICATION, RISK FACTORS AND ETIOPATHOGENESIS OF THROMBOEMBOLISM IN ONCOLOGY

A term venous thromboembolism includes:

- superficial venous thrombosis (thrombophlebitis),
- deep vein thrombosis (phlebothrombosis),
- pulmonary embolism,
- thromboses in other locations (portal vein in 34-40%, mesenteric vein, inferior and superior venae cavae, pelvic venous plexus),
- central venous catheter thrombosis (CVCT).

Risk factors in relation to:

- **patient -** history of thrombosis, infection, elderly, obesity, other illnesses, smoking, thrombocytosis, congenital or acquired thrombophilic conditions (Leiden mutation of f.V, antiphospholipid syndrome),
- **malignancy - histology** (tumors of the brain, pancreas, stomach, kidneys, uterus, lungs, ovaries, urinary bladder, testes) and advanced cancers (metastatic stage has a 6-19-fold higher risk),
- **treatment - surgery** (especially abdomen and pelvis), immobilization, presence of CVC, systemic therapy (chemotherapy, estrogen receptor modulators - tamoxifen, anti-angiogenic agents - bevacizumab, thalidomide / lenalidomide + dexamethasone).

Selected thrombogenic pathogenetic factors:

a) Direct influence of tumor cells

- increased production of pro-inflammatory cytokines (TNFα, IL-1, IL-6) with increased secretion of procoagulant factors;
- releasing of Tissue Factor (TF), which stimulates thrombin production;
- Cancer procoagulant (CO) is a protease produced by tumor cells (cancers of kidney, stomach, acute promyelocytic leukemia) that activates f. X;
- some mucins released from adenocarcinomas may stimulate f. X.

b) Treatment related factors

- Chemotherapy (taxanes, CDDP, 5FU, MMC) leads to decreased levels of ATIII, protein C and S, increased vWF endothelial damage, cytokine release, TF.
- Anti-angiogenic drugs (bevacizumab, some TKI) - block endothelial function of VEGF and increase the risk of venous and arterial thrombosis (stroke, MI). Anticoagulant therapy with concomitant bevacizumab treatment in clinically non-severe VTE (subsegmental pulmonary embolism, limb thrombosis) is not contraindicated.
- EGFR inhibitors (cetuximab, panitumumab) and HT (tamoxifen, megestrol).

9.2 VTE DIAGNOSTICS

a) Diagnostics of deep vein thrombosis

Patient history, physical examination (unilateral limb edema in 80%, pain in 75%, erythema in 26%, swelling of the face, neck, supraclavicular region), complete blood count with differential, basic coagulation lab, biochemistry. In patients with a high suspicion and without contraindications, the use of anticoagulant therapy may be considered prior to imaging (Doppler US, CT or MRI angiography). D-dimers are of limited significance in patients with malignancies.

b) Diagnostics of splanchnic vein thrombosis

Up to 20–30% of patients with hepatocellular carcinoma have portal vein thrombosis at the time of diagnosis and these patients have significantly worse survival(6 vs. 16 months). Mesenteric vein thrombosis can lead to intestinal infarction with 30-day mortality of up to 20%. Risk factors include congenital thrombophilic conditions (antithrombin III deficiency, protein C and S deficiency, Leiden mutation of f.V, prothrombin G20210A mutation) and acquired thrombophilic conditions (malignancies, myeloproliferative diseases with JAK2F617F mutation - polycythemia vera, essential thrombocythemia), paroxysmal nocturnal hemoglobinuria, intra-abdominal surgery, pancreatitis. Clinical manifestations include abdominal pain, ascites, hepatomegaly, nausea, vomiting, anorexia, diarrhea. US, CT-angiography, MRI are used in diagnosis.

c) Diagnostics of pulmonary embolism (PE)

Clinical manifestations include dyspnoea (85%), chest pain (40%), tachypnoea (29%), cough (20%), tachycardia, haemoptysis, syncopy, hypoxia and cardiogenic shock. At the same time, deep vein thrombosis is found in 50–70%. Asymptomatic patients with a random PE finding should be treated as symptomatic PE patients. We perform basic examinations with ECG, heart and lung X-ray, CT-AG, ventilation-perfusion scintigraphy, ECHO, troponin helps to further risk-stratify patients.

9.3 PRINCIPLES OF PROPHYLACTIC ANTICOAGULATION THERAPY IN CANCER PATIENTS

- The NCCN guidelines panel (2018) recommends prophylactic anticoagulation therapy in all hospitalized patients with active cancer and in worsening clinical status. Those are not patients admitted for short-term chemotherapy or surgery (e.g. biopsy).
- In patients after major surgery (intra-abdominal and pelvic surgery, anesthesia> 2 hours, advanced cancer, age over 60 years, obesity, history of VTE), VTE prophylaxis for 4 weeks is recommended; 10 days is enough for minor surgeries.

- Prophylaxis is not recommended in outpatient cancer patients; it can be considered in the high-risk subgroup according to the Khorana score.
- Routine prophylaxis of thrombosis is not recommended in CVC or port placement.

The Khorana score for prediction of venous thromboembolism in cancer patients

Patient characteristics	Score
Tumors with very high risk of VTE (brain, stomach, pancreas)	2
Tumors with high risk of VTE (lung tumors, lymphomas, urogynecological tumors except the prostate and testes)	1
Pre- chemotherapy platelet count ≥ 350 x 10^9/l	1
Pre- chemotherapy leukocyte count > 11 x 10^9/l	1
Hemoglobin level< 100 g/l = <10g/dl	1
BMI ≥ 35 kg/m2	1

The Khorana score allows risk-stratification of outpatients into low risk (score 0), medium (score 1-2), and high risk (score ≥ 3) groups. The incidence of VTE is in low risk group - 0.3%, in medium risk group - 2% and in high risk group - 11.1% (these patients may be individually assessed for anticoagulant therapy).

9.4 Anticoagulant therapy in VTE

Anticoagulation therapy prevents thrombus growth, fatal pulmonary embolism, recurrent thrombosis and post-thrombotic syndrome. Low-molecular-weight heparin (LMWH) is recommended for initial therapy, unfractionated heparin can be used in patients with CHRI (Cl_{kr} <0.5 ml / s), fondaparinux in patients with HIT.

Initial LMWH therapy should be at least 5–10 days long (for iliofemoral phlebothrombosis and PE with admission) and maintenance therapy with LMWH (preferentially) or warfarin for at least 3 months, in proximal phlebothrombosis or pulmonary embolism for 6 months. If active cancer and risk factors persists long-term anticoagulation with 80% of the therapeutic dose can be considered.

Anticoagulants and their doses used in VTE therapy:

Drug	Therapeutic dose
enoxaparin (Clexane)	100IU anti-Xa (1mg)/kg s.c. 2x/day
enoxaparin (Clexane Forte)	150IU anti-Xa(1,5mg)/kg s.c. 1x/day
nadroparin (Fraxiparine)	95IU anti-Xa(0,01ml)/kg s.c. 2x/day
nadroparin (Fraxiparine Forte)	190IU anti-Xa(0,01ml)/kg s.c. 1x/day
dalteparin (Fragmin)	200 IU anti-Xa/kg s.c. 1x/day
unfractionated heparin (Heparin)	5000-10000 IU i.v. bolus + kont. 1000IU/h. therapeutic range of 1.5-2.5 (APTT ratios)
fondaparinux (Arixtra)	7,5mg s.c. 1x/day

Anticoagulants and their doses used in VTE prophylaxis:

Drug	Prophylactic dose
enoxaparin (Clexane)	0,4ml (40mg) s.c. 1x/day
nadroparin (Fraxiparine)	0,3ml s.c. 1x/day
dalteparin (Fragmin)	5000 IU anti-Xa s.c. 1x/day
unfractionated heparin (Heparin)	5000 IU s.c. 2-3x/day
fondaparinux (Arixtra)	2,5mg s.c. 1x/day

9.5 SPECIFIC SITUATIONS

Thrombolysis is considered in pulmonary embolism with right ventricular dysfunction or massive ileo-femoral thrombosis not responding to anticoagulation. Recombinant plasminogen activator tPA - alteplase (Actilyse), preferably administered by a catheter, is used in pharmacomechanical thrombolysis. Absolute contraindications of tPA are intracranial haemorrhage, CNS tumors, iCMP in the previous 3 months, recent trauma, head surgery and ongoing bleeding.

Recurrent VTE occurs in up to 10–17% of patients anticoagulated with warfarin and in 6–9% patients treated with LMWH. A change from warfarin to LMWH or an increase in LMWH of 25% of the dose is recommended.

Thrombocytopenia and the need for anticoagulation - full anticoagulation can be given for PLT ≥ 50 x 10^9/l , implantation of a caval filter can be considered with a lower platelet count and an inability to transfuse.

Caval filters may be indicated in patients with proximal phlebothrombosis and / or in PE for which anticoagulation is not possible or has not been effective. Furthermore are also indicated in patients after repeated PE with severe cardiac dysfunction. Extractable filters are preferred.

Therapy of superficial thrombophlebitis - ATB, NSAID, when in the vicinity of a.femoralis anticoagulation for 3 months can be considered.

Splanchnic vein thrombosis therapy - full anticoagulation in acute thrombosis, in chronic asymptomatic and incidentally detected thrombosis is not recommended.

Anticoagulation in CKD - in creatinine clearance <0.5 ml / s, dose reduction of LMWH and monitoring of anti-Xa activity (blood sampling 3-4 hours after administration) is required; for Cl_{kr} < 0,25 ml/s LMWH is not recommended.

Drug dose adjustments in patients with severe renal function impairment (Cl_{kr} = 0,25-0,5 ml/s):

Indication	Enoxaparin dosing
Prophylaxis of VTE	2000IU (20mg, 0.2ml) s.c. 1x/day
Therapy of VTE	100IU/kg (1mg/kg) s.c. 1x/day

9.6 CONTRAINDICATIONS OF ANTICOAGULANT THERAPY

Absolute:

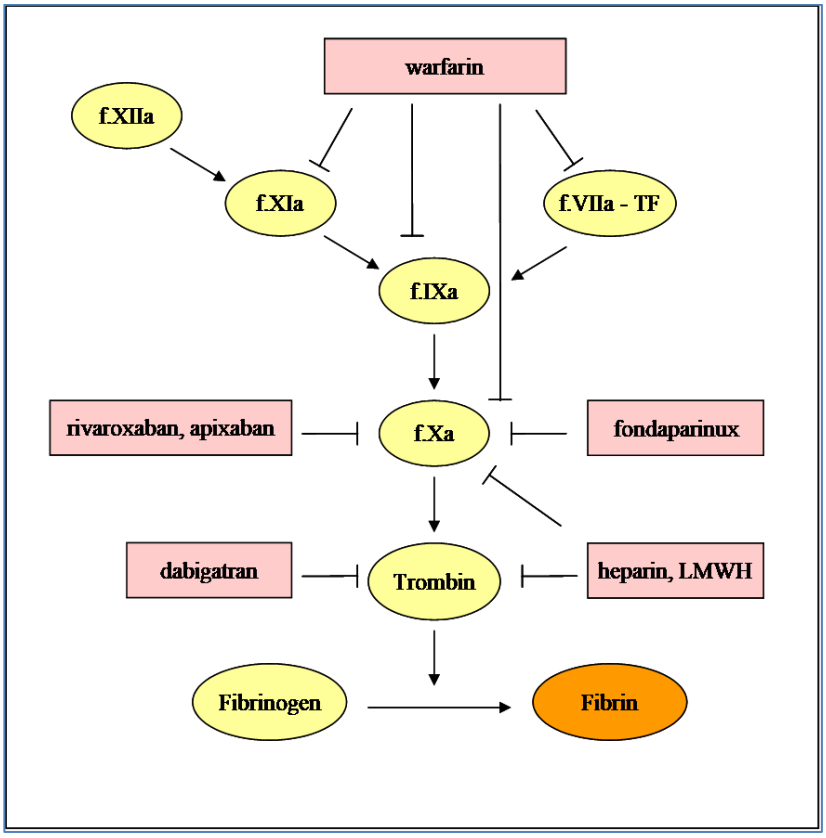
- recent intracranial haemorrhage (cerebral or spinal cord lesions with high risk of bleeding)
- active bleeding requiring more than 2 transfusions / 24 hours.

Relative:

- thrombocytopenia< 50 x 10^9/l,
- chronic bleeding, recent GIT ulcer disease,
- recent surgery with high risk of bleeding (in the past 3 days),
- risk of falls, noncompliance,
- spinal anesthesia / lumbar puncture (discontinue LMWH 12-24 hours before and re-initiate 4 hours after, otherwise risk of spinal or epidural hematoma with persistent paralysis).

9.7 BRIEF CHARACTERISTICS OF SELECTED ANTICOAGULANTS

Scheme of coagulation cascade and sites of action of some anticoagulants:



Warfarin Orion 3mg a 5mg – warfarin inhibits carboxylation of amino acids of prothrombin complex factors (f. II, VII, IX, X) and proteins C and S. It has a half-life of 20–60 hours. It is necessary to co-administer with LMWH until the therapeutic range (INR 2-3) is achieved. Warfarin anticoagulation is useful in patients with stable cancer, but there is a risk of multiple drug interactions (eg, capecitabine increases warfarin levels by 57% and INR by 91%) and LMWHs are more effective in secondary oncology VTE prevention.

Heparin, 5000IU/ml – heparin is a naturally occurring mixture of mucopolysaccharides of which activity is conditioned by the presence of antithrombin III, which inhibits factors IIa and Xa with which it forms stable complexes. Heparin accelerates their formation by 1000-fold, it does not have a fibrinolytic activity. Half-life after i.v. administration is 1 hour, after s.c. about 2 hours. The antidote is protamine sulphate where 1 mg neutralizes 100 IU of heparin.

Clexane 2000IU (20mg)/0,2ml až 10000IU(100mg)/1ml – enoxaparin is a low molecular weight heparin that has high anti-Xa and low anti-IIa activity that is mediated by antithrombin III. It also has other antithrombotic mechanisms of action (inhibits f. VIIa, decreases vWF release). The half-life is 5-7 hours. Patients with renal insufficiency are at increased risk of bleeding, therefore dose reduction and monitoring of anti-Xa activity is recommended. The antidote of enoxaparin is protamine, which is able to neutralize about 60% of the anticoagulant activity of LMWH.

Arixtra 2,5mg/0,5ml a 7,5mg/0,6ml - fondaparinux is a synthetic substance, antithrombotic activity is the result of antithrombin III-mediated selective inhibition of f. Xa which fondaparinux potentiates by 300-fold. It does not affect routine coagulation tests, therapy monitoring is performed by monitoring of anti-Xa activity. The half-life is 17-21 hours, 70% of fondaparinux is excreted as unchanged compound via the kidneys and should therefore not be used in patients with Ccreat <0.5 ml / s. Its antidote is not known.

New oral anticoagulants (dabigatran, rivaroxaban and apixaban) are approved for the prophylaxis and therapy of VTE, but in the studies conducted up to this date, cancer patients have been represented only in low numbers therefore, NOACs are not yet recommended in oncology.

9.8 HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Type 2 HIT - occurs in about 1.2–2.7% of patients treated with heparin, usually occurs between 5th and 10th day of treatment. It is an immunological reaction where heparin and less frequently also LMWH binds to a platelet factor 4 (PF4) and heparin / PF4 complexes on the platelet surface and induce production of a specific antibodies. These antibodies further activate platelets, cause thrombin formation, and lead to a consumption thrombocytopenia and thromboses.

Diagnosis:

- 50% decrease in platelet counts,
- time association with heparin administration,
- thrombotic complications (arterial and venous thromboses, necrosis at injection site),
- immunohematological tests (detection of HIT antibodies).

Treatment:

- discontinue heparin or LMWH,
- other anticoagulants - fondaparinux or direct thrombin inhibitors, warfarin up to PLT ≥ 150x109 / l,
- US screening of LL veins.

In heparin therapy, it is recommended to monitor platelet count prior to initiation of the treatment and every 2-3 days for the first 14 days and then once every 2 weeks.

10 NUTRITION IN CANCER PATIENTS

Tereza Fučíková

Nutritional support is an important part of cancer care. Maintaining good nutritional status is essential for preserving patient's performance, quality of life, and possible ways for application of cancer therapy.

Malnutrition (malnutrition) is defined as a long-term state of nutrition that does not meet the needs of the human organism and does not meet its demands, and in which body reserves of both macronutrients and micronutrients are exhausted. From the clinical point of view, protein malnutrition is the most serious, in which catabolism develops due to an inflammation of the organism, proteolysis occurs mainly in skeletal muscles and sarcopenia develops. Malnutrition worsens the prognosis of the disease, increases the risk of toxicity of the anticancer treatment and may be the cause of worse treatment outcomes. The degree of malnutrition affects the expected survival of patients. Effects of nutritional intervention are better in patients before the development of manifest malnutrition, so it is necessary to look for patients at nutritional risk and initiate a nutritional intervention before the development of malnutrition.

10.1 EVALUATION OF NUTRITIONAL STATUS

Evaluation of nutritional status and its monitoring during oncological treatment is an important part of workup in both hospitalized and outpatient patients.

Nutritional risk indicators used:

- **anamnestic data** - weight change (loss of ≥ 5% of usual body weight in 3 months or ≥ 10% in 6 months), low food intake, anorexia, vomiting, diarrhea,
- **anthropometric data** - BMI, arm circumference, current weight, skin fold width,
- **nutritional risk assessment questionnaire** - nutritional screening questionnaires are used to identify patients at nutritional risk or patients with advanced malnutrition in a simple and timely manner,
- **biochemical markers of malnutrition** - total protein, albumin, prealbumin (when interpreting serum levels it is necessary to take into account the clinical condition of the patient, these are negative acute phase proteins),
- **diagnosis with nutritional risk** - typically tumors of the ENT area, upper part of the digestive tract (esophagus, stomach, pancreas), generalized tumors,
- **therapy with nutritional risk** - radiotherapy to the area of swallowing (ENT area, esophagus, epigastrium), concomitant chemoradiotherapy, highly emetogenic chemotherapy, cytostatics inducing mucositis of the gastrointestinal tract, extensive surgical procedures.

10.2 NUTRITIONAL INTERVENTIONS IN CANCER PATIENTS

Appropriate nutritional intervention should be selected individually after evaluation of the patient's nutritional status. As a general rule, if the gastrointestinal tract is functional, we always choose the

enteral route of administration of nutrition that helps maintaining GIT and the intestinal mucosal barrier intact. When the gastrointestinal tract is unused, there is a risk of bowel failure. Energy requirements in patients ranges from 25 to 35 kcal / kg of ideal body weight, protein requirements are 1–2 g / kg of ideal body weight, we always need to take into account the clinical status of the patient (increased protein requirements resulting from acute inflammation, in catabolism, etc.).

Nutritional intervention options include dietary recommendations, sipping, enteral tube nutrition and parenteral nutrition, as well as the use of some appetite-promoting drugs. Well-established supportive therapy during cancer therapy also plays an important role.

Dietary recommendations

Every patient should be advised about suitable diet. General recommendations are to consume energy-rich and protein-rich food, to consume food in smaller portions, to avoid intense taste and olfactory sensations. It is possible to use a nutritional therapist who takes patients nutritional history, permors anthropometric measurements, evaluate nutritional needs of the patient and develops a nutritional plan, as well as properly educates the patient.

Sipping

Sipping is considered an enteral nutrition. This is drinking solutions with a defined composition of all the necessary nutrients. The advantage of the sipping is a high content of energy and protein in a relatively small volume of fluid. Depending on the patient's individual needs, a variety of products (diabetic, fat-reduced, etc.) can be chosen. Sipping can serve as a dietary supplement if the amount and composition of the diet is insufficient to ensure adequate nutrition. We make efforts to maintain the patient's body weight and performance status. Sipping products can also be used in palliative care and terminal patient care.

Enteral TF

Enteral TF is application of defined nutritional solutions to the gastrointestinal tract via various types of TFs. For administration of enteral nutrition we can use nasogastric or nasojejunal tube, percutaneous endoscopic gastrostomy (PEG), surgical gastrostomy or nutritional jejunostomy. We choose the method of application individually according to the current situation, in patients where long-term dependence on enteral nutrition is assumed we prefer PEG or nutritional jejunostomy, otherwise we choose nasogastric or nasojejunal probe. Enteral nutrition is safer, cheaper and more natural compared to parenteral nutrition. Enteral nutrition is well tolerated in most cases. Insertion of PEG is very often indicated in patients with tumors in the ENT area before initiation of curative (chemo) radiotherapy to prevent unwanted weight loss and the associated complications during cancer therapy. Contraindications to enteral nutrition are acute abdomen (ileus, GIT bleeding, peritonitis), shock, early post-GIT surgery states and disorders where resorption area of GIT is compromised.

Parenteral nutrition (PN)

Parenteral nutrition (PN) is defined as applying specialist nutritional products directly into the venous system. It is not a physiological way of providing nutrition, therefore it brings a higher risk of complications compared to enteral nutrition. Parenteral nutrition can be divided into total and partial. In total parenteral nutrition (TPN), nutrient intake is ensured solely via the venous route, indication for total PN are GIT dysfunction disorders (including radiation enteritis, severe diarrhea, malabsorption states, GIT obstruction). In partial parenteral nutrition (PPN), nutrient intake is ensured by both enteral

and venous routes, partial PN is indicated when the enteral route cannot meet the patient's nutritional needs.

Adequate venous access should be ensured prior to initiating PN. Venous accesses for PN administration are divided into peripheral and central. Peripheral venous access is chosen in case of short-term application of PN (usually for up to 7 days) or for the bridging period before securing the central venous access. There is a high risk of phlebitis or thrombophlebitis associated with prolonged application of peripheral PN. Only preparations for parenteral nutrition intended for this purpose can be applied to the peripheral venous system (lower osmolarity of the solution is necessary). More often, PN is applied via the central venous access (i.e., distal end of the catheter is located in the region of the cavoatrial junction). For central PN application, central venous cannulas tunneled or non-tunneled (eg, Broviac catheter), peripherally inserted central catheter (PICC), or venous ports are used. Subcutaneous catheter tunneling reduces the risk of catheter infection.

Central venous access preference for PN application

Non-tunneled central venous catheter	Use in hospital, shorter time - usually for up to 2 weeks
Tunneled central venous catheter	Use at home, long-term application
PICC	Use at home or in hospital, mostly used for several months
Venous PORT	Patients with already inserted venous port for anti-tumor therapy

When administering PN, catheter-related complications such as catheter sepsis, thrombotic complications may develop. Furthermore, metabolic complications such as refeeding syndrome, hyperglycemia, ionic disruption, etc. may arise. Refeeding syndrome threatens with careless nutritional intervention when moving the patient from catabolic to anabolic phase where increased supply of potassium, magnesium and phosphorus is needed, if these nutrients are not adequately substituted risk of complications associated with hypokalaemia, hypophosphatemia, hypomagnesaemia.

PN can be applied by all-in-one system where all macro and micronutrients are contained in a single bag (they are separated first and mixed later, just prior to the administration to the patient) or multi-bottle systems where individual nutrients are stored separately.

Supportive treatment

In patients at high nutritional risk, it is important to emphasize supportive treatment to address symptoms that may interfere with their food intake. Proper analgesic therapy, nausea and vomiting following anticancer treatment therapy , depression therapy, diarrhea and constipation therapy are all extremely important.

Pharmacotherapy in nutritional care

In case of inappetence, hormonal preparations increasing appetite such as megestrol acetate, corticosteroids may be used. Some psychopharmaceuticals can also be used.

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CLINICAL ONCOLOGY

11 MALIGNANT TUMORS OF THE HEAD AND NECK

Kateřina Licková, Miloslav Ambruš

Head and neck tumors are a heterogeneous group of malignant cancers. This group includes all malignant tumors in the head and neck area except CNS tumors. Head and neck tumors represent 6–10% of all malignant neoplasms (WHO), of which more than 40% occur in the oral cavity. The highest incidence is reported in men around 60 years of age, in this peak, incidence is 2:1 relative to incidence in women of this age group. With an incidence of 115.7 and a mortality of 9.42 patients per 100,000 inhabitants, the Czech Republic ranks 16th in world statistics both for mortality and incidence. The incidence of these tumors has almost doubled in the last 30 years. This increase is most pronounced in tumors of the oropharynx and hypopharynx areas, on the contrary incidence of laryngeal carcinoma stayed practically stationary.

Significant geographical differences in incidence can also be observed - in general, these tumors are more common in India and Southeast Asia. In Europe, the increasing incidence trend is described in France, while the low incidence is observed in the Scandinavian countries. Squamous cell carcinomas of the head and neck are associated with a difficult treatment and high morbidity related to the primary disease. Biological behavior of these tumours is characterized by aggressive locoregional invasion and a high tendency to relapse. Long term observed five-year survival rate of patients is approximately 50–60%.

11.1 ETIOLOGY

As with most malignant tumors, etiopathogenesis is not exactly known. Alcohol consumption, tobacco smoking, caries, poor nutritional status and immunity status are the main contributors to their development.

In groups where excessive consumption of hard spirits and in tobacco smokers, this type of malignant disease is much more common than in the general population. Excessive alcohol consumption is also associated with personality disorder and other undesirable complications, such as poor hygiene standards (especially in dental care). Caries dentition is then a frequent source of chronic infections of the oral cavity, which affect food intake and subsequently lead to malnutrition that results in failure of body repair and defense processes. Alcoholics are 2 to 6 times more likely to develop these tumors than general population. For heavy smokers, the risk may be up to 20 times higher depending on the number of cigarettes smoked per day. Alcohol and tobacco are both one of the most carcinogenic substances , when combined, their effect is cumulative and the risk of developing carcinoma of the head or neck increases up to 40 times.

Undeniable is also the effect of viral superinfections, especially human papillomaviruses (HPV). In the palatine tonsil and tongue root region, up to 50% of the tumor cells contain papillomavirus DNA. So far it has not been clearly explained why HPV infection is the most prevalent in these areas. One theory suggests that the main cause is the presence of deep crypts lined with single-layered epithelium, a surface ideal and highly accessible for viral infection. This arrangement of epithelium layers also allows penetration of the basal layers of the epithelium and further spreading. Moreover, there is less mechanical replacement of epithelial cells at these sites.

HPV-positive carcinomas have a better prognosis than HPV-negative carcinomas due to the lower p53 mutation frequency. With consideration to this risk factor, TNM classification for HPV negative and HPV positive oropharyngeal tumors has been revised.

EBV, among other viral infections is associated with the development of nasopharyngeal carcinoma.

Molecular biology has brought quite a lot of light into the issue of the risk of developing, in particular, the recurrence of malignant tumors of the head and neck. Tumor cells in areas of the head and neck have high expression of the epithelial growth factor receptor (EGFR) - in up to 95%. This factor carries a mutated KRAS gene, producing a KRAS protein that promotes or directly triggers cell proliferation and thereby triggers uncontrolled cell growth, causing a high frequency of recurrence of these tumors.

11.2 Clinical signs, symptomatology

The clinical picture of the head and neck tumors is in most cases characterized by an inconspicuous, gradually developing symptomatology. The clinical symptoms depends on the site of lesion. In nasopharyngeal carcinoma, the patient very often reports impaired breathing through the nose, sometimes nasal bleeding, ear buzzing – e.g. when tumor ingrows into the orbit - there is a protrusion of the eyeball and a double vision. For oral cavity malignancies, very often the first symptom is a foreign body feeling that prevents normal swallowing, or painful swallowing, which may also be associated with excessive bad breath. In laryngeal tumors, the patient most often notices impaired vocal comfort, hoarseness or cough provocation. However, the first sign of a malignant process in the head and neck area is painless gradually increasing swelling on the external part of the neck.

11.3 Diagnostics

The diagnostic algorithm begins with a detailed medical history focused on risk factors. Through physical examination we can detect pathological changes in the oral cavity, oropharynx or salivary glands and enlargement of the lymph nodes in the supraclavicular area and in the epididymis.

Examination at a specialized ENT department is recommended in suspicion of cancer in this area. Otorhinolaryngologist then performs a comprehensive examination, which includes epipharyngoscopy, laryngoscopy, otoscopy, palpation and ultrasound examination of lymph nodes in the neck. Part of the examination is also biopsy of the suspected tissue for histological examination purposes. If histology confirms clinical suspicion, computer tomography, magnetic resonance, or ultrasonography examinations should be made to accurately determine the extent of the tumor involvement, in case of laryngeal carcinoma, microscopic laryngoscopy should be done. Based on these examinations we determine the T (tumor size) and N (the extent of lymph node involvement). This process is primarily necessary to determine possibilities of surgical treatment of the pathology found. Possibilities for surgery treatment of the local finding are dependent on the extent of the of organ affection and on the M parameter (metastatic affection of distant organs and lungs and liver, into which tumors of the head and neck most often metastasize).

The basic examination for the exclusion of a metastatic lung involvement is a X-ray - summation image of the lungs, which can be supplemented by a CT scan. If metastatic liver disease is suspected, the basic examination is ultrasound of the liver, possibly supplemented by computed tomography with a contrast agent.

11.4 Differential diagnostics

Up to 98% of the head and neck tumors are squamous cell carcinomas with variable degrees of differentiation. The rest of the cases are malignant lymphomas (or nodal syndromes in chronic leukemia) and malignant melanomas. Cylindroma, although benign tumor, behaves malignantly by its destructive growth and can rarely be found in the area of the nasopharynx.

11.5 TNM classification

Any diagnosis must be verified histologically.

T – is evaluated during complex ENT examination, on the basis of CT examination or MRI examination with histologization of the pathological process. It describes the size of the pathological process and involvement of surrounding anatomical structures or organs.

N – the definition of M categories are the same for all of head and neck locations except for the nasopharynx and thyroid. The midline lymph nodes with the exception of the thyroid gland are considered equilateral. Evaluation is performed on the basis of clinical examination, CT examination and ultrasound examination of cervical nodes.

Nx: lymph nodes cannot be assessed
N0: no regional lymph nodes metastasis
N1: one ipsilateral lymph node metastasis present, size less than 3cm
N2a: one ipsilateral lymph node metastasis present, size 3-6 cm
N2b: more than one ipsilateral lymph node metastasis present, sizes less than 6cm
N2c: bilateral lymph nodes metastases present or at least one contralateral lymph node involved, all sizes less than 6cm
N3: at least one lymph node metastasis bigger than 6cm

M – the definition of M is the same for all head and neck locations; the severity of the disease is determined by X-ray of the lungs and US of the liver.

Mx: lymph nodes cannot be assessed
M0: no distant metastasis
M1: metastasis to distant organs (beyond regional lymph nodes)

Table 1 - Classification of stages based on TNM classification

St. 0	Tis	N0	M0
St. I	T1	N0	M0
St. II	T2	N0	M0
St. III	T3	N0	M0
St. IV	T4	N0–1	M0
	T1–3	N1	M0
	TX–4	N2–3	M0
	TX–4	NX–3	M1

Anatomical location-based classification

- Lip, oral cavity (C 00, C04)
- Pharynx - oropharynx, nasopharynx, hypopharynx (C10, C11, C13)
- Larynx (C 32)
- Cavity, paranasal sinuses (C 31)
- Salivary glands (C07, C08)
- Thyroid (C 73)

11.6 TREATMENT OPTIONS

Treatment of malignant tumors in the head and neck area is based on the location of the primary tumor, the extent of the disease described by histopathological examination and the general condition of the patient. Close co-operation between otolaryngologist, radiation oncologist and other specialists is necessary when selecting a suitable therapeutic procedure. Great emphasis is placed on the patient's quality of life; minding the relation between effectiveness of the treatment and its toxicity.

Surgery together with radiotherapy both represent the main therapeutic options for tumors in the head and neck area. In general, radiotherapy ± chemotherapy is preferred whenever the patient requires organ preservation or the tumor is unresectable or there is no possibility for surgery treatment. For the treatment of early T-stages (cT1 and selected cT2) without lymph node involvement (cN0), treatment should be monomodal (radiotherapy or surgery), while in locally advanced disease (cT3-cT4 or any T, cN +) the treatment is multimodal (surgery followed by radiotherapy ± chemotherapy). Concomitant (platinum-based) chemotherapy has been shown to increase overall survival rates in cancer stage III and IV. Induction and adjuvant chemotherapy is less effective than concomitant therapy. Another alternative to concomitant therapy is the combination with cetuximab, an epidermal growth factor receptor inhibitor. After primary radiotherapy or concomitant radio-chemotherapy, a surgical solution is usually reserved for the eventual persistence of locoregional disease. The indication of adjuvant treatment after surgery depends on the extent and location of the tumor, lymph node involvement and next risk factors. Tumor treatment in this area is multidisciplinary and each decision is discussed in a special team.

11.6.1 Overview of Cancer Treatment Modalities

Radiotherapy

- **Curative**

Curative radiotherapy is performed in patients with a small extent of diseases (T1, T2), where radiotherapy is equivalent for surgical treatment in terms of long-term survival. In addition, radiotherapy is a method with organ preservation. Furthermore, it is a method of choice in patients refusing surgery or in whom surgical treatment is contraindicated due to co-morbidities. A dose received can reach up 70 Gy in7 weeks.

- **Concomitant radiochemotherapy**

Concomitant radiochemotherapy may be considered for locally advanced head and neck tumours (T3, 4 N +). The aim of combined therapy is to achieve long-term local control. Combined therapy is usually more effective than using individual treatment modalities alone, but it increases the rate of acute side effects (mucositis and haematological complications). These complications may lead to unplanned and undesirable interruption of radiotherapy.

Epithelial tumors have up to 95% positive EGFR. Therefore, the effect of radiation therapy can also be potentiated by biological response modifiers.

- **Postoperative (adjuvant)**

Post surgery radiotherapy is indicated in cases of insufficiently wide or unclear edges (less than 0.3 mm) of tumour excised, extracapsular spread (when in lymph node pathology), in lymph nodes involvement generally, in pT3 or pT4 stage if angioinvasion, lymphangioinvasion or perineural spread is present. The effectiveness of postoperative radiotherapy is significant and increases the survival rate by up to 30%. A dose received is 60-66 Gy in 6–7 weeks.

- **Preoperative (neoadjuvant)**

The aim of neoadjuvant radiotherapy is to reduce the tumor mass and allow radical surgical removal of the tumor,or performing of debulking procedure. The target tissue is usually a primary tumor and regional lymph nodes. However it is not used routinely as it worsens the healing process, increases tissue bleeding during surgery and worsens postoperative fibrosis of the subcutaneous tissue.

- **Palliative**

The indication for palliative radiation therapy depends on the extent of the disease and the patient's condition. The aim of palliative radiotherapy is to alleviate the patient's problems, such as pain or bleeding. Palliative radiotherapy is short, we do not have to take into account the late toxicity of the treatment and our only effort is to reduce adverse effects of the cancer and thus improve the quality of life of the patient. We use higher than normal daily doses of 3–4 Gy, e.g. 10-12 fractions of radiation of 3 Gy 5 times a week.

Fractionation and doses of radiation therapy

The standard fractionation is 5 times a week and the dose applied is 1.8-2.2 Gy

Technique and planning of radiotherapy

The patient is lying on his back in the supine position during irradiation of the head and neck tumors. Shoulder and head fixation is provided by a thermoplastic mask made individually for each patient so that the shoulders are pushed caudally. The mask is attached to a special mat to ensure an almost 100% reproducible position.

Chemotherapy

In this group of tumors, chemotherapy is essentially used in two basic indications. Firstly, as a single palliative treatment of metastatic disease, and secondly in combination with radiotherapy as a treatment of locally advanced tumors. The treatment is based on platinum derivatives (mainly cisplatin) and 5-fluorouracil.

Immunotherapy

Immunotherapy is used in metastatic disease and also in locally advanced tumors in concomitance with radiotherapy. In both cases, very good efficiency has been demonstrated.

Immunotherapy consists of therapy with agents directed against structures specific for tumor tissue. Epidermoid carcinomas in the head and neck area need epidermal growth factor (EGF) for their growth

and are therefore characterized by high expression of its receptor (EGFR). The monoclonal anti-EGFR antibody (cetuximab) is able to specifically block EGFR and prevent tumor proliferation.

Pic. 1 Summary of head and neck cancer therapy

11.6.2 Treatment modalities by cancer site

Oral cavity tumors

Anatomical location-based classification

- Malignant neoplasm of lip,
- Malignant neoplasm of base of the tongue,
- Malignant neoplasm of other and unspecified parts of the tongue,
- Malignant neoplasm of gum,
- Malignant neoplasm of mouth floor,
- Malignant neoplasm of palate,
- Malignant neoplasm of other and unspecified parts of the mouth.

Oral cavity cancers tend to grow locally. They spread primarily ipsilaterally, rarely crossing the midline. Metastatic spread to the lymph nodes is relatively late and mostly also ipsilateral. Early stages cancers are treated surgically by local excision; alternatively brachyradiotherapy can be used because oral cavity is readily accessible by interstitial application of needles or use of plastic conductors. Locally advanced by surgery treatable stages are treated by tumor resection and cervical lymph node block dissection. Postsurgery radiotherapy is indicated if affected lymph node is found in the histological specimen or when there are positive resection margins. Curative radiotherapy is an alternative to surgery in locally advanced tumors. Either alternative fractionation regimens, concomitant radiochemotherapy regimen or radiotherapy with cetuximab may be used.

Prior to initiating radiotherapy for oral cavity cancers, dental evaluation and treatment is always required.

Laryngeal cancers

Anatomical location-based subcategories

- supraglottis
    - suprahyoid epiglottis

    - aryepiglottic algae
    - arytenoid region
    - infrahyoid epiglottis
    - ventricular algae (false vocal ligaments) - sinus Morgagni
- glottis
    - vocal ligaments
    - leading commission
    - back commission
- subglottis

In stages I and II cancers of the supraglottic and glottic regions, the 5-year survival is up to 95%, in subglottic cancer it is only 40%. This is related both to the extent of lymphatic drainage of the given anatomical areas and to the histological type of cancer found and, last but not least, how easily the tumor is found by a basic examination. In supraglottic and glottic regions, there predominantly well differentiated squamous cell carcinomas are found, in the subglottic region, cancers have less differentiated forms that behave more like tumors evolved from the airway epithelium, which are highly radioresistant.

Lymphatic drainage of individual areas of larynx:

- Glottis region has very poor lymphatic supply. Lymphogenic spread is mainly to the supra- or subglottis regions. In the case of tumors limited to the vocal cords, at the time of diagnosis the incidence of nodal involvement is 0%, 1.7% in T2 stage, and 20-30% in T3 and T4 stages.
- Subglottis: lymph drains through the cricothyroid membrane to the pre- and paratracheal cervical nodes in the upper mediastinum and to the lower deep cervical nodes.
- Supraglottis: at the time of diagnosis, ipsilateral nodes are affected in 55% and bilateral cervical lymph nodes in 16% of the patients.

The treatment strategy depends on a number of factors. In addition to the expected adverse local effect of the treatment, some of them are: voice retention, possibility for surgery (general condition of the patient). Very important for the patient outcome is his compliance in the follow-up.

In T2 stage cancers of supraglottis, partial laryngectomy or radical radiotherapy may be the method of choice. In more advanced findings, stages T3, T4 we choose total laryngectomy with node dissection and adjuvant radiotherapy. Postoperative radiotherapy is indicated in positive resection margins or invasion to the soft tissues of the neck, thyroid cartilage, as well as for the spread of the tumor to the subglottis and for metastatic involvement of the lymph nodes.

Pharyngeal cancers

- Malignant neoplasm of oropharynx,
- Malignant neoplasm of nasopharynx,
- Malignant neoplasm of hypopharynx.

Oropharyngeal cancers

Anatomical location-based subcategories

- root of the tongue,
- lower surface of the soft palate,

- uvula,
- tonsils,
- tonsillar fossa and tonsillar arches.

Regional lymph nodes

- subdigastric, superior cervical (most commonly jugulodigastric node), parapharyngeal, middle and posterior cervical, submaxillary,
- tonsillar fossa tumors have the highest incidence of lymph node involvement (up to 60-70%); soft palate tumors metastasize mostly to the posterior nodules.

Treatment strategy

In localized disease, surgery or radiotherapy is the method of choice. In higher stages of disease, the combination of both modalities increases local disease control. If in single use both can also be combined with neoadjuvant chemotherapy.

Irradiation of regional lymph nodes is always indicated if there is an evidence of the involvement of regional lymph nodes.

Hypopharyngeal cancers

At the time of the diagnosis, more than 80% of the patients have palpable cervical lymph nodes.

Treatment strategy

Treatment strategy depends on the location of the tumor, its resectability and radicality of the procedure itself. For operable tumors of stages T3, 4, surgery with subsequent radiotherapy is the most appropriate choice. In the case of inoperable mass, concomitant chemotherapy and radiotherapy may be considered. In case of lymph nodes involvement we irradiate bilateral cervical lymph nodes and supraclavicular lymph nodes.

Nasopharyngeal cancers

Anatomical location-based subcategories

- roof and posterior wall of the nasopharynx (from hard palate and soft palate border down to skull base),
- lateral wall of the nasopharynx or fossa of Rosenmüller
- inferior wall of the nasopharynx (posterior surface of soft palate).

Squamous cell carcinomas, anaplastic carcinomas - lymphoepitheliomas (not lymphoma), adenoid carcinomas, non-Hodgkin's lymphomas, and rarely sarcomas can occur in the nasopharynx area.

Regional lymph nodes

Lymphatic vessel network structure is very rich, the lymphatic supply passes through the midline (retropharyngeal, submastoideal, internal jugular lymph nodes). More advanced diseases infiltrate anterior and posterior cervical lymph node chains and adrenal glands. Enlarged lymph nodes are palpable at the time of the diagnosis in up to 80% of patients.

Treatment strategy

Because of anatomical localization, rich lymphatic supply, high radio- and chemosensitivity, radiochemotherapy is the preferred method of choice. However, surgical resection with sufficient margin is almost impossible in this area.

Paranasal Sinus Tumors

Tumors of these areas are usually diagnosed in locally advanced stage, but lymphogenic metastasess are present in only 15% of the cases. The vast majority of tumors in this area are squamous cell carcinomas, small salivary glands tumours, melanomas and rarely estesioneuroblastomas of the nasal cavity also occur. The treatment is usually combined - surgery with postoperative radiation therapy.

Salivary gland tumors

Malignant processes in salivary glands are accounting for less than 4% of all head and neck tumors.

Histology

- *Low grade:*
    - mucoepidermoid low-grade
    - acinar cell carcinoma
- *High grade:*
    - mucoepidermoid high-grade
    - mixed (pleiomorphic adenoma)
    - adenoid cystic (tendency to perineural invasion)
    - adenocarcinoma
    - spinocellular
    - undifferentiated

Treatment strategy

Surgery

Surgical intervention is fully indicated after histological verification of the tumorous process. In the malignancy process with a high degree of malignancy, a radical dissection of cervical lymph nodes is also necessary.

Adjuvant radiotherapy is indicated in:

- the case of a macroscopic or microscopic residual disease - a recurrent disease,
- high-grade diseases,
- the case of clinically positive cervical lymph nodes.

Palliative radiotherapy is indicated individually, in advanced, relapsing, inoperable tumors, and in patients with generally poor condition.

Thyroid cancers

The incidence of this type of cancer is not high, accounting for 0.8% of all cancers, occurring in 4 cases per 10,000 inhabitants. Histopathologically, thyroid tumors are generally classified into tumors resulting from malignant transformation of follicular cells (papillary, follicular, carcinoma oxyphilic, or mixed forms) and parafollicular cell (medullar) cancers, which account for 5-10% of all total thyroid malignancies. It is likely that de-differentiation of these two basic types of tumors then produce aggressive anaplastic carcinomas.

Thyroid carcinoma treatment is based on partial or total thyroidectomy. Depending on the nature of the tumor, adjuvant or curative radioiodine treatment (papillary, follicular carcinoma, clear cell carcinoma) follows at specialized departments of nuclear medicine. In anaplastic carcinoma or in non-iodine accumulating tumors, chemotherapy may be considered in the treatment strategy.

Radiation treatment strategies

- **Curative radiotherapy** is indicated in non-radioiodine-capturing tumors if inoperable or when surgery is contraindicated.
- **Adjuvant radiotherapy** is indicated in well-differentiated tumors with insufficient or no accumulation of radioactive iodine, or when the tumor has infiltrated surrounding connective tissue, in metastatic involvement of the lymph nodes, or tin he presence of tumor residue in the surgical field. Postoperative radiotherapy is always indicated in anaplastic thyroid cancer and medullary cancer.
- **Concomitant radiochemotherapy** is rarely considered. In anaplastic carcinomas, external irradiation can be potentiated by a chemotherapy.
- **Palliative radiotherapy** is indicated individually according to the local findings and general status of the patient.

Note: Regional lymph nodes in this type of cancers are cervical and superior mediastinal nodes (prelaryngeal, middle and lower jugular, and possibly also the superior jugular, supraclavicular, pre- and paratracheal, superior mediastinal).

Neck cancer metastases, primary tumor not found / unknown

Metastatic cervical lymph nodes of unknown primary origin represent a very heterogeneous entity. The most common histological types found are carcinomas, adenocarcinomas and undifferentiated carcinomas. The basic examination is an endoscopic examination of the ENT area and contrast-CT of the head and neck area. If primary tumor is not found, endoscopic examination under anesthesia is performed and biopsy is taken from given ENT sites - nasopharynx, tongue root, piriform sinus and homogeneous tonsillectomy is performed. Negative results of these examinations are followed by bronchoscopy, esophagoscopy and PET / CT.

If primary tumor localization is still not found after examinations above have been performed, treatment program is initiated (50-80% of al the primary tumors are located in the oropharynx area).

12 BREAST CANCER

Milan Brychta

Mammary gland (breast) cancer is the most common malignant cancer in women, but it does not avoid the male population either. It is characterized by high variability of individual types. In particular, its treatment is influenced by many factors that allow to choose from a wide selection of therapeutic approaches. A number of specialists from various medical fields are involved in its treatment. Thanks to improving early diagnosis rate and modern treatment procedures, the mortality of the disease is decreasing slightly but steadily, despite the increasing incidence.

12.1 EPIDEMIOLOGY

With the exception of skin tumors, breast cancer is the most common cancer in women in the Czech Republic. In 2015, 7,102 new cases were detected (132.4 cases per 100,000 women) and 1,609 women died. The incidence and mortality rates have stabilized compared to 2016. The mammary gland carcinoma in men is significantly less frequent, the incidence is about two orders of magnitude lower than in women and is about 1 case per 100 000 men.

12.2 ETIOLOGY

The exact mechanism of primary breast cancer is unknown. The most common breast cancer is carcinoma, which is mostly influenced by hormonal and genetic factors.

We know both risk and protective factors affecting the incidence of the disease.

Risk factors can be divided into:

1. Hormonal - early onset of menarche before 12 years and late menopause, after about 50 years of age, nulliparity, age at first birth - the incidence of breast cancer and prolonged use of hormonal contraception or hormone replacement therapy increases with age at first birth.
2. Previous incidence of breast cancer in woman or first degree female relatives, where the incidence in one woman increases the risk twice and in two women three times. The incidence of malignant tumor in one breast increases the risk of malignant tumor in the other breast 5-fold compared to the normal population.
3. Lifestyle with a negative impact of alcohol consumption, smoking and obesity (carcinogenesis is due to a higher conversion of androstenedione into estrogen in adipose tissue with the help of natural aromatases). Exposure to radiotherapy before 45 years of age also has a negative effect.
4. Inherited dispositions are mainly proven mutations of BRCA1 and BRCA2 genes, gene mutations in ataxia telangiectasia-ATM, gene associated with 53-TP53 transformation, 2-CHEK2 checkpoint kinase, phosphatase and tensiomine-PTEN homologues, cadherin 1-CDH1 and partner and the BRCA2 -BRCA2 / PALB2 locator.

Protective factor is especially breastfeeding – every 12 months breastfeeding reduces risk by 4.3% and physical activity. The role of phytoestrogens is unclear, while the protective effect has been demonstrated in the Asian population, it has not led to a change in risk in the Western population.

12.3 SYMPTOMATOLOGY

Clinical signs - local

Tactile breast resistance is present in about 60% of patients. Pain, pressure, and feeling of tension in the breast are reported by about 20% of patients. Specific is the image of orange peel (peau d'orange) with typical ridges. A special unit is the inflammatory carcinoma (erysipeloid), expressed by redness of the skin, where the carcinoma is based on infiltration of skin lymphatic vessels by malignant cells and this finding (TNM-T4d) is a contraindication to surgery. Inverted nipple or pathological secretion from the breast can be observed.

Clinical signs - locoregional

When assessing the locoregional manifestations of the disease, it is important to know the specifics of lymphatic drainage of the breast. Network of lymphatic vessels begins from the areola and lymph drainage is realized in several main directions. Approximately 75-95% of the lymph flows through the lymph node (LN) of the axilla (approx. 50 nodes) and further into the adrenal glands and 5-25% into the parasternal nodes. Further drainage of the lymph goes to the subclavian area. There are connections to the nodules, liver nodes, intercostal nodes, and connections to the second breast. Axillary lymph nodes are practically divided into 3 levels in cranio-caudal order III. (apex of the axilla with neurovascular bundles in the vicinity), II. (middle part of axillary body of fat), I. (lower part of axilla). The lymph node enlargement may be related to different quantity of LNs and may be of varying degrees. A typical tumor-infiltrated LN is of a solid to hard consistency. A locoregional advanced symptom is the connection of several nodes into an enlarged rigid nodal packet.

Clinical signs of advanced disease

Sign of advanced cancer is the detection of metastatic disease to other organ systems, such as bones in 20–60%, lungs in 15–25%, liver in 5–15%, brain in 5–10%. Locoregional metastasis occurs in 20–40% of cases, when there are satellite subcutaneous nodules – called metastatic lenticules – in scars after surgery or in the surroundings.

Signs of distant dissemination are derived from the site of the affliction, the most common symptoms being pain in a certain area (skeletal or liver affection), shortness of breath or cough (lung affection), neurological symptoms (such as dizziness, headache, visual impairment in brain involvement).

12.4 DIAGNOSTICS

Making the right diagnosis is the basis for successful treatment. The diagnosis includes assessment of the local extent of the disease, evaluation of possible distant manifestations of the disease by means of staging examinations, which together with histopathological examination enable classification of the full extent of the disease.

Anamnestic data

Family history is the basic foundation block, which may indicate a possible familial burden. Gynecological data, e.g. early menarche, late menopause, higher age of first birth. Breastfeeding is referred to as a protective factor. The finding of pharmacological anamnesis is important, e.g. for possible connection with the use of older generation contraceptives.

Physical clinical examination

Inspection – when evaluating the breast by looking (sitting, standing, bending forward) we observe differences in breast configuration, shape and size, signs of skin tension from the subcutaneous tissue.

Palpation – we always consider both sides of the paired organ during palpation examination. Breast palpation is usually performed by the circular or meandering method. We also palpate the areas of both the axils, the epididymis and the neck.

Instrumental examinations

By default, both breasts have X-ray diagnostic mammography done in two projections. Typically, we see an image of a focal **tipped lesion (spike)** or an image of **clusters of microcalcifications**. We can observe a thickening of the skin cover above the superficial lesion or a solid dense tissue.

Ultrasonography (US) of breasts is a routine supplementary diagnostic examination to X-ray mammography and is always done when taking biopsy material.

Ductography with retrograde contrast instillation may give some clues during the filling of the ducts with the contrast medium, we use it in pathological secretion from the nipple area.

Basic staging examinations

- Lung X-ray, liver ultrasonography, skeletal scintigraphy,
- CT examination - facultative diagnostic examination,
- Magnetic resonance imaging is used to detect small lesions, in severe dysplasias, and to evaluate suspected relapses. MR of the breasts is also useful in lobular carcinoma.

Laboratory examination

KO, biochemical analysis of serum, examination of tumor markers: CEA (carcinoembryonic antigen), Ca 15-3.

Examination of biological material

Cytological verification is performed, for example, in pathological secretion from the nipple by imprinting the secretion on a slide followed by microscopic examination.

Histological verification is the basic examination and an unavoidable condition for the diagnosis of breast cancer. The aim is to obtain sufficient material for histopathological examination, immunohistochemical (IHC) examination and molecular biological examination. Material collection is performed from a puncture biopsy of a suspected tumor in the breast and / or a suspected affected node under control under ultrasound, CT or MR (corecut biopsy) or by performing a stereobioptic puncture. It is also possible to use surgical local extirpation of the material from the site or peroperative sampling of the material.

Sentinel lymph node examination is a mini-invasive surgical procedure that obtains the nearest collesting lymph node near the tumor. Biopsy is performed as a part of the diagnosis of the disease, otherwise it is a routine part of the surgical treatment of breast cancer (sentinel lymph node extirpation). If the lymph node is free of tumor cell infiltration during histological examination, the patient does not

have to be subjected to a more extensive procedure in the area of the axilla (exenteration). Detection of the sentinel lymph node is performed using a Tc 99m radiopharmaceuticals or by staining with the Patentblau contrast agent, which is instilled peritumorally or intratumorally.

Knowledge of the histological type of cancer and, depending on the extent of tumor spread, classification by appropriate stage is the basis for adequate treatment. In Czech Republic the most commonly used classification of malignant tumors is the TNM international classification.

12.5 Differential diagnostics

In differential diagnostics it is necessary to assess both local symptoms and distant findings. **Of all palpable breast lesions, benign resistance is found in 80%, which often leads to underestimation of the findings**. The most common are adenoma, simple cystic changes, abscess, lipoma, epithelial hyperplasia, cystic mastopathy, fibroadenomas, ductal papillomas, sclerosing adenosis. Increased attention should be paid to breast redness, symptoms of possible inflammation (mastitis) should be immediately treated and the inflammatory variant of cancer should be excluded.

In the general population, the average time elapsing between the detection of indeterminate breast resistance and the initiation of tumor therapy is reported as 5 months. On the other hand, the radiation load associated with repeated mammography examination for non-specific findings should be considered. It is, however, mandatory to examine each suspected breast lesion by X-ray mammography and to perform biopsy verification if uncertain.

If lymph nodes are swollen, it is necessary to think about the symptoms of malignant lymphoma, where the palpation finding resembles an inflammatory node of soft consistency. Non-specific lymphadenopathy in the neck and breast can also be of infectious origin. If the first symptom is swelling of the entire upper limb overflowing over into the chest and lymphadenopathy is not present, consideration should be given to the superior vena cava syndrome with an advanced lung tumor.

12.6 Pathology

The mammary gland is a derivative of the sweat gland from the ectoderm. Normal adult mammary gland consists of epithelial and stromal elements. The epithelial component consists of lactiferous ducts with transient breastfeeding function. The stromal component consists of adipose and fibrous connective tissue.

Developmental embryonic mammary gland may be the basis of primary mammary carcinoma in women and men. Due to its histogenetic nature and immaturity of primary cells, cancer of the **accessory gland** has a very unfavorable course of the disease.

The mammary gland may be the site of benign breast disease and primary or secondary malignant tumors. The most common **benign diseases** with the risk of transformation are: epithelial hyperplasia, cystic mastopathy, fibroadenomas, ductal papillomas, sclerosing adenosis. Secondary malignancies – metastases, which propagate into the mammary gland, come mostly from the secondary breast, from the thyroid gland, generalization of malignant lymphomas.

The most common **primary malignant breast tumors** are epithelial tumors – carcinomas located in almost 50 % of the cases in the upper external quadrant of the breast. Mesenchymal tumors – sarcomas are rare. Infiltration of the mammary gland with malignant lymphoma may also occur.

Histological classification of carcinomas

The first group consists of **non-invasive (non-infiltrating) carcinoma in situ**. They occur in approximately 10 % of all cancers. These are **lobular carcinoma in situ (LCIS)** or **ductal carcinoma in situ (DCIS)**. A special unit of DCIS is intraductal carcinoma – Paget's nipple carcinoma, where the infiltration comes from the ducts and spreads to the epidermis of areola.

The second group is much more numerous with appearance in 80-85 % of cancers. These are **invasive (infiltrating) carcinomas**. The most common variants in about 70% of cases are **invasive ductal carcinomas (current NST classification)**: mucinous, tubular, medullar, adenoid cystic, scirrhous, comedo carcinoma, invasive ductal carcinoma with predominantly intraductal component. **Invasive lobular carcinoma** is present in 10% of casse.

Inflammatory (erysipeloid) carcinoma is a special clinical-pathological unit (enlarged red breast with tumor infiltration of skin lymphatic vessels). **Cystosarcoma phyllodes** is initially bordered by a benign phylloid tumor that develops into a malignant variant with rapid growth and increasing tumor volume.

Histological grading: G1 - well differentiated, G2 - moderately differentiated, G3 - poorly differentiated, G4 - undifferentiated (anaplastic) tumor.

In addition to grading, proliferative activity grading (KI-67 or MiB) and immunohistochemical determination of estrogen receptors (ER), progesterone receptors (PR) and cerbB2 growth receptor (HER2) are an integral part of histological examination.

A specific oncological-pathological view of the histological breakdown of breast carcinomas is the division of these tumors into 5 biological subtypes (see table), in which histological prognostic and predictive indicators of tumor cells are taken into account. Individual subtypes have different prognosis (going from luminal type A with the best prognosis to triple negative subtype with the worst prognosis) and at the same time predict the choice of systemic therapy.

Tab. Biological subtypes of mammary gland carcinoma

Luminal type	Characteristics
Luminal A	ER and PR positive, HER2 negative, grade 1,2, KI67 low (<20%)
Luminal B HER negative	ER positive PR negative, HER2 negative, grade 3, KI67 high (> 20%)
Luminal B HER positive	ER positive PR any, HER2 positive, KI 67 any
HER pozitivní	ER or PR negative, HER2 positive
Basal like - triple negativ	ER or PR negative, HER2 negative

We consider ER and PR positive at 10% or more.

12.7 THERAPY

The treatment of breast cancer is as individualized as possible with respect to the patient and her disease. It usually combines locoregional methods (surgery and radiotherapy) and systemic methods

(chemotherapy, hormone therapy, biological therapy) in a different order. An integral part of the treatment is supportive therapy, which affects the symptoms and findings caused by diseases, which possibly accompanies the patient's own oncological therapy. Immunotherapy is not currently used modality, but the theoretical assumptions and results of some studies put it in the position of a method with a promising perspective.

The assessment of therapy is done through a multidisciplinary team. When assessing therapy, two basic aspects that shape and modify the design of therapy need to be considered. The first is the patient, her age, general condition, co-morbidity, previous and current therapy. The second is the tumor, its staging, histopathological findings and the resulting prognostic and predictive factors.

Surgical treatment

Surgical treatment is the oldest of treatment modalities used in breast cancer. This treatment has gone from maximization to minimization. Since Haldsed's operation in the late 19th century, in which the entire breast and pectoral muscle were removed, we are currently moving towards tumorectomies in which only a tumor bearing with a safety margin of healthy tissue is removed. Surgery in the area of sentinel lymph nodes in the axilla underwent a similar development. From the dissection (exenteration) of the axilla - removal of all nodes in all three levels of the axilla, we minimized surgery to remove correctly detected sentinel nodes. The current surgical standard of segmentectomy (synonymous with lumpectomy or tumorectomy) with removal of the sentinel node significantly outweighs the more radical procedure - ablation (mastectomy) with axillary exenteration. However, these more radical breast treatments will always have an unquestionable place in the treatment of breast cancer, especially in erysipeloid cancer, in patients with diffuse microcalcifications in more than half of mammary glands, in patients with previous breast irradiation, in patients with unfavorable tumor-to-breast ratio, and in patients with BRCA positivity.

Another possibility of surgery is palliative surgery of orthopedic, neurosurgical, thoracic or abdominal surgery to eradicate mostly solitary manifestations of metastatic disease.

Radiotherapy

Breast cancer radiotherapy (RT) is carried out in the form of external high-energy irradiation (teleradiotherapy) and also uses the method of brachyradiotherapy. Postoperative adjuvant radiation significantly reduces the number of local recurrences. The target volume is the breast after partial surgery or thoracic wall after radical surgery. If lymph nodes are affected, the target volume also includes axillary nodes, the area of the glandular lymph nodes, and parasternal lymph nodes. Doses for adjuvant teleradiotherapy on thoracic wall or breast after partial surgery are recommended at 45-50 Gy / 1.8-2 Gy per day. After partial surgery we increase the dose on the primary tumor bed and scar to 9–12.6 Gy / 1.8 Gy per day as boost by teleradiotherapy or we can use the possibility of interstitial puncture of brachyradiotherapy. In brachyradiotherapy, plastic catheters or metal needles are usually inserted into the tumor bed, which then irradiates the target volume from the inside.

Palliative external irradiation can be performed for advanced primary findings or for localized metastases, most commonly found in the skeleton, for which lower doses are used. In some cases of diffuse occurrence of bone metastases, systemic applications of Strontium Sr^{89} or Rhenium Re^{186} radioisotopes can be used.

Hormonal therapy

Hormonal therapy (HT) is part of a comprehensive oncological treatment, a treatment with systemic effect. The basic premise for effective hormonal treatment is the **presence of hormone receptors** (estrogen and progesterone) on the surface of tumor cells. Due to the signaling of estrogens through the estrogen-receptor complex, tumor cells transform and proliferate. Higher conversion of adrostenedione to estrone in adipose tissue with the contribution of natural aromatases (membrane-bound enzymes) also contribute to carcinogenesis.

If both estrogen and progesterone receptors are present on cancer cells, hormonal therapy is indicated for both adjuvant treatment and the treatment of locally advanced or metastatic disease. The basic drug is antiestrogen **tamoxifen**, which acts as a competitive inhibitor on the cell receptors. **Aromatase inhibitors** (inhibition of steroid enzyme synthesis – exemestane and non-steroid inhibitors: anastrozole, letrozole) are switched to in the case of tamoxifen intolerance or failure.

Hormonal treatment in postmenopausal women is usually initiated by the administration of the antiestrogen tamoxifen and after its failure it is switched to aromatase inhibitors.

Hormonal treatment in premenopausal women is initiated by the administration of LH-RH analogues – goserelin (Zoladex) with reversible ovarian ablation in very young at-risk patients. In middle-aged, low-risk patients, treatment is initiated with tamoxifen.

Among other hormonal preparations, pure antiestrogen Fulvestrant (Faslodex) is used with higher antitumor activity and minimal undesirable side effects.

Modern methods to enhance the effectiveness of hormone therapy are substances used to overcome hormonal resistance, which are considered to be a part of the group of biological therapy substances (mTOR, CDK4/6).

Chemotherapy

The systemic effect of chemotherapy (CHT) is advantageously used during its application. Administration of cytostatics in effective combinations is used in neoadjuvant indication (to reduce primary tumor – downstaging – to allow radical surgery), also in adjuvant indication (to minimize the risk of early dissemination) and in the treatment of advanced stages of the disease with palliative intent (to inhibit tumor progression). The most potent cytostatics include: doxorubicin (risk of cardiotoxicity increasing with dose accumulation), epirubicin, docetaxel, paclitaxel (risk of neuropathy), vinorelbine, methotrexate, capecitabine, cyclophosphamide, fluorouracil, gemcitabine.

Most commonly used schema

- FAC: fluorouracil, adriamycin (doxorubicin), cyclophosphamide,
- AC: adriamycin, cyclophosphamide,
- TAC: Taxotere (docetaxel), adriamycin, cyclophosphamide,
- AC / T: adriamycin, cyclophosphamide, paclitaxel (or docetaxel-Taxotere),
- XENA: capecitabine and vinorelbine.

Biological treatment

Biological treatment, better designation being “targeted”, because its aim is to target and selectively aim at certain "targets" on tumor cells and thus eliminate their division. While two targets were preferred in breast cancer ten years ago (receptor EGFR -HER2 and VEGF), the number of targets has now increased (mTOR, CDK 4/6, PARP, PI3K / Akt) and the spectrum of anti-HER drugs in particular has expanded. The biological therapy of anti-HER preparations requires immunohistochemical determination of HER2 receptor positivity. Therapeutic inhibition of the HER receptor is performed on the extracellular portion - trastuzumab or pertuzumab, optionally in combination, or on the intracellular, tyrosine kinase portion - lapatinib.

Another monoclonal antibody is bevacizumab with activity against vascular endothelial factor.

New preparations targeting other targets (affecting other signaling pathways) are everolimus (affecting the mTOR pathway), abemaciclib, ribociclib or palbociclib (affecting CD4/6 kinases) and olaparib (inhibition of PARP proteins).

12.8 THERAPEUTIC COMPLICATIONS

Complications of surgical treatment

After radical surgery, **lymphedema** of the respective **upper limb** may develop. Measures to reduce lymphoedema are: avoid sudden heat changes (sauna), avoid pressure changes during the onset of swelling (diving, hiking, long airplanes), on the same extremity: do not measure blood pressure, do not wear rings, bracelets and watches, do not take blood samples , do not administer injections, protect the limb from insect bites, do not sleep with the limb under the body, do not carry heavy weights i nthe limb.

Complications of radiotherapy

Acute changes in radiotherapy are most often manifested as skin changes of I. degree (erythema), II. degree (wet desquamation), III. degree (necrotic changes).

If partial acute pneumonitis occurs, it is usually limited to that part of the lungs that is adjacent to the irradiated target volume

Late changes after radiotherapy:
Skin changes limited to irradiated volume - hyperpigmentation, fibrosis of the skin and subcutis, telangiectasia.

Partial pulmonary fibrosis may occur in the extent of irradiated volume with a typical sickle cell image at CT scan.

Late change after radiotherapy may also be plexopathy of cervicobrachial plexus. It is a neuropathy with a variable neurological deficit.

Lymphoedema of the respective upper limb is caused by the disease itself, surgical intervention and radiotherapy. Swelling can range from intermittent to monstrous lymphedema with impaired patient's quality of life.

Complications of hormonal treatment

Hormonal drugs are relatively well tolerated. Tamoxifen may cause hot flashes, thromboembolic event predominantly in the lower limbs, or an increase in the uterine mucosa (risk of development of endometrial cancer). Rarely, thrombocytopenia, leukopenia and osteoporosis may occur. When using aromatase inhibitors, non-specific symptoms such as nausea, vomiting, headache, flush, sweating may occur. The risk of osteopenia is increased.

Complications of chemotherapy

When properly monitored, acute side effects of chemotherapy (haematological toxicity: leukopenia, thrombocytopenia and non-haematological toxicity: nausea, vomiting) are managed with supportive therapy. In the case of administration of cardiotoxic cytostatics (doxorubicin), sequential radiotherapy may result in the accumulation of cardiac and pericardial adverse effects with a decrease in the ejection fraction. Acute pneumonitis may develop following administration of cyclophosphamide. Peripheral neuropathies are associated with paclitaxel administration.

12.9 Follow-up

Post-therapeutic monitoring is important for detecting early local recurrence or early detection of developing relapse. Follow-up includes anamnestic data from the last follow-up, locoregional and total physical examination in 4-6 month intervals for 5 years and once a year thereafter. Mammalogical examination (MG + ultrasound) is performed once a year. Gynecological examination (palpation + ultrasound) with hormone therapy (tamoxifen) twice a year. Depending on the severity of the risk of generalization, examinations (lung x-ray, ultrasound of the liver, skeletal scintigraphy) should be performed every 12 months during the period of highest risk of relapse, for a maximum of the first five years after the treatment is over. Examination of tumor markers (CEA, Ca 15-3) is controversial and the yield of their monitoring is being questioned.

12.10 Prognosis

Survival of breast cancer is predicted by the following prognostic factors: tumor size, axillary node involvement (number of affected nodes and extent of involvement), histopathological findings (degree grading), presence or absence of hormone receptors, biological activity - proliferation status (ploidy, percentage of cells in the S phase).

In general, as the disease progresses, the risk of failure of treatment leading to shortening of the patient's life increases. At present, the prognosis for the survival of each stage of the disease is reported as follows: about 80% of patients with T1-3 without axillary node involvement achieve 5-year survival. Patients with T2 findings and N1 involvement have a 5-year survival of approximately 70%. Patients with N2-3 findings have a 5-year survival of approximately 40%. The median survival of patients with distant metastases is 24 months, with the exception of longer survival in those where only generalization to the bone is found.

13 MALIGNANT TUMORS OF THE LUNG

Jan Dvořák, Tomáš Blažek

13.1 EPIDEMIOLOGY

Malignant tumors of the trachea and lungs are a serious public health problem. In the Czech Republic in 2016 the total incidence of new disease was 64 cases per 100 000 people, which translates to 86/100 000 in men and 43/100 000 in women. Lately, there has been a decline in the incidence in men, however unfortunately the trend is not the same in women. Mortality in lung tumors is highest of all cancers. In 2016 the mortality was 73 per 100 000 men and 33 per 100 000 women. The median age of diagnosis is approximately 70 years of age.

We divide Lung Carcinomas into two basic groups:

Each group has similar biological behavior of tumor cell clones, which results in the specific guide of therapy in each group.

The first group is called ***Non small cell lung cancer - NSCLC*** which comprises 80% of lung tumors. It is characterized by low growth activity and a penchant towards locoregional lymphatic spread. Early stages of NSCLC are primarily treated surgically with subsequent chemotherapy, while locally invasive stages are treated with radiotherapy, chemoradiotherapy, or even surgery and chemotherapy (chemoradiotherapy). Generalized and locally aggressive tumors are treated systemically.

The second group (approximately 20% of diagnoses) is comprised of ***Small cell lung cancer - SCLC***. They are characterized by fast growth activity and a penchant towards hematogenous spread. The basics of SCLC treatment is the administration of systemic chemotherapy and radiotherapy.

As of 2015, the newest the **WHO Classification of Tumors** divides lung tumors into epithelial, mesenchymal, lymphohistiocytic, and ectopic. More information is found in section 13.6.

13.2 ETIOLOGY

The development of lung carcinomas requires the involvement of a number of factors (multifactorial theory). The causal relationship between smoking and the development of lung carcinomas has been clearly established. It is generally accepted that smoking 20 cigarettes a day for more than 20 years increases the risk of developing the disease 50x. This risk is also seen in non-smokers who spend long times in smoke infested areas. Tumors are also caused by mechanical particles in the environment (eg dusty factories), chemical exposure (heavy metals - cadmium, chromium, nickel, asbestos - leading to mesothelioma, formaldehyde and PVC production) and ionizing radiation (uranium mines - occupational disease, presence of radon in unventilated areas). Chronic inflammatory lung disease together with a weakened immune system can lead to the initiation of tumor transformation.

13.3 SYMPTOMATOLOGY

Clinical signs can be divided into **local** (intrathoracic), **advanced** (extrathoracic and metastatic) and **paraneoplastic symptoms.**

Local signs (intrathoracic)

The most common symptom (reported by 75% of patients) is **cough.** The cough can be in the form of a dry cough to a productive cough with expectoration of sputum comprised of mucous, blood and necrotic matter. **Hemoptysis** is reported in up to 50% of patients. It range from small streaks of blood in sputum or up to massive terminal hemoptysis. It is a negative prognostic factor, and is considered an urgent state in oncology which requires treatment (medication - application of hemostatic and/or irradiation). **Dyspnea** is most often seen in advanced stages or in infectious complications resulting in obstruction of respiratory pathways or with atelectasis due to fluidothorax. Fluidothorax is caused by obstruction of main lymphatic pathways or due to direct damage to the pleura due to the tumor. (typical recurrent effusions are a symptom of mesothelioma). The pleural effusions may also be accompanied by irritative cough and pain. In centrally located tumors, tumor infiltration may cause **stridor** (wheezing) due to the narrowing of the main airways. The reason for **hoarseness** is usually pressure on *nn. recurrent* in its mediastinal path, often due a meta process in the lymph nodes. Disorders of swallowing (**dysphagia)** can be caused by infiltration or pressure on the esophagus due to enlarged lymph nodes.

Chest pain manifests according to the localization of the tumor infiltration, most often caused by interfering with the pleura or nervous plexus of intercostal nerves or *plexus brachialis*. Of all lung tumors, 5% disseminated by direct growth into the thoracic wall. By infiltrating the area of the pleural cupula, **Pancoast syndrome** may occur, which is characterized by affection of the brachial nervous and vascular bundles, and affection of the first ribs (pain in the shoulder region). Sometimes, even sympathetic nervous bundles can be affected leading to **Horner's Syndrome** (ptosis, miosis, enophthalmos). Advanced tumors in the area of the upper mediastinum can create **Superior Vena Cava Syndrome,** with varying forms of manifestation. According to the character of affection/pressure, we can see increased fill of nodes of the neck with expanded collateral flow on the chest, edema of the eyelids and conjunctival leakage, swelling of the face and neck, sometimes affecting the entire upper half of the body. This is also an urgent state in oncology needing treatment, which depends on the overall state of the patient, histological type and prognosis of the disease. In chemosensitive small cell carcinomas, treatment is preferred by medication, i.e application of corticosteroids and systemic Chemotherapy, or in some cases Radiotherapy, after which one can assume a quick onset action due to cytoreduction or reduction of the tumor mass compressing the vena cava.

On the other hand, in resistant tumors (NSCLC) the onset of the effect of radiotherapy or chemotherapy is usually very slow, which is insufficient in the treatment of the acute phase of the disease. Therefore, patients in good overall status with an expected survival longer than 3 months prior to oncological treatment are indicated to an intervention which includes the introduction of an expandable stent into the superior vena cava to decompress and restore venous return from the vein.

Advanced signs (extrathoracic and metastatic)

In the locoregional lymphatic tumor propagation, most often the clavicular and cervical scalene lymph nodes are affected. Neurological problems develop when vertebral bodies are affected by ingrowth.

Distant metastatic manifestations most often affect the CNS, bones, liver, and adrenal gland. Metastatic affection of the brain is often accompanied by headache and nausea, with eventual vomiting, change in vision,uncertainty during walking, and other neurological symptoms. If distant metastases are identified as the first symptom of the disease, it is a very serious prognostic factor, with a survival time of several months. Distant metastases are present in 95% of small cell carcinomas, in 80% of adenocarcinomas and in 50% of squamous cell carcinomas.

Paraneoplastic symptoms

Most often manifesting in small cell carcinomas. The mechanism of these manifestations is often complex in nature. General symptoms include fatigue, weight loss, anorexia. Neurological symptoms are divided into central (brain atrophy, mental degeneration including dementia, psychosocial degradation, impaired coordination, balance disorders) and peripheral with manifestations of neuropathy.

Coagulation and autoimmune connective tissue disorders may also occur. Myasthenia - muscle weakness expressed as general fatigue. Endocrine disorders arise depending on ectopic production of hormones, eg hyponatraemia and water retention (SIADH syndrome), hypercalcaemia, polyuria, gynecomastia, and Cushing's syndrome may occur.

13.4 DIAGNOSTICS

The diagnostic process is usually performed in internal and pulmonary departments.

Anamnestic data

Taking a personal and occupational history may alert us to possible links with risk factors. The anamnestic data provides us with information regarding the nature of the symptoms, their intensity and the duration of symptoms.

Clinical Physical Examination

During inspection, we assess the general condition/state of the patient, looking at the posture of the body, upper limbs and chest. Next, utilizing palpitation, we palpate the supra clavicular and cervical lymph nodes. We also percuss the chest and spine, and finally we auscultate the lungs bilaterally.

Functional Examination

Functional examination of the lungs is provided by spirometry, which is normally indicated and performed before radical surgery.

Imaging Examination

A posterior-anterior chest radiograph, while standing is the first examination to be performed. It is able to show more severe pathological findings, such as atelectasis, fluidothorax or bulky tumors. For an accurate diagnosis, it is necessary to use a CT of the thorax and adrenal glands, which nowadays is a part of the standard staging examination, however the area of mediastinal nodes is known for its poor/low sensitivity and specificity. For more accurate diagnostics we utilize Positron Emission Tomography (PET), especially in the diagnosis of solitary lesions (distinguishing benign from malignant nodes), as well as to determine the extent and stage of the disease (mediastinal involvement, indication of surgical treatment options) and in planning radiation therapy (eg to differentiate tumorous involvement and healthy structures). Utilization of MRI brain scanning in the staging of the tumor is recommended for SCLC and in

more advanced NSCLC tumors. In addition, for complete staging, it is recommended to also perform a USG of the abdomen (to exclude liver or adrenal metastasis) and skeletal scintigraphy to exclude skeletal dissemination.

Interventional Examinations

Performing fibrobronchoscopy with a flexible bronchoscope (possibly in combination with endobronchial ultrasound EBUS) serves as a possible intrabronchial assessment of the lower airways.

During the examination, suspected material is collected for cytological or histological verification (suction of secretion, brush swab, bioptic excision, transbronchial puncture of mediastinal or hilar lymph nodes). Performing bronchioloalveolar lavage is used for cytological, bacteriological and microbiological examination.

Investigations utilizing video assisted thoracoscopy or video assisted mediastinoscopy are carried out with the aim of obtaining material (most often lymph nodes) for histological verification when it is impossible to use a less invasive method. A trans-thoracic biopsy under CT control is used to verify peripheral lesions in the lung parenchyma.

The aim is to obtain sufficient histological material for a detailed examination of the tumor type and its molecular characteristics, according to which the optimal treatment strategy will be chosen.

Laboratory Examinations

Erythrocyte sedimentation, blood count, biochemical examination of the serum.
Examination of tumor markers is of additional importance only, as the sensitivity of individual markers varies between 25-70% only. Markers examined for NSCLC include: SCC (for squamous cell carcinomas), CEA (carcinoembryonic antigen for adenocarcinomas). Markers examined for SCLC include: NSE (neuron specific enolase), CEA, and Calcitonin.

Examination of Biologic Materials

The goal of histological verification of lung tumors is to correctly classify the disease into specific groups of carcinomas. A representative sample of biological material for histopathological examination is usually obtained during fibrobronchoscopy, trans-thoracic biopsy, video assisted thoracoscopy, or eventually video assisted mediastinoscopy.

It is necessary to determine the histological subtype with the obtained material (possibly repeat biopsies) for molecular testing,

- A: Histological subtypes: adenocarcinoma, large cell carcinoma and NSCLC not otherwise specified - NOS.
    - Examination of activated mutations EGFR, ALK, (considering ROS, BRAF) or PD-L1 expression (see immunotherapy)
- B: Squamous cell carcinoma - Consideration of EGFR and ROS examinations in non-smokers (never smokers)

In exceptional cases, if it is not possible to obtain sufficient material for histopathological examination, due to the danger in delay of treatment, the minimum requirement for initiation of oncological treatment is cytological examination.

Knowledge of the histological subtype of tumor, and the extent of tumor spread with classification of tumor via appropriate stage is the basis for adequate treatment. Our country most commonly utilizes the TNM international classification of tumors. The current version of TNM 8 has been valid since 2017.

Stage of the Tumor:

Occult Carcinoma	TX	N0	M0
0	Tis	N0	M0
IA	T1mi T1a	N0 N0	M0 M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a T1b T1c T2a T2b T3	N1 N1 N1 N1 N1 N0	M0 M0 M0 M0 M0 M0
IIIA	T1a T1b T1c T2a T2b T3 T4 T4	N2 N2 N2 N2 N2 N1 N0 N1	M0 M0 M0 M0 M0 M0 M0 M0
IIIB	T1a T1b T1c T2a T2b T3 T4	N3 N3 N3 N3 N3 N2 N2	M0 M0 M0 M0 M0 M0 M0
IIIC	T3 T4	N3 N3	M0 M0
IVA	Any T Any T	Any N Any N	M1 a M1 B
IVB	Any T	Any N	M1 C

From a practical point of view, we divide the stages of lung tumors as follows:

NSCLC:

- initial stages: T1,2 N1 M0,
- locally advanced stages: T1-4 N1-3 M0,
- very advanced stages with generalization: M1.

SCLC -in small cell lung cancer, two stages are distinguished:

- **Limited** disease comprises stages I-III (any T, any N, M0) which can be safely treated with radical doses of radiotherapy. Excluded are stages T3-4 with multiple lung foci or in bulky tumors and nodes, which prevent dose escalation to radical Radiotherapy (60 Gy).
- **Extensive** disease includes stage IV and T3-4 with multiple lung foci or bulky tumor and nodes which are too large for radical radiotherapy.

13.5 Differential Diagnostics

Differential diagnostics is very demanding in both terms of anatomical and functional context. Careful consideration of local, advanced and paraneoplastic symptoms should be considered. During inspection, we assess the general state of the patient (activity, cachexia), patient behavior (psychosocial well-being), posture and upper limbs, other active symptoms (cough, breathing difficulties, hoarseness of voice) and chest configuration (bulges in supra clavicular zone in Pancoast tumor).

With palpation, we perform a check of the clavicular and cervical lymph nodes in order to detect pathological lymphadenopathy. Chest percussion should be symmetrical; if however the percussion is dull, it may signify effusion. Percussion of the spine which is painful may reveal possible metastasis. Auscultative findings are often variable: weakened or absent breath sounds may indicate fluidothorax or tumorous masses, while other findings may include tubular breathing, rales, rhonchi, and wheezing. Fluidothorax is often accompanied by dyspnoea and pain, with a typical X-ray finding which is usually indicated by an absent costophrenic angle , which is obscured by the fluid.

The effusions do not only have to be of malignant origin (typical in mesothelioma), but may be caused by various non-specific or specific inflammations (i.e. tuberculosis). Hemoptysis is most commonly observed in chronic bronchitis, as well as in bronchogenic carcinomas, but cardiogenic origin should also be considered. When movement of the upper limb is limited including in the resting position, it is important to consider Pancoast tumor, however the issue may also be of neurological or post-traumatic origin. Superior vena cava syndrome with pronounced lymphadenopathy may indicate malignant lymphoma. If a small lesion is detected in the lung parenchyma, histological verification should be performed. Benign lesions are predominant, however malignant lesions, whether primary or secondary (metastasis), should always be excluded. In order to more precisely diagnosis we can utilize PET examination in solitary lesions (to distinguish between benign from malignant lesions), and to further verify the possible persistence of the disease after treatment or to assess unclear relapse.

13.6 Pathology

The lungs are a paired organ located in the chest cavity covered by a visceral pleura. They are part of the respiratory system, more specifically the lower respiratory tract. Lymphatic drainage goes from the respective area of the lung into the ipsilateral hilar lymph nodes, then on both sides to the paratracheal, subcarinal, mediastinal and supraclavicular nodes.

Histological classifucation of Lung Tumors: (Currently valid as of the 2015 WHO version)

Histological types and subtypes	
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma	8250/3
Acinar adenocarcinoma	8551/3
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma	8144/3
Minimally invasive adenocarcinoma	
Non Mucinous	8256/3
Mucinous	8257/3
Preinvasive lesions:	
Atypical adenomatous hyperplasia	
Adenocarcinoma in situ-	8250/0
Mucinous	8250/2
Non Mucinous	8253/2
Squamous cell carcinoma	8070/3
Keratinized squamous cell carcinoma	8071/3
Basaloid squamous cell carcinoma	8072/3
Non- Keratinized squamous cell carcinoma	8083/3
Preinvasive lesions - squamous cell carcinoma in situ	8070/2
Neuroendocrine Carcinoma	
Small Cell Carcinoma	8041/3
Combined Small Cell Carcinoma	8045/3
Large Cell Neuroendocrine Carcinoma	8013/3
Combined Large Cell Neuroendocrine Carcinoma	8013/3
Carcinoids	
Typical Carcinoid	8240/3
Atypical Carcinoid	8249/3
Preinvasive lesions	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0
Large Cell Carcinoma	
Adenosquamous Carcinoma	
Sarcomatoid carcinoma	
Pleomorphic Carcinoma	8012/3
Spindle cell carcinoma	8560/3
Giant Cell Carcinoma	
Carcinosarcoma	8022/3

Histological types and subtypes	
Pulmonary Blastoma	
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT Carcinoma	8023/
Salivary gland-type tumors	
Mucoepidermoid carcinoma	
Adenoid cystic carcinoma	8040/3
Epithelial-myoepithelial carcinoma	8200/3
Pleomorphic adenoma	8562/3
Papillomas	
Squamous cell papilloma	8940/0
Exophytic	8052/0
Inverted	8052/0
Glandular papilloma	8053/0
Mixed Squamous and Glandular Papilloma	8260/0
Adenoma	8560/0
Mesenchymal Tumors	
Lymphohistiocytic tumors	
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0
Metastatic tumors	

Histological grading

G1 - Well differentiated, G2 - Moderately differentiated, G3 - Poorly differentiated, G4 - undifferentiated (anaplastic) tumor.

13.7 THERAPY

13.7.1 Review of Non-small cell lung cancer (NSCLC) Treatment

In beginning stages surgical resection is the only curative method in the treatment of non-small cell lung cancer. The type of surgery is proportional to the extent of the findings and the state of the patient (lobectomy, pneumonectomy with lymph node staging, including hilar and mediastinal lymphadenectomy). After radical surgery, adjuvant chemotherapy is indicated from stage T2 and above. Also in the case of lymph node involvement, either hilar (N1) or mediastinal (N2). Post-operative radiotherapy is indicated in cases of mediastinal Lymph node (N2) involvement. In non-radical surgery, meaning microscopic (R1) or macroscopic (R2) residue, re-resection is primarily indicated, or even chemoradiotherapy (RT-CHT).

In locally advanced stages, it is recommended that up to N1 affection, surgical action be attempted followed by chemotherapy (see chemoradiotherapy above). In patients with N2/3 affection, radical chemoradiotherapy is the standard procedure. Neoadjuvant chemotherapy can be initiated in a highly selected few patients with non-bulky N2 involvement, and radical surgery is then possible if down-staging occurs. If there is no regression after initial chemotherapy, radical chemoradiotherapy (RT-CHT) is then pursued.

Radiotherapy is the **main treatment method in locally advanced disease**. It is normally performed via external radiation - teleradiotherapy. A combination of Radiotherapy and concomitant chemotherapy is considered a radical treatment approach. Sequential administration, meaning, first, administration of the chemotherapeutic agent and afterwards radiotherapy, achieves worse treatment results compared to concomitant administration (RT-CHT). Radical radiotherapy in combination with chemotherapy is a relatively toxic regimen and cannot be applied to all patients with advanced disease. In case of low effectivity and numerous comorbidities, radiotherapy is usually indicated independently.

A special modality is called SABRT (*Stereotactic Ablative Body Radiotherapy*). It is a **radical treatment method**, reaching similar respectively only slightly worse results compared to surgical treatment. In principle, it is a technique of stereotactic radiotherapy (see chapter radiotherapy). Application of a radiobiologically high dose of radiation in a small number of fractions (4-10) into a precisely defined volume. This method is used in the therapy of localized staged NSCLC T1-2 NO M0. It is reserved for a narrowly selected group of patients in whom surgery is contraindicated, ie. patients with severe comorbidities, who would not be able to undergo general anesthesia, patients with low performance status (CI 80-70%), or older age. Age is one of the factors, however the exact limit is not defined, it more often depends on the biological age of the patients. Technically, this method is more demanding due to the application of a biologically highly effective dose. Therefore, it is important to avoid irradiation of healthy tissues. Tumor tracking or gating techniques are used in order to achieve this (see the chapter on radiotherapy). In the case of tracking, X-ray contrast markers (gold seeds) are placed into the tumor area, their position and movement are continuously monitored during irradiation. This procedure is used in Cyber knife irradiation. The gating method, on the other hand, uses irradiation only at certain stages of the breathing cycle (inhalation), when tumor movements associated with breathing are minimized. This procedure is used in linear accelerators.

Brachytherapy is most commonly used in palliative indications in the treatment of lung carcinomas. It is performed in patients, with the goal to clear airways, release atelectasis after tumor stenosis, and improve the patient's respiratory comfort. Technically, the procedure is based on the introduction of a brachytherapy catheter under bronchoscopic control intraluminally into the tumor region of stenosis, respectively after it. The HDR after-loading technique (see the chapter on radiotherapy) is used for irradiation. Complications of the procedure may include massive bleeding from large vessels after irradiation with terminal hemoptysis. Therefore, this method should not be indicated for centrally located tumors surrounding main vascular bundles.

An alternative to brachytherapy is laser treatment with insertion of a bronchial stent.

Therapy of very **advanced and generalized stages** is individualized treatment, all depending on the general state of the patient. Palliative radiotherapy is used to stabilize local findings, to reduce tumor foci in the treatment of superior vena cava syndrome, in the treatment of painful Pancoast tumors,

during hemoptysis, in the presence of skeletal dissemination, eventually, brain affection and more. In palliative chemotherapy, careful consideration is given to combination therapy of cytostatics (platinum based + taxanes or vinca alkaloids) or mono therapy (platinum, gemcitabine, taxanes). In the selection of treatment, we take into account the general state of the patient, comorbidities and nutritional status. If however, the airways become constricted/restricted by pressure from the surroundings (tumor/ lymph nodes), bronchoscopy with implantation of stents can be used to temporarily facilitate breathing into the lower airways.

External Lung Radiation Doses for NSCLC:

- Conventional Radiotherapy with radical (curratiative) approach, 59,4–66,6 Gy/1,8 Gy
- Palliative Radiotherapy – usually 30 Gy/3 Gy/10 fractions or 40 Gy/2,5 Gy/16 fractions
- SABRT (stereotactic radiotherapy) – 60 Gy in 4–10 fractions, or 50 Gy in 5 fractions

Systemic Treatment of NSCLC

Chemotherapy

The basics of treatment regimens are based on platinum derivatives (complex of cis-DiamineDichloroplatinum - cDDP)) or carboplatins (CBDCA), especially in combination with other cytostatics (etoposide, docetaxel, paclitaxel, gemcitabine, vinorelbine). For adenocarcinomas, the compound pemetrexed is included in the mix.

Biological (targeted) therapy is currently being used mainly as a palliative and maintenance therapy in NSCLC. Therapy is targeted to mutated membrane receptors involved in signal transduction. We distinguish several types of mutations - EFGR, ALK, ROS1. Targeted treatment is chosen according to the type of mutation. Gefitinib, erlotinib, afatinib, osimertinib (tyrosine kinase inhibitor of EGFR kinase) are used in histological variants of adenocarcinoma, large cell carcinoma, and non specific NSCLC with positive activation **mutations of EGFR +**. These tumors may also show **ALK or ROS1 mutations**, in these cases, treatment with crizotinib, ceritinib, alectinib, brigatinib (which is currently under EMA approval), ALK tyrosine kinase inhibitors and MET kinases are preferred.

In the absence of mutations, a combination of chemotherapy and bevacizumab (blocker of VEGF) may be used as first line therapy in selected cases.

Recently, immunological therapy targeting programmed death receptor (PD) or programmed cell death ligand (PD-L1) has been introduced in the treatment of non-small cell lung cancer, which play an important role in the anti-tumor response including the activation of cytotoxic lymphocytes. These drugs, so-called checkpoint inhibitors, are inherently anti-PD or anti-PDL1 antibodies which modify the course of the immune response in favor of the immune system (Tc lymphocytes). This group includes pembrolizumab, nivolumab, atezolizumab, durvalumab. Availability of the drugs depends on the specific situation, current registration of the drugs and eventual insurance payment options. See more details in the chapter of immunotherapy. Unlike systemic chemotherapy, both targeted treatment and immunotherapy have different adverse reaction/side effect profiles (changes in skin adnexa, palmar-plantar erythema - hand-foot syndrome, paronychia, stomatitis, pneumonitis, colitis, and thyroiditis).

13.7.2 Treatment overview of Small Cell Lung Carcinomas SCLC

Due to the biological nature of this type of tumor which has significant metastatic potential, treatment should be approached the same as a systemic disease.

Surgical intervention is chosen to a much lesser extent than NSCLC. It usually occurs in small lesions, when the finding cannot be verified histologically. Planned surgery is indicated in patients with a very limited stages of the disease (T1 NO M0).

In limited stages of the disease, it is standard to sue **combined treatment of chemotherapy and radiotherapy**. Concomitant chemoradiotherapy is more effective than sequential irradiation. Prophylactic irradiation of the brain lowers the incidence of brain metastases, which improves the asymptomatic period and long term survival.It is recommended in patients who are in complete remission or partial remission with doses of 25,2–30,6 Gy/1,8 Gy/fraction.

Patients in primarily extensive stages of disease are treated with **systemic chemotherapy**. Independently administered teleradiotherapy with paliative indication is most often used in order to reduce the tumor mass, improvement of superior vena cava syndrome or irradiation of metastasis located in the brain and skeleton.

Doses of external irradiation of the lungs in SCLC:

- Conventional Radiotherapy with radical (curative approach), 50–60 Gy / 1,8 Gy.
- Palliative radiotherapy – usually 30 Gy / 3 Gy / 10 fractions.

Chemotherapy SCLC

The basis of treatment regimens are again based on platinum derivatives (cDDP / CBDCA). The standard first-line treatment in the limited stages is the use of a **platinum derivative and etoposide**. In other lines of treatment, the same regimen can be used in case of a longer duration of response to the first line of treatment or topotecan, cyclophosphamide, ifosfamide and others.

The treatment of malignant effusions, which can occur in 35% of cases of lung carcinomas, is presented in the chapter on pleural tumors.

13.8 Post Treatment Complications

Complications of Surgical Treatment

Thanks to improvements in diagnostics, postoperative and supportive therapy,postoperative morbidity and mortality has significantly decreased in the past few years. After pulmonary resection, 25% of patients are prone to cardiac arrhythmias. The most common complication after operations on lung tumors includes pulmonary atelectasis (20-30%) with clinical signs of dyspnea, and tachycardia. Its prevention lies in respiratory rehabilitation and the administration of drugs which lessen bronchospasms.

Complications of radiotherapy

Acute side effects of radiation depend on the amount of absorbed dose (tolerable does in lung tissue = 30 Gy) and the sensitivity of irradiated tissues (radio-sensitivity). The radiation sensitivity of the lung parenchyma increases from the hilum to the periphery. Radiodermatitis is not a major complication

when utilizing multi-field irradiative techniques. Acute esophagitis may be grounds for discontinuation, or sometimes an exception reason for discontinuation of treatment. Radiation damage of the trachea and main bronchi, for example after brachy radiotherapy or stereotactic radiation, results in fits of dry, non-productive cough. Acute radiation pneumonitis is the most common complication of radical radiotherapy in lung tumors. Manifestation of problems is usually within 1-3 months (median 6 weeks) after radiation treatment and depends on the total dose, fractionation, and the volume of irradiated lung tissue. The most common symptoms include pain, fever, cough, and shortness of breath. The pathogenesis is an inflammatory reaction with vascular congestion of the bronchial and bronchiolar mucosa, with degradation of lymphatic follicles and subsequent fibrous exudation due to increased capillary permeability. This will reduce the viable respiratory area. X-ray signs of pneumonitis (blurring due to atelectasis or effusion, and beginnings of fibrotic changes) are generally confined to the irradiated area, but may well exceed the target volume limits. In concomitant treatment with chemoradiotherapy, significant increases of toxic manifestations (pneumonitis, mediastinitis, esophagitis) should be expected. The treatment of these complications is problematic and requires administration of corticosteroids, antibiotics and a restful regimen.

Pulmonary fibrosis is a delayed complication during radiation treatment. It usually manifests between the 6th to 12th months (median 6 months). Typically well defined changes can be seen on x-ray only in the location of the original target volume. Corticoid therapy does not have any effect anymore.

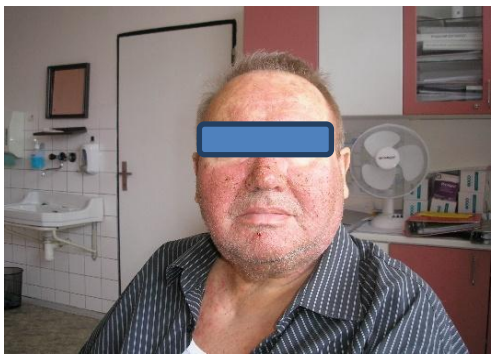
Complications of chemotherapy

When properly monitored, the most common acute side effects of chemotherapy (hematological toxicity: leukopenia, thrombocytopenia and non-hematological toxicity: nausea, vomiting) are managed by supportive therapy.

The co-administration of cardiotoxic cytostatics (doxorubicin) and radiotherapy in SCLC may lead to the summation of adverse events on the heart and pericardium in those at risk for coronary heart disease. Acute pneumonitis may also develop following administration of cyclophosphamide. Peripheral neuropathies (paraesthesia, dysesthesia, and impaired mobility of the lower extremities in particular) may be associated with paclitaxel administration.

Complications of biological therapy

- **Anti-VEGF - bevacizumab**: hemoptysis, bleeding. A high risk is seen in squamocellular carcinoma which is why this drug is contraindicated in these circumstances. Take into careful consideration patients with brain metastases.
- **Anti-EGFR treatment:** most often are skin changes - shown in the picture below



- **Anti ALK therapy**: interstitial lung pneumonitis, long QT interval.
- **Anti PD therapy**: most often toxicity is low but it can lead to serious autoimmune inflammations (myositis, pneumonitis, myocarditis, encephalitis, and more).

13.9 Follow Up

Post treatment follow up is individually based on the type of tumor, stage of the tumor and treatment progression. The follow up includes health history information from the time from the last visit, including chest CT and locoregional physical examination, most often occuring every 3 - 6 months in NSCLC for a period of 2 years after which it is 2x a year for the next 5 years, and finally 1x a year. In the case of SCLC, where the risk for a timely relapse is higher, the patient is followed up every 2-3 months in the first year, every 3-4 months in years 2 and 3, every 4-6 months in years 4 and 5, and finally 1x a year after.

13.10 Prognosis

The severity of lung cancer is evidenced by the finding that only 20–25% of patients are suitable for radical surgery at the time of diagnosis. The vast majority of new cases are diagnosed in advanced and generalized stages. In NSCLC, the best prognosis is achieved in patients in the initial stages after radical surgery with the 5-year survival rate being 50-80%. In patients with locally advanced findings, 5-year survival decreases to 30% and median survival ranges from 18 to 24 months.

Patients with generalized affections at the time of diagnosis have a median survival time of 12-18 months. The worst situation is in SCLC, where the mean survival time in untreated patients is 2-3 months, and with chemotherapeutic treatment the survival time extends to 12-14 months. Patients treated with combined chemoradiotherapy have the longest mean survival time of 14-16 months.

14 MALIGNANT TUMORS OF THE PLEURA

Jan Dvořák

14.1 EPIDEMIOLOGY

Malignant mesothelioma is the only primary pleural cancer. It is a relatively rare disease with an incidence of 0.1% of all cancers and with an increasing incidence in recent years. At the time of diagnosis, the median age is approximately 60 years. Occurrence in men is 5-times higher than in women.

14.2 ETIOLOGY

Mesothelioma occurrence is directly related to the inhalation of asbestos microscopic fibers, especially in industrial areas. The time from asbestos exposure to disease diagnosis is decades long (20–40 years). Smoking is also considered a risk factor.

14.3 SYMPTOMATOLOGY

The disease is predominantly characterized by a protracted course with subtle symptoms and the time from development of mesothelioma until diagnosis is made may range from months to years. The symptoms may be similar to those of lung tumors. The most common symptoms in mesothelioma are pain (infiltration of the parietal and visceral pleura and surrounding structures), dyspnoea and cough (based on fluidothorax). More than 90% of patients report the presence of fluidothorax, usually haemorrhagic. Rarely, paraneoplastic symptoms occurs.

14.4 DIAGNOSTICS

The diagnostic process is similar to lung cancer decision making.

MRI is important in the first phase of the disease for assessing localized findings´ chest wall infiltration and subsequent decisions about surgery treatment.

Histological and immunohistochemical verification requires a sufficient amount of biological material, which is generally obtained by videothoracoscopic biopsy.

14.5 DIFFERENTIAL DIAGNOSTICS

Pain in malignant mesothelioma originates from pleural irritation or infiltration of surrounding structures (mediastinum, heart, diaphragm). Pleuritic pain often has an inflammatory origin, but may also be a manifestation in lung tumors. Infiltration in the lung apex area may be similar to Pancoast's tumor possibly even with symptoms of Horner syndrome. In X-ray, we usually observe the obstruction of the costophrenic angle due to fluidothorax. CT scans can detect pleural thickening, pleural effusion, lung atelectasis, infiltration of soft tissues and bones. Most of these symptoms can also be seen in other lung tumors. Malignant pleural effusion is present in lung carcinomas (35%), breast carcinomas (25%) and in malignant lymphomas (10%). Pericardial effusion may also be caused by mesothelioma infiltration (another cause - inflammatory pericarditis)

14.6 Pathology

Mesothelioma derives from mesodermal epithelium and may have mesenchymal or epithelial differentiation. Immunohistochemical examination can distinguish 3 basic types: **epithelioid** (50%) is characterized by direct spreading through the pleura, occurrence of the pleural effusion, moreover, frequently metastases in the lymph nodes (up to 40%) and infiltration of the surrounding structures (thoracic wall , mediastinum, pericardium, diaphragm) can be found. For the second type - **sarcomatous** (occurring in 15%), distant metastases are typical. The last type is **mixed** type (occurring in 35%) combining symptoms of both.

Parietal and visceral pleura spread is typical. In advanced disease, lymphogenic and hematogenic dissemination is frequent. Lymphogenic metastases to the mediastinal lymph nodes are described in half of the patients. Hematogenic dissemination affects bones, liver, adrenal glands, brain.

14.7 Therapy

Surgical treatment

Curative surgery (pleuropneumonectomy or pleurectomy) is only possible in small localized findings that are usually diagnosed by a coincidence. These surgeries are adjuvantly supplemented by chemotherapy and radiotherapy.

In more advanced findings it is possible to perform palliative surgery - pleural decortication, which prevents formation of the pleural effusion.

Radiotherapy

This method does not affect patient survival. Due to very limited radiosensitivity of mesothelioma, it is reserved for palliative treatment. It is mainly used to affect local pain symptoms.

- **Postoperative radiotherapy:** 50–60 Gy / 2 Gy / 25-30 fr.
- **Palliative RT -** typically 30 Gy / 3 Gy / 10 fractions.

Chemotherapy

Chemotherapy also does not affect patient survival. Systemic chemotherapy treatment also has a palliative effect due to its limited efficacy (up to 20%). Currently, the preferred regimen is a **combination of cisplatin and pemetrexed.**

Treatment of malignant effusions

The impulse for the treatment of malignant effusions is the detection of malignant cells in the effusion fluid or histological positivity of the material obtained by pleural biopsy. Recurrent effusions are a frequent manifestation of malignant mesothelioma. The aim of the treatment is to reduce effusion and / or prevent atelectasis. We try to achieve this by means of pleurodesis.

Pleurodesis is most often performed by instillation of the following substances into the pleural cavity: talc, bleomycin, doxorubicin, BCG. In rapid filling effusions, insertion of pleuroperitoneal shunt (a

catheter that is placed subcutaneously and drains the transudate into the peritoneal cavity) may be an alternative to pleurodesis.

14.8 POST-THERAPEUTIC COMPLICATIONS

The incidence of treatment complications depends, similarly to lung tumors, on the treatment applied. The risk of pneumothorax increases with repeated transthoracic effusion punctures.

14.9 FOLLOW-UP

A similar algorithm as for lung tumors can be used for follow-up of the patients

14.10 PROGNOSIS

Prognosis of the disease is poor. Of the early stage patients who undergo radical surgery, about 20% survive for 5 years. Median survival from the time of the diagnosis is reported in the range of 8–30 months, depending on the stage of the disease. Patients with an epithelioid type of mesothelioma have a median survival of 22 months compared to 6 months for the other types.

15 ESOPHAGEAL CANCER

Markéta Šejdová, Marián Liberko

15.1 EPIDEMIOLOGY

Is considered less common cancer. It is found up to 7 times more often in men (especially squamous cell carcinoma), and is most often diagnosed in the 7th decade of life. Because of environmental and dietary factors, variability in incidence is high; it is most common in China and in the Middle East belt. Europe is one of the regions with a low incidence of oesophageal cancer.

15.2 ETIOLOGY

Esophageal cancer has two major histological subtypes: squamous cell carcinoma and adenocarcinoma. The majority of esophageal cancers are squamous cell carcinomas (90%), but in recent years the incidence and mortality of adenocarcinomas has increased.

The incidence of squamous cell carcinoma is influenced by smoking and excessive consumption of alcohol, especially distillates. These 2 risk factors combined potentiate their negative effect. The risk of developing adenocarcinoma is increased in gastroesophageal reflux, Barret's esophagus and obesity. A protein-poor, fat-rich diet and exposure to nitrosamines also increase the risk of developing esophageal cancer, both squamous and adenocarcinoma.

15.3 SYMPTOMATOLOGY

Early stages tend to have no significant symptoms. Later, after esophageal lumen is significantly stenotized, dysphagia usually occurs as a first symptom. Other symptoms are: odynophagia, food regurgitation, vomiting of undigested food, weight loss, coughing, hoarseness (paresis of recurrent laryngeal nerves), recurrent bronchopneumonia due to food microaspirations. Metastatic spread may be manifested by ascites, dyspnoea in fluidothorax, tumor cachexia.

15.4 DIAGNOSTICS

For visualization of esophageal involvement and collection of material for histology, esophagogastroscopy is a basic diagnostic method. To determine the extent of the disease and especially if considering surgery, it is also necessary to perform another examination - endosonography of the esophagus which helps to assess the degree of invasion of the esophagus wall and involvement of regional lymph nodes. Staging examinations include CT scan of the chest, abdomen and lesser pelvis. Additionally PET / CT can also be performed. Optionally, bronchoscopy can be added to exclude fistula formation, especially in tumors located near the tracheal bifurcation. In patients considered for multimodal therapy, functional examination should be done: spirometry, ergometry, heart sonography, assessment of the nutritional status.

15.5 Differential diagnostics

It is necessary to differentiate malignant and benign disorders- esophageal achalasia, Barett's esophagus. In case of a malignant finding a biopsy is necessary to detect the exact type of the tumor.

15.6 Pathology

Squamous cell carcinoma occurs mainly in the upper 2/3 of the esophagus and is the most common (90%) esophageal cancer. Adenocarcinoma - most often occurs in the lower 1/3 of the esophagus or gastroesophageal junction. Less common histological types include small cell carcinoma, sarcoma, primary lymphoma, or metastatic involvement from another primary tumor site. Esophageal cancer most commonly metastases to lymph nodes, liver and lungs.

15.7 Therapy

Patients with esophageal cancer are treated within a multidisciplinary team. The extent of the disease (stage), the patient's performance status and his co-morbidities determine treatment strategy chosen. The treatment of patients with esophageal cancer also varies depending on the histological cell type.

Early stages - cT1-2 cN0 M0

Patients with early, operable stage of the disease are indicated for primary radical surgery - transthoracic esophagectomy. Possible alternatives for very early stages (T1a) are endoscopic procedures: endoscopic mucosal resection and endoscopic submucosal dissection. In patients having early stages of esophageal cancer who refuse to undergo surgery or in whom surgery is contraindicated due to comorbidities, definitive chemoradiotherapy is a possible alternative that shows better results than radiotherapy alone.

Locally advanced stages – cT3-4, nebo cN1-3 M0

Surgery alone is not recommended because of low R0 resection rates and shorter survival time when compared with multimodal therapy.

- **Squamous cell carcinoma**

Non-adjuvant chemoradiotherapy with subsequent re-staging and surgery is a standard course of action for patients in a good general condition. Cytostatics such a cDDP / fluoropyrimidines, CBDCA / paclitaxel are given concomitantly with irradiation, possibly potentiated by FOLFOX treatment regimen. An alternative for patients refusing surgery, or for whom surgery is contraindicated due to comorbidities is definitive chemoradiotherapy (regimen similar to neoadjuvant therapy) that is having better results than radiotherapy (with subsequent patient follow-up or with salvage esophagectomy).

- **Adenocarcinoma**

Perioperative chemotherapy is the standard practice in adenocarcinomas of the distal esophagus and gastroesophageal junction. The options are: 3 cycles before and 3 cycles after surgery (ECF / ECX / EOF / EOX), or currently preferred FLOT regime 4 cycles before and 4 cycles after surgery, which achieves a higher rate of complete pathological remissions, R-0 resections and prolongs DFS and OS. The second treatment strategy option for adenocarcinomas is non-adjuvant chemoradiotherapy with subsequent surgery. Chemotherapy regimens are similar to squamous cell carcinoma treatment regimes. There is no direct comparison for the efficacy of perioperative chemotherapy and neoadjuvant chemoradiotherapy, but comparative studies are ongoing now.

Metastatic disease and palliative therapy

Metastatic esophageal cancer is an incurable disease with poor prognosis. Most patients die within a year after diagnosis is made despite proper cancer treatment. Palliative chemotherapy is possible and slightly more effective in adenocarcinomas than in other types. Regarding the general condition of the patient, monotherapy or a combination of cytostatics is considered. Targeted transtuzumab (anti-Her2) therapy in combination with cDDP / fluoropyrimidine may be considered as the first-line in patients with gastroesophageal junction adenocarcinoma, assuming Her2 tumor expression. In the second line, a combination of taxanes and ramucirumab (anti-VEGFR) is possible. Targeted treatment is reserved only for patients in a good general condition: PS 0-1. Symptomatic therapy alone is indicated in patients with a worse general condition.

For tumors that bleed and painful metastases, radiotherapy (external or brachytherapy) can also be used for palliative purposes. Another treatment option is an insertion of the stent into the region of esophageal stenosis to restore the patency of the esophagus. Due to the frequent progression of the condition and frequent impossibility for a causal treatment, it is necessary to ensure a way for food intake. For this purpose, stent insertion, PEG insertion, laser removal of esophageal lung tumor or radiotherapy (external or brachytherapy) are used.

15.8 Post-Therapeutic complications

After radical surgical treatment, swallowing disorders and negative effect on food intake may occur. After radical radiotherapy, fibrous changes of the esophagus and resulting problems (stenosis, occlusion) may occur.

15.9 Follow-up

After radical treatment, follow-up should be every 3 months, after 2 years the interval can be longer, physical examination should always be done. Based on the problems and findings made during examination - endoscopy, imaging examination, etc should be ordered.

15.10 Prognosis

Over the past 30 years, patient survival has improved, but still, as most of the patients are diagnosed in late stages of the disease, survival remains very poor. Only about 1/3 of patients after radical treatment (surgical or chemoradiotherapy) survive for 2 years. 5-year survival is about 10%. Important prognostic factor is the rate of weight loss, more than 10% means poor prognosis.

16 GASTRIC CANCERS

Markéta Šejdová, Marián Liberko

16.1 EPIDEMIOLOGY

Gastric cancers are among the most common cancer diseases worldwide with significant differences in their incidence in different regions. The highest incidence is in China, Japan, East Asia, Eastern Europe and South America. In Western Europe and the United States, unlike in other cancers, the incidence of gastric cancer is declining. Another interesting trend is a decrease in the incidence of tumors of the distal part of the stomach and an increase in the incidence of proximal adenocarcinomas of cardia and gastroesophageal junction with more aggressive behavior and worse prognosis, the incidence of this type of cancer increased dramatically in patients under 40 years.

16.2 ETIOLOGY

As for other diseases, risk factors for gastric cancer are obesity, increased caloric intake, a fat-rich and high-salt diet, fiber-poor diet, and dietary nitrosamines consumption. Insufficient intake of vitamin A and C, smoking, alcohol abuse, chronic atrophic gastritis, Helicobacter pylori infection and Ebstein-Barr virus also act as predisposing factors. Barret's esophagus is a precancerosis occuring in patients with gastroesophageal reflux and later may develop to gastroesophageal junction carcinomas. Carcinomas also occur more frequently on surfaces affected by polyps and at the site of anastomosis after resection procedures in ulcer disease. Approximately 1-3% of gastric tumors are part of hereditary cancer syndromes: hereditary diffuse gastric cancer, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome.

16.3 SYMPTOMATOLOGY

Gastric cancer has no typical symptoms. The most common manifestation is non-characteristic pressure feeling or pain in the epigastrium and sudden or gradual loss of appetite, nausea is also frequent. In advanced disease processes when pylorus is obstructed, vomiting of undigested food during gastrectasis occur. Dysphagia may be the first symptom of a cardiac tumor. Bleeding leading to gradual anemization may also manifest the disease. Weakness, fatigue and weight loss are common general manifestations. Ascites, fluidothorax and tumor cachexia are manifestations of generalized disease.

16.4 DIAGNOSTICS

Obligatory examinations include esophagogastroscopy with a biopsy of a suspected tumor mass or in a normal endoscopic findings and suspected diffuse gastric cancer - random gastric biopsy. An important method to determine the depth of invasion of the stomach wall and to assess regional lymphadenopathy is endosonography. Prefered staging method is CT scan of the chest, abdomen and lesser pelvis (especially in women who are at risk of metastases spread to the ovary - the so-called Krukenberger tumor). It is important to determine the level of tumor markers: CEA, Ca19-9, Ca72-4, which are important for diagnosis and later for monitoring an effect of the treatment.

Facultative examinations include scintigraphy of the bone, PET / CT of the trunk (in suspicion of spreading and before radical surgery being considered). In some cases, exploratory laparoscopy (possibly with peritoneal lavage) is performed to exclude serose surface spreading.

16.5 Differential diagnostics

Differential diagnosis clearly depends on the first symptoms that a patient presents with. The most important is the differentiation of benign peptic ulcer and benign polyp. If the malignancy of the disease is confirmed, precise histological examination and tumor type determination are required, as different treatment strategies apply to different diseases. These are mainly GIST - gastrointestinal stromal tumors (70% have origo in the stomach), primary lymphomas (most often MALT's stomach). Other tumors are less common: squamous cell carcinoma, small cell ca, undifferentiated carcinoma, carcinoid, sarcomas, or metastases from another primary tumor (melanoma, lobular-breast cancer).

16.6 Pathology

90% of stomach cancers are adenocarcinomas. Based on Lauren classification following types of gastric cancers are recognized: intestinal type (development often on precancerous surfaces- gastric atrophy, intestinal metaplasia, more often found in men, incidence higher in older age, Helicobacter pylori infection and dietary habits predispose), diffuse type (unrelated to precancerosis surface, younger age, more often found in women, hereditary factors contribute, worse prognosis) and mixed type.

Other histological types are GIST, MALT, carcinoid, sarcoma and other rare types.

16.7 Therapy

Patients with gastric cancer are treated within a multidisciplinary team. The extent of the disease (stage), the patient's performance status and his co-morbidities determine the type of treatment strategy chosen. The treatment of patients with gastric cancer also varies depending on the histological type identified. Surgical resection of early stages is potentially curative, however, most patients have relapse of the disease after resection. Therefore, a multimodal approach is the standard for stage IB and higher.

Early stages cT1 N0 M0

For tumors T1a and T1b stage, treatment options include endoscopic mucosal resection or endoscopic submucosal dilation. In early stage tumors not suitable for endoscopic treatment, the method of choice is subtotal or total gastrectomy with lymphadenectomy.

Advanced stages cT>1 N1-3 M0

In cases of localized disease, with no obvious signs of generalization, in a patient with generally good health status, we choose a radical treatment strategy - usually a multimodal approach.

Nowadays, ideal way of practice is considered perioperative chemotherapy and then radical surgery. Either 3 cycles of chemo before and 3 cycles after surgery (ECF / ECX / EOF / EOX), or FLOT regimen of 4 cycles before and 4 cycles after surgery is possible.

The second way of managing advanced stages of these cancers is primary radical surgery - partial or total gastrectomy with removal of pericardial and perigastric nodes - D1 dissection, including larger and lesser omentum. In order to further radicalize the procedure, it is recommended to also excise lymph nodes around left gastric artery , common hepatic artery., splenic artery and truncus coeliacus - D2 dissection. Adequate postoperative care is necessary after the procedure. Based on a definitive histological finding (depth of invasion into the stomach wall, lymph node involvement, positive resection margins, residual disease), the patient is indicated for adjuvant chemoradiotherapy or independent chemotherapy usually using fluropyrimidine-based regimens and platinum derivatives.

Metastatic disease

Due to non-specific manifestations in early stages, a patient is often diagnosed late in inoperable or generalized disease stage (most often liver, lung and bone metastases). Depending on the patient's main complaints, we consider palliative surgery - palliative conjunctival surgery (gastroenteroanastomosis), palliative radiotherapy, or palliative chemotherapy.

The prognosis of generalized disease is poor, most patients die within 1 year of generalization. Targeted therapy offers partial improvement in the prognosis of patients with metastatic gastric cancer. For tumors that express Her2, a combination of cDDP / fluoropyrimidine and trastuzumab (anti-Her2) in the first line is possible. The second line is a combination of paclitaxel and ramucirumab (anti-VEGFR). In another line, irinotecan use is possible - but must be considered for each patient individually due to the limited efficacy of palliative chemotherapy in later stages of the treatment ,pre-treatment, and the patient's general condition. Depending on the patient's general condition, only symptomatic, supportive care is often provided

16.8 Follow-up

In the first year after radical therapy, follow-up every 3 months is advised, we check patient´s clinical status, laboratory values - blood count, biochemical parameters, cancer markers: CEA, Ca19-9, or Ca72-4. After 6 months we perform gastroscopy; CT scan of the abdomen and lesser pelvis and X-ray of the lungs once a year. In the 2-nd and 3-rd year of remission, clinical examination, laboratory testing, CEA and Ca19-9 values should be measured every 6 months. Gastroscopy, abdominal and lesser pelvis CT scan and lung X-ray should be done once a year. In the following years, all of the above examinations should be done once a year. In case of new symptoms appearing we proceed accordingly. Long-term vitamin B12 substitution in patients after proximal or total gastrectomy is fully indicated. It is suitable to cooperate with the outpatient nutrition clinic for sipping prescription.

16.9 Prognosis

Only in patients after radical surgery with a disease limited to submucosis, the 5-year survival rate is up to 85%. Unfortunately, at this stage of the disease, there are a few patients found and most of these cases are likely incidental findings discovered during surgery which was usually indicated for another reason. Despite radical treatment, in tumor invasion through the stomach wall, only about 50% of patients survive for 5 years. When locoregional lymph nodes are affected, 5-years survival rate falls below 20%, and in distant metastases almost no one survives for 5 years.

17 MALIGNANT TUMORS OF THE LIVER, GALLBLADDER AND BILIARY TRACT

Markéta Šejdová, Marián Liberko

17.1 HEPATOCELLULAR CARCINOMA

17.1.1 Epidemiology

Europe is not considered an area with a high incidence of hepatocellular carcinoma as opposed to East Asia, where HCC accounts for up to 50% of all tumors. The incidence coincides with high incidence of hepatitis B and hepatitis C in these areas. However, there is generally higher incidence of HCC in developing countries.

17.1.2 Etiology

In up to 90% of cases hepatocellular carcinoma occurs on the background of liver cirrhosis. Major etiological factors include hepatitis B and C, liver cirrhosis on an alcoholic basis or on toxonutritive etiology. Aflatoxin in food is considered another etiological factor. Some metabolic diseases such as hemochromatosis, Wilson's disease and porphyria cutanea tarda also increase the risk of developing HCC.

17.1.3 Symptomatology

Generally speaking, symptoms of the disease are non-specific. Early stages can be completely asymptomatic and usually HCC in this stage is discovered during liver examinations ordered for other reasons. More advanced disease stages manifest as abdominal pain, abdominal discomfort, fatigue, elevated temperature, anorexia, weight loss, icterus and signs of portal hypertension. Generalized disease usually manifests as ascites, encephalopathy and cachectization of the patient.

17.1.4 Diagnostics

Ultrasound is the first choice imaging method and can also be used as a screening tool for risk groups. To more accurately assess the extent of the disease and to consider the possibility of surgery treatment it is appropriate to scan all the abdomen and lesser pelvis, or order MRI liver examination. Additional examinations such as CT angiography are to determine the possibility of resectability of the tumor. Hepatocellular carcinoma is one of the few malignancies in which the diagnosis can be made only based on the results of imaging methods (CT or MRI) - abnormal arterial oxygen saturation and late (venous) contrast elution results are typical. In the case of ambiguous findings in imaging examinations, biopsy for histological verification is necessary to accurately determine the nature of the lesion. Laboratory testing for high levels of alpha-fetoprotein, which is produced in 70% of hepatocellular carcinomas can be made, however, lower values, may also be present in simple cirrhosis. To exclude generalization of the disease we then use CT scan of the chest, skeletal scintigraphy or PET / CT. Before any intervention is considered,

important part of the diagnostic process is also examination of the functional status of the liver parenchyma using Child-Pugh classification.

17.1.5 Differential diagnostics

Other diseases of the hepatobiliary tract (benign and malignant) and in particular the exclusion of metastatic liver disease from another tumor.

17.1.6 Pathology

Hepatocellular carcinoma types described are multinodular, large, and diffuse type; more detail in pathology textbooks.

17.1.7 Therapy

Prognostic factors are AFP value, patient performance status and liver function test results (Child-Pugh classification). Surgical treatment alone is potentially curative, although only a small proportion of the patients can undergo surgery (mainly due to the extent of the disease and poor functional status of the cirrhotic liver parenchyma).

One possible way is to perform a liver transplant - it treats both the tumor and associated liver cirrhosis, a disadvantage is the subsequent immunosuppression. Indications for liver transplantation follow so-called Milan criteria. Another surgical treatment option is a liver resection: typical and atypical depending on the extent of the disease. Contraindications of the surgery, even with surgically accessible tumors, may be a liver failure, Child-Pugh class B and C and generalized disease.

Other treatment methods only have palliative effect (catheter ablation, microwave ablation, embolization and chemoembolization, radiotherapy, chemotherapy - of minimal importance). A possibility for systemic treatment of generalized hepatocellular carcinoma is targeted therapy. For this type of treatment tyrosine kinase inhibitors are available; in the first line sorafenib, after progression of the disease -regorafenib.

17.1.8 Complications

Liver transplantation can cause a number of complications, tissue rejection, development of other tumors due to immunosuppression,etc. Surgery in general may be complicated by bleeding, injury to surrounding tissues, shock, decompensation of so far non-existent liver lesion. Both chemotherapy and radiotherapy are accompanied by nausea and vomiting, and in chemotherapy in addition to haematological toxicity, liver failure may occur.

17.1.9 Follow-up

Patients should be followed up at an interval of 3 months for the first 2 years, followed by an interval of 6 months, hepatic function tests and CT/MRI imaging of liver should be done in patients after radical treatment. Patients during palliative therapy should be followed every 2 months.

17.1.10 Prognosis

Size of the tumor and its differentiation are prognostic factors. Prognosis is worse when cirrhosis, metastases, worse performance status of the patient, or high AFP values are present. In patients undergoing curative resection, the 5-year survival rate is about 20%. Generalization of the disease is common - mostly to the liver, lymph nodes, lungs and bones. Most patients are diagnosed late, when resection is impossible.

17.2 CANCER OF THE GALLBLADDER AND BILIARY TRACT

17.2.1 Epidemiology

Gallbladder cancer is more common in women, bile duct cancer is equally represented in both genders. Most often diagnosis is made in age over 70.

17.2.2 Etiology

In gallbladder cancer, cholecystolithiasis (so called porcelain gallbladder) and polyps are risk factors. Risk factors for biliary tract cancer are biliary tree anomalies, ulcerative colitis, primary biliary cirrhosis, and primary sclerosing cholangitis.

17.2.3 Symptomatology

Gallbladder cancer: Early stages are usually asymptomatic and can be coincidentally discovered in cholecystectomy assessment for other causes. Late stages symptoms can be similar to a benign gallbladder disease: nausea, vomiting, pressure in the right hypochondrium, loss of appetite, weight loss, in late stage also icterus and recurrent cholangitis can occur.

Biliary tree cancer: painless icterus is the most common symptom in these patients.

17.2.4 Diagnostics

Gallbladder tumors are often diagnosed incidentally in a tissue removed during cholecystectomy (resecate). Prior to a planned resection procedure of a known gallbladder cancer, liver function tests, abdominal CT scan and lung CT scan are recommended to determine the extent of the disease. In icterus patients or in patients with operable cancer of the biliary tract as a preoperative examination, MRCP is indicated as a surgery feasibility confirmation method. ERCP is a method suitable for obtaining a tissue sample for histological examination or detailed examination of a stenosis of unclear etiology but also suitable for invasive solution of obstructive jaundice by the insertion of a stent. Before surgery CEA and Ca19-9 values should be measured.

17.2.5 Differential diagnostics

It is necessary to distinguish between benign and malignant disease, which is often very difficult due to the difficulty of biopsy procedure.

17.2.6 Pathology

About 85% of gallbladder tumors are adenocarcinomas, the remaining 15% may have squamous or mixed differentiation. First, the tumor spreads locally, then lymph nodes and liver are frequently affected - either through direct ingrowth or via the bloodstream spread. The vast majority of cancers of the bile duct are adenocarcinomas (90%), rarely adenosquamous carcinoma, leiomyosarcoma can occur. They spread mainly locoregally and metastasize to the liver.

17.2.7 Therapy

Surgery

The only potentially curative method is a surgery. Although cholecystectomy is usually indicated in cases other than for suspicion for malignant tumor, in about 1-2% of cholecystectomies, a malignant gallbladder tumor is found. In non-advanced pT1a tumors (spread limited to mucous membranes), sufficient procedure is a simple cholecystectomy. In advanced disease stages, wedge resection of the liver bed of the gallbladder and lymphadenectomy in the area of the porta hepatis is also indicated with the aim to achieve R0 resection. In bile duct carcinomas, resectability is only possible in about 20% of tumors. Prior to surgery, profound diagnostic process (CT, MRI, MRCP) is required to ensure feasibility of the surgery. If the finding is to be inoperable also palliative procedures can have a good effect on the patient. Palliative procedures include endoscopic methods - insertion of a stent into the bile duct or when the patient is relieved of biliary tract obstruction via ERCP or PTC.

Radiotherapy

The role of adjuvant external radiotherapy is yet not clearly established. It can be considered in more advanced findings with positive lymph nodes and in R1 resection procedures. In extrahepatic bile duct cancers (so-called Klatskin tumor), brachytherapy may have a good palliative effect. Radiation source is inserted via external (percutaneous transhepatic) drainage access into the external biliary tract. Ir 192 HDR gamma emitter is used as the radiation source.

Chemotherapy

Adjuvant chemotherapy based on fluoropyrimidines or gemcitabine has a limited benefit in terms of prolonging the survival of the patients. 5-year survival rate is reported to be 5-15%. However, chemotherapy can have palliative and analgesic effect. Slightly better results are achieved by a combination of both methods, ie chemoradiotherapy. In generalized disease, the cDDP / gemcitabine is a standard combination used.

17.2.8 Complications

Surgery may be complicated by bleeding and injury to surrounding tissues. Chemotherapy is associated with nausea, vomiting and haematological toxicity. Liver failure may occur. Brachytherapy via insertion of external devices can lead to cholangitis.

17.2.9 Follow-up

Patient should be monitored at regular basis on a department where major treatment was provided for him - surgery, gastroenterology, oncology. Monitoring in patients after a curative intervention includes oncological markers and CT every 3 months for 2 years, after that every 6 months, and 5 years after

intervention, the monitoring interval can be extended to one year. During palliative therapy, follow-up every 2–3 months is recommended.

17.2.10 Prognosis

The prognosis is affected by a lymph node involvement and a local spread. Gallbladder cancer that only affects mucosa has a 5-year survival rate of about 80%, while patients with lymph node involvement have a 5-year survival rate of 0-10%. In patients with bile duct cancer, the prognosis is related to the extent of disability, patients with distal bile affection have a slightly better prognosis, median survival is 12-20 months.

18 MALIGNANT TUMORS OF THE PANCREAS

Markéta Šejdová, Marián Liberko

18.1 EPIDEMIOLOGY

Malignant tumors of the pancreas are a disease that affects older patients, usually over 70, more often men. The incidence and mortality curves rise practically simultaneously, due to a late diagnosis time and chemo- and radio-resistance of the disease. It is one of the most malignant diseases with poor prognosis even in the early stages. Over 2/3 of new cases are diagnosed in the metastatic stage.

18.2 ETIOLOGY

The main risk factors for pancreatic cancer are smoking and alcohol. The composition of the diet is also not negligible - the increased amount of fat and meat in the diet means an increased risk, the sufficiency of fruits and vegetables lowers the risk of developing pancreatic cancer. Other risk factors include diabetes mellitus I. and II. type (often this may be the first manifestation of pancreatic cancer). A small percentage of cancers are genetically determined. Carriers of BRCA2 mutation, patients with Lynch, Peutz-Jeghers, Li-Fraumeni syndrome and individuals with a history of chronic pancreatitis or infected by Helicobacter pylori are at higher risk.

18.3 SYMPTOMATOLOGY

In the early stages symptoms are very uncharacteristic and may resemble functional dyspeptic syndromes. Later on, there is a pain in the epigastrium with propagation to the left side and to the back. Clinical picture is characterized by a pain, loss of appetite, weight loss and general deterioration of the patient. In more advanced tumors, the pain is permanent, sometimes the patient assumes a relief position where the pancreas moves away from the retropancreatic nerve plexuses (bending forward, prone position, kneeling position). In case of tumors in the head of the pancreas, the first symptom of the disease may be an obstructive icterus. Ascites and liver metastases are also often present.

18.4 DIAGNOSTICS

Due to the asymptomatic nature of the early stages and the lack of screening, the diagnosis is often made late. Often (reported in up to 2/3 of the cases), the very first symptoms of the disease may already be due to metastases, particularly in the liver, or causing obstruction of the biliary tract in tumors of the pancreatic head. However, it is necessary to obtain a comprehensive picture of the extent of the cancer spread in order to decide about all therapeutic options. Basic, so-called obligatory examination methods include ultrasound of the abdomen, endoscopic ultrasound to assess the local progression of the disease and FNAB for tissue specimen collection. When considering surgery it is necessary to perform CT-scan of the abdomen and lesser pelvis or MR, MRCP, CT-angiography to assess the involvement of vascular structures. Other examinations include lung X-ray and tumor marker screening, especially for Ca19-9 and CEA, which are important both for diagnosis and later for monitoring the effect of the treatment. Other additional and individually optional methods are ERCP, PET / CT, or explorative laparotomy/laparoscopy

(for verification by biopsy analysis). Based on the patient's problems, we also indicate other examinations, such as skeletal scintigraphy for skeletal pain diagnostics.

18.5 Differential diagnostics

Differential diagnosis clearly depends on the first symptoms a patient presents with to the doctor. In case of an unclear dyspeptic problems, first, it is necessary to exclude other diseases of the gastrointestinal tract (malignant, benign). In an obstructive icterus, one needs to exclude stenosis of the bile ducts caused by a tumor or by an external compression. Possible causes of compression are lymphadenopathy or cancer of the surrounding organs. Obstruction of the bile ducts also resulting in the obstructive icterus can be caused by lithiasis.

18.6 Pathology

95% of all cases of pancreatic cancer are ductal adenocarcinoma of the outlet type originating from the exocrine part of the pancreas. Typically there is a pronounced stromal response around tumors mass, which is believed to be the cause of the tumor chemo and radio-resistance. Due to the frequent perineural spread, severe back pain is also typical. Other types of pancreatic cancer include acinar cell carcinoma, papillary carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, mucinous carcinoma, or papillary-cystic carcinoma. Rare diseases include endocrine pancreatic tumors, so-called neuroendocrine tumors with better prognosis, different treatment and often with the production of specific hormonal substances (insulin, glucagon, gastrin, VIP, serotonin).

Cystic neoplasm accounts for about 10-15% of all cystic lesions of the pancreas. The most common cancers of this type are: serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm. Mucinous neoplasms have a potential for malignancy or may be malignant at the time of the diagnosis. Non-mucinous lesions do not have the malignant potential.

18.7 Therapy

The therapy of pancreatic cancer is dependent on the extent of the disease. In multidisciplinary team environment it is necessary to cooperate X-ray technician, surgeon, gastroenterologist, oncologist and radiation oncologist to determine the optimal treatment strategy. The disease can be categorized as resectable, potentially resectable, locally advanced and metastatic.

Resectable tumor

In general, if technically possible in the early stages of the disease, the patient is indicated for surgery. However, this is usually true in less than 20% of patients. Pancreatic resection is performed (Whipple, Traverso-Longmire procedure), resection of collecting lymph nodes and the target is R0 resection. Adjuvant chemotherapy is indicated after surgery. 6-month gemcitabine therapy is a standard choice. Presently, a modified FOLFIRINOX regimen, which is commonly used in metastatic disease in patients in good general condition, has been shown as a possible alternative in adjuvant administration. An alternative is adjuvant chemoradiotherapy, especially in R1 resection.

Potentially resectable tumor

Preoperative treatment is recommended. An option is a non-adjuvant chemotherapy (mFOLFIRINOX for 3 months) then re-staging with resection consideration. Preferred alternative is a non-adjuvant chemotherapy for 3 months, then re-staging; in response to chemotherapy, chemoradiotherapy is continued with further re-staging and resection.

Locally advanced disease

Those are only pancreatic tumors that are not considered to be potentially resistant. The treatment options are similar to those of a potentially resectable disease except for a subsequent surgery.

Metastatic disease

Over 2/3 of the patients are diagnosed in the metastatic stage; most often mets in the liver are present. The prognosis is poor, most patients die within a year from diagnosis. Overall median survival is approximately 8–10 months. For a long time, gemcitabine monotherapy has been the standard choice in metastatic pancreatic cancer. Currently, mFOLFIRINOX is the option for patients in PS 0-1 with normal liver function tests. It prolongs survival approximately two times when compared with gemcitabine, but at the cost of higher toxicity. Another new treatment option is the combination of gemcitabine and nab-paclitaxel but also only for patients in a good general condition ,PS 0-1 without abnormalities found in liver function tests. After progression of the tumor during first-line of palliative chemotherapy, treatment for the next line may be considered, but usually due to the aggressiveness of the disease, poor patient status and chemoresistance, it is indicated only in a small proportion of the patients. New treatment option is also the combination of fluoropyrimidine and nanoliposomal irinotecan. Only symptomatic and supportive treatment is indicated in patients already in a poor general condition - PS 3-4.

18.8 Follow-up

After resection procedure and adjuvant therapy, the patient is followed every 3 months for the first year, then every 6 months. The follow-up examination includes clinical examination, CBC, biochemistry lab, tumor markers, lung X-ray every 6 months and sonography or CT of the abdomen and lesser pelvis every 6 months for the first year. After palliative treatment in incurable disease stages, follow-up as needed.

18.9 Prognosis

Pancreatic cancer is rarely curable disease. The greatest chance for the patient exists when the tumor is localized only in the pancreas and is resectable. However, this stage of the disease is detected in less than 20% of the patients and even in completely resected tumors, the 5-year survival rate is only about 5%. In tumors smaller than 2 cm with no lymph node metastases and no growth through the pancreatic capsule, the 5-year survival is about 20%. Taking into account patients with all stages of the disease, the 5-year survival is only about 1%, with the majority of patients dying within one year. Unfortunately, pancreatic cancer is still a very poorly treatable disease with poor therapeutic results, and therefore, the treatment strategy is always strictly considered, taking into account the extent of the disease, the patient's general condition, so that it benefits the patient and does not impair his quality of life.

19 COLORECTAL CARCINOMA

Markéta Šejdová, Marián Liberko

19.1 EPIDEMIOLOGY

Colorectal cancer is the second most common cancer in men (after prostate cancer) and women (after breast cancer). The incidence is higher in men. The Czech Republic ranks among the leading in the incidence of this disease worldwide. The risk of developing colorectal cancer increases from about 50 years of age and is most commonly diagnosed around the 70s. Left-sided cancers are more common.

19.2 ETIOLOGY

The specific cause of the disease is unknown, but many factors - especially dietary habits, obesity, physical inactivity, smoking, environmental influences are associated with the onset of the disease. Increased risk of development is associated with, for example, a diet rich in fat, sausages and low in fiber, vitamins. Crohn's disease and a history of ulcerative colitis are also risk factors for colorectal cancer. Another risk factor is the presence of adenomatous polyps in the intestine. Higher risk of malignant transformation is found in villous and tubulovillous polyps. Approximately 5–10% of colorectal carcinomas are genetically determined: Lynch syndrome - hereditary non-polyposis colorectal carcinoma (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, carriers of the BRCA1,2 mutation.

19.3 SYMPTOMATOLOGY

The initial stages of the disease are asymptomatic, sometimes indeterminate abdominal discomfort, flatulence, change of stool character, loss of appetite; symptoms commonly attributed to other diseases (gallbladder, gastroduodenal ulcer, irritable bowel). It can be simplified as, the symptoms of right-sided tumors are: indeterminate pain, abdominal pressure, fatigue, weakness due to the manifestation of anemia from chronic, occult blood loss. In left-sided tumors it is often alternation of constipation and diarrhea, sometimes symptoms from intestinal occlusion (ileus) - nausea, vomiting. In the area of the rectum, apart from bleeding, it is a feeling of fullness, pressure, constraints on the stool, urgency, tenesmus.

19.4 DIAGNOSTICS

Due to the high incidence of the disease in the Czech Republic, colorectal cancer **screening** has been introduced. It can be divided into two parts. In the first group of 50-54 year-olds, a test for blood in stool is done annually. In case of negative finding, repeat the test once a year. In a positive occult bleeding test, screening colonoscopy at accredited sites is indicated. In case of a negative finding in colonoscopy, further colonoscopy is indicated after 10 years. In case of positive tumor finding - surgical and oncological treatment. If polyps are found, a control colonoscopy according to valid recommendations is ordered. In the second group of subjects aged 55 years and over, a faecal occult blood test or a primary screening colonoscopy is possible. The next procedure is selected accordingly to the finding, similarly to the first group.

Per rectum examination is simple and may reveal a lesion within 8-10 cm of the sphincter. The examination should be an automatic part of the physical examination. It is irreplaceable clinical examination, the only one that can practically determine tumor fixation.

Colonoscopy provides information on the entire colon mucosa, and is also used to obtain a biopsy specimen to determine the etiology of a possible lesion. **Histological findings** are required prior to initiation of treatment, except in cases where the patient is acutely operated for an ileous condition. Tests to determine the extent of the disease (staging) include X-ray examination of the chest (in more advanced tumors, chest CT is preferable), CT examination of the abdomen and pelvis. In rectal tumors, we complement this with MRI of pelvis and endosonographic examination of the rectum to determine the extent of the tumor, i.e. the depth of invasion through the intestinal wall. Complete biochemical sampling, complete blood count, tumor markers (especially CEA, Ca 19-9) are among the basic examinations.

19.5 Differential diagnostics

It is necessary to exclude other organic disorders of the intestine, non-malignant - Crohn's disease, ulcerative colitis.

19.6 Pathology

95 % of the tumors are adenocarcinomas; the rest are small cell carcinomas, squamous cell carcinomas, carcinoids, undifferentiated carcinomas. Non-epithelial malignancies are lymphomas and sarcomas, mucosal melanomas.

In addition to classical histology, molecular-biological methods are now used more frequently to investigate prognostic and predictive disease markers. In stage II it is an MSI examination - examination of MMR proteins expression in tumor tissue. When considering treatment for stage IV, it is essential to consider the mutation status of the RAS and BRAF oncogene that are examined by the PCR method.

19.7 Therapy

Colon

Stage 0 (Tis, N0, M0)

Tis tumors are indicated (unless otherwise contraindicated) for endoscopic procedures (local excision or polypectomy into healthy tissue) and follow-up by the gastroenterologist; adjuvant oncological treatment is not indicated.

Stage I (T1-2, N0, M0)

Treatment of localized, but more advanced, intestinal tumors consists of primary resection with removal of lymphatics (the necessary extent of the procedure is dependent on the location and size of the tumor). The procedures are performed mostly during laparotomy, newly also by laparoscopy, if the extent of the finding allows it. Surgical treatment is essential in colorectal cancer and is the first method of choice. Adjuvant cancer treatment is not indicated.

Stage II (T3-4, N0, M0)

Primary surgical treatment. Adjuvant chemotherapy according to definitive histology is possible after molecular examination of MMR in tumor tissue. Patients of II. clinical stage with MMR defect, i.e. MSI-H, do not benefit from fluoropyrimidine-based adjuvant chemotherapy. In patients without MMR defect, i.e. MSS, MSI-L, chemotherapy is indicated for 6 months.

Stage III (T any, N1-2, M0)

Primary treatment is surgery. Adjuvant chemotherapy based on fluoropyrimidines and oxaliplatin (FOLFOX) is always indicated in patients in good general condition. 6 months of adjuvant chemotherapy have long been standard. Due to the considerable neurotoxicity of oxaliplatin, often irreversible, possibilities have been sought to reduce the duration of oxaliplatin administration without adversely affecting patient survival. A new standard for at least a portion of patients in stage III - in particular pT3 pN1 - is a 3 month adjuvant chemotherapy based on fluoropyrimidines and oxaliplatin (XELOX).

Stage IV (T any, N any, M1)

Patient care is secured through a multidisciplinary team. Colorectal carcinoma is most commonly generalized into nodules, liver, lung, peritoneum. It is an incurable disease. In the treatment of metastatic colorectal cancer chemotherapy and targeted treatment (according to the mutation status of RAS, BRAF) are used. An important part is also cooperation with the surgeon - liver metastasectomy, pulmonary metastases (primarily or after previous non-adjuvant cancer treatment); methods of metastasis treatment by catheter ablation or microwave ablation.

Spectrum of cytostatics used in the treatment of colorectal cancer (both adjuvant and palliative) includes mainly fluoropyrimidines: 5-fluorouracil; or an oral derivative capecitabine, other formulations widely used are oxaliplatin, irinotecan and combinations thereof. In highly pre-treated patients, a new cytostatic agent, tipiracil / trifluridine, may be given.

Another possibility of treatment are preparations of targeted (biological) therapy. They are monoclonal antibodies binding to specific receptors (cetuximab and panitumumab: anti-EGFR, bevacizumab: anti-VEGF, aflibercept: solubile VEGF receptor), and a family of tyrosine kinase inhibitors (regorafenib – blocking a number of intracellular kinases and signaling pathways).

For monoclonal antibodies, it is necessary to know the mutation status of RAS and BRAF oncogene, since anti-EGFR preparations are completely ineffective in mutated RAS and, in addition, their application is associated with lower survival compared to chemotherapy without monoclonal antibodies, with the exception of anti-VEGF preparations, which can be administered in both mtRAS and wild type RAS. The combination of anti-EGFR and anti-VEGF preparation concomitantly is not recommended due to toxicity and lower survival of patients treated with this combination. Sequential administration, on the other hand, is standard in the continuous care of patients with generalized colorectal cancer. Due to advances in imaging, surgery, oncological and supportive care, the median survival of patients with generalized colorectal cancer is now approaching 30 months.

Rectum

The rectum can be divided anatomically into the lower (up to 5 cm), middle (5–10 cm) and upper (10–15 cm) from the anal verge. For small tumors (T1) local surgical or endoscopic procedures are possible. In early but more advanced stages (T2) the possibility of primary surgery with postoperative chemotherapy and radiotherapy according to definitive histology. In more advanced tumors: T3 N1, evaluated according

to MRI of pelvis, EUS is recommended for neoadjuvant chemoradiotherapy followed by surgery. As rectal tumors tend to recur locally, the therapeutic effort is aimed at preventing these recurrences. Neoadjuvant radiotherapy and chemoradiotherapy have proven to be good methods that can significantly reduce the number of local recurrences. The reason for neoadjuvant chemoradiotherapy is lower toxicity of the treatment to the patient, possibility of tumor downstaging and possibility of more sphincter-sparing procedures.

Surgical treatment of rectal tumors involves resection of the rectum, mesorectum from surrounding structures in the lesser pelvis. This procedure is called total mesorectal excision (TME). By introducing this type of operation in combination with preoperative cancer treatment, the number of local recurrences of rectal cancer in the lesser pelvis was significantly reduced. If resection cannot be performed for low tumor placement, rectal amputation (abdominoperineal resection - Miles operation) with permanent stoma is performed. The alternative in patients refusing surgery, stoma, or surgery contraindicated for internal comorbidities the possibility is definitive chemoradiotherapy.

19.8 Post-treatment complications

Post-treatment complications are related to the method of therapy used. Surgical treatment may be acutely accompanied by bleeding, peritonitis, shock, and injuries to important organs. Of the late complications, the most common are intestinal stenosis in anastomosis, adhesions and sphincter disorders. If subtotal or total colectomy is required, rapid peristalsis, frequent diarrhea and weight loss are typical. As almost always with irradiation of lesser pelvis, radiotherapy is characterized by acute tenesmus and diarrhea, which disappear after the end of therapy. Late complications may include chronic enteritis / colitis accompanied by diarrhea or passage disorders due to post-radiation stenosis of the intestinal loops. Chemotherapy is associated with haematological toxicity, nausea, vomiting and diarrhea, which are typical of preparations containing 5-FU, neurotoxicity with oxaliplatin and diarrhea with irinotecan.

19.9 Follow-up

Regular follow-ups are necessary. Regular follow-up is necessary. Usually every 3 months during the first two years after treatment, every 4 months during the 3rd year, every 6 months 4-5 years after treatment and then once a year. In addition to basic examinations, such as clinical examination, blood count, biochemistry, tumor markers and endoscopic controls are required (control colonoscopy a year after surgery, in case of incomplete colonoscopy prior to surgery due to obstruction or acute surgery in the ileum, another colonoscopy is indicated as soon as possible). Imaging examinations are indicated according to the severity of the disease.

19.10 Prognosis

Prognosis is given mainly according to the extent of the tumor – by determining the TNM classification – i.e. depth of the invasion through the intestinal wall (T), involvement of the lymph nodes (N) and presence or absence of metastases (M). Five-year survival rates are reported to be about 90% for stage I, about 66% for stage II, and only about 10% for stage IV (generalization of the disease).

20 ANAL CARCINOMA

Martina Kubecová, Markéta Šejdová

20.1 EPIDEMIOLOGY

Anal carcinoma belongs to uncommon malignant tumors, in Czech republic it makes up less than 1-2% of GIT tumors. It is more often diagnosed in women than in men. Incidence in the Czech Republic is gradually increasing, but mortality fortunately stagnates.

20.2 ETIOLOGY

Infection with sexually transmitted human papillomaviruses, oncogenic HPV16 and 18 is a key risk factor for tumor etiology. The prevalence of population is significant and infection is proven in up to 80 percent of patients with anal cancer. The issue of anal cancer is topical and serious, especially since it has been shown to be associated with sexually transmitted infection. Latencies in the range of decades from an infection of oncogenic viruses to the outbreak of cancer can be assumed. In the future, a reduction in incidence can be expected due to the higher rates of HPV vaccination. Other risk factors include smoking and immunosuppression of the patient for any cause.

20.3 SYMPTOMATOLOGY

Symptoms such as bleeding, pain, rectal pressure and anal discomfort are present. The diagnosis is delayed because these symptoms are mostly attributed to benign affections (whether by the patient or by the doctor). Shame also plays a role in delayed diagnosis.

20.4 DIAGNOSTICS

The examination includes a thorough examination of the rectum, an endoscopic examination describing the size of the lesion, an assessment of whether the tumor will grow into adjacent organs and biopsy collection. In women, gynecological examination as well. An additional examination is an anorectic endosonography to assess the depth of invasion and determine is peri-rectal nodes are affected. Ultrasound is used to assess the inguinal lymph nodes; if a tumor is suspected, a biopsy is recommended.

Another examination is pelvic CT to determine the extent of the finding and determine the involvement of pelvic and inguinal nodes.

To assess and exclude eventual metastatic involvement, the patient should be subjected to CT or ultrasound of the liver and X-ray of the lungs.

20.5 DIFFERENTIAL DIAGNOSTICS

It is necessary to distinguish a number of benign affections such as hemorrhoids, absceses, fistulae and peri-rectal affections, as well as malignant tumors, such as rectal adenocarcinoma with ingrowth into anal sphincter. The final differentiation will be done by histological examination.

20.6 Pathology

Most anal tumors are squamous cell carcinoma, rarely cloacogenic carcinoma, basaloid carcinoma, and transitional zone carcinoma. Small cell carcinoma, melanoma and adenocarcinoma may be an unusual finding in the anus.

20.7 Therapy

Surgical treatment

Previously considered standard, it is now reserved for small superficial lesions. Abdominoperineal resection with permanent stoma is reserved for local recurrence and tumors poorly responsive to conservative treatment, i.e. persistence of the tumor with prior radiochemotherapy.

Radiotherapy

It is in most cases a method of choice. External radiotherapy to the lesser pelvis and inguinal lymph nodes is usually combined with concomitant chemotherapy. Cytostatics include cisplatin, fluorouracil and mitomycin. Radiotherapy uses a combination of external and interstitial techniques as a boost on the residual tumor area. Anal carcinomas respond well to this treatment and complete remission is expected in 80-90% of patients. Anal carcinomas regress gradually, complete remission may occur 3 months or more after the end of treatment.

20.8 Post-treatment complications

Acute – during and after radiotherapy, the patient feels the urge to defecate and has a diarrhea. Beside that, acute skin reactions sometimes occur in the form of quite extensive desquamation and epitheliolysis with secretion in the irradiated area, especially in obese patients. However, this reaction subsides quickly.

Late complications may include sphincter insufficiency, radiation proctitis and enteritis and possibly stenosis or ulceration of small intestine loops. However, late-onset side effects are very rare with newly used radiation techniques and adherence to all treatment recommendations. However, the worst complication is tumor recurrence, so it is always necessary to use tumoricidal doses of radiation in order to minimize the number of recurrences.

20.9 Follow-up

Follow-up serves for early detection of recurrence or generalization of the tumor. It is performed at short intervals (3 months) for 2 years after treatment, when the disease is most likely to relapse. Later, the inspection intervals may be longer.

It includes careful per rectum examination (per vaginam in women), palpation of the inguinal area, anoscopy and biopsy of suspected relapse. Restaging of the disease includes abdominal and pelvic CT scan and lung x-ray.

20.10 PROGNOSIS

Prognosis always depends on the lymph node involvement and the stage of the disease – in T1 and T2 tumors, the 5-year survival is more than 80%. In diseases with a nodal positivity, the 5-year survival is about 40%.

21 KIDNEY CARCINOMA

Eva Kindlová

21.1 EPIDEMIOLOGY

Malignant tumors of renal parenchyma account for 1–2% of all malignant tumors in the adult population, the most common being carcinoma. Incidence in the Czech Republic is steadily rising and is reported to be the highest in the world. Tumors occur in all age groups, but the highest incidence is in the 5th - 7th decade. It affects men about twice as often as women.

21.2 ETIOLOGY

Risk factors for the development of kidney cancer are obesity, smoking and antihypertensive therapy. Hereditary-linked kidney cancer is also known. The best known is the autosomal dominant disease – von Hippel-Lindau with a familial occurrence of kidney cancer. Cause of this disease is the loss of VHL gene on the short arm of the 3rd chromosome.

21.3 SYMPTOMATOLOGY

In about half of the cases, renal cancer is completely asymptomatic and is found accidentally during, for example, ultrasonographic examination of the abdomen. The clinical symptoms can vary and can be divided into **local**, **locoregional** and **generalized**.

Local – microscopic or macroscopic hematuria is the most common symptom. Classical, often described triplet of symptoms (macroscopic hematuria, pain and palpable tumor) occurs in less than 10% of patients.

Locoregional – these symptoms usually occur in locally advanced tumors:

- dilated collateral veins, edema of the lower extremities,
- pulmonary embolism in the case of obstruction of inferior vena cava,
- acute varicocele.

General – may be present in generalized disease, but are also part of paraneoplastic syndromes in localized disease:

- fatigue, anorexia, fever, weight loss to cachexia,
- anemia but also erythrocytosis, hypertension, liver dysfunction (Stauffer syndrome),
- hypercalcaemia, amyloidosis,
- in metastatic spread, symptomatology depends on the affected site
    - skeleton - pain, pathological fractures,
    - lungs - shortness of breath, cough,
    - CNS - headache, vertigo, nausea, confusion…

21.4 Diagnostics

Diagnosis is set based of the following examinations:

a) physical exam
b) urine examination – chemical + sediment
c) complete blood count, sedimentation, blood biochemical examination
d) ultrasound – basic imaging method – finding solid expansion in kidney parenchyma, its extent, differentiation from cyst, sometimes finding on renal and inferior vena cava, finding in liver parenchyma
e) CT with contrast medium administration – clarifies previous findings and evaluates the condition of regional lymph nodes and adrenal glands and finding on the second kidney
f) MRI does not provide any other significant information compared to CT, however it can be used in case of allergy to contrast agent or for detailed imaging of thrombus in inferior vena cava
g) angio-CT only in indicated cases when considering the possibility of partial renal resection or nephrectomy in anatomical abnormalities – e.g. ren arcuatus
h) X-ray of the lungs or lung CT – to exclude metastatic involvement; or lung scintigraphy – to exclude pulmonary embolism. This should be done for all more advanced findings.
i) Brain CT, skeletal scintigraphy – in case of clinical suspicion of generalization to these organs
j) other specialized examinations according to clinical findings

21.5 Differential diagnostics

In the case of an ambiguous finding for kidney cancer, it is possible to consider another tumor disease based on other structures of the abdominal cavity, e.g. a benign tumor or a cyst, inflammatory processes or injuries - all of these can usually be ascertained by previous examinations. The definitive diagnosis will be clearly determined by histological examination.

21.6 Pathology

The most common variant of kidney cancer is clear cell renal cell carcinoma, which is based on epithelial cells of the proximal tubule - it accounts for about 75% of all kidney tumors. Other variants include papillary renal carcinoma (10-15%), chromophobic renal carcinoma (5%) and other, much rarer tumors.

21.7 Therapy

The basic and only curative treatment of kidney cancer is **surgery**. In case of radical intervention in localized disease, no further treatment is indicated, only follow-up. Kidney cancer can cause metastases – often to the lungs, CNS, skeleton, liver, skin, subcutis, lymph nodes and adrenal glands or can cause recurrence in previous tumor site. If possible, surgical removal of metastases and continued systemic therapy – **biological therapy or immunotherapy** – is indicated. **Radiotherapy** may have a very good palliative effect in metastases located mainly in the CNS, skeleton or recurrence in site. Symptomatic treatment is also important and can significantly improve the general condition of the patient.

21.7.1 Local treatment

Radical surgical treatment – in localized disease

- Radical nephrectomy
- Local recurrence

Palliative surgical treatment – in metastatic renal cell carcinoma, in case of local recurrence

- palliative nephrectomy is indicated if there are conservatively unsolvable local symptoms such as non-controllable bleeding,
- cytoreductive nephrectomy is indicated individually depending on the general condition of the patient and the extent of the disease and carried out before systemic treatment is initiated,
- in the case of a limited number of operable metastases, their surgical removal is indicated. Surgical removal of metastases is recommended when affecting at most two organ sites.

21.7.2 Systemic treatment of metastatic kidney cancer

Kidney cancer is chemoresistant, except for the sarcomatoid variant, where chemotherapy can be used to treat the sarcomas. Even here, however, the response to treatment is very low.

Systemic renal tumor therapy is based on **biological (targeted) therapy** using **tyrosine kinase inhibitors TKI:**

- Sunitinib – inhibitor of platelet-derived growth factor receptors, vascular endothelial GF receptors, stem cell factor receptor - KIT,
- Pazopanib – a potent multi-site TKI – at vascular endothelial growth factor receptors – VEGFR, a platelet-derived growth factor receptor (PDGFR) inhibitor,
- Sorafenib – inhibits the activity of target receptors present in tumor cells and in the vascular system of the tumor,
- Cabozantinib – a selective inhibitor of vascular endothelial growth factor receptor (VEGFR).

monoclonal antibody:

- Bevacizumab - binds to a protein called vascular endothelial growth factor – VEGF – a key factor in abiogenesis, thereby inhibiting VEGF binding to its receptors on the surface of endothelial cells – neutralizing receptor activity, leading to regression of tumor vascular network, normalizing of persistent vascular network and prevention of new tumor formation.

mTOR inhibitors:

- Temsirolimus - binds to intracellular protein (FKPB-12) and the protein / temsirolimus complex binds to mTOR, inhibiting it and preventing its activation, which controls cell division,
- Everolimus - selective inhibitor of mTOR.

Another very important systemic treatment suitable for kidney tumors is **immunotherapy:**

- Interleukin-2 - mimics the activity of natural human interferon alpha - antiviral effects. Detailed mechanism of antitumor activity is not yet known, however known is a significant decrease in DNA, RNA and protein synthesis with antiproliferative effects of various types of human tumors,

- Nivolumab - a human monoclonal antibody that binds to the PD-1 receptor (programmed death receptor) and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity and participates in the control of the T-cell immune response. Binding of the PD-1 receptor to PD-L1 and PD-L2 ligands that are expressed on antigen-presenting cells or may be on tumor or other cells in the tumor microenvironment results in inhibition of T-cell proliferation and blockade of cytokine secretion. Nivolumab enhances the T-cell response, including the anti-tumor response, by blocking PD-1 receptor binding to PD-L1 and PD-L2 ligands.

Different **scoring systems** are used for renal cancer and their result determines categorization of the patient into his appropriate prognostic group.

The MSKCC scoring system of 2002 (Motzer et al. 2002) – Table 1 is used in the first line of targeted multikinase inhibitor therapy and bevacizumab, and modified MSKCC criteria (Hudes et al. 2007) for treatment with temsirolimus – Table 2.

Tab. 1 MSKCC scoring system from 2002: applies to TKI and bevacizumab treatment

LDH > 1.5 times the upper limit of the standard
hemoglobin < lower limit of the standard
corrected serum calcium > 2.5 mmol / l
Karnofsky index ≤ 70 %
interval <1 year from diagnosis to start of systemic treatment

Good prognosis: no factor
Medium prognosis: 1 or 2 factors
Poor prognosis: 3 or more factors

Tab. 2 Scoring system for temsirolimus (Hudes et al. 2007)

LDH > 1.5 times the upper limit of the standard
hemoglobin < lower limit of the standard
corrected serum calcium > 2.5 mmol / l
Karnofsky index ≤ 70 %
2 and more affected organs
interval <1 year from diagnosis to start of systemic treatment

Poor prognosis: presence of 3 or more factors

In patients with a good or moderate prognosis, we have the possibility to start treatment with TKI inhibitors - sunitinib or pazopanib or a VEGF inhibitor (in combination with interferon alpha). In patients with poor prognosis, we need to use mTOR or TKI inhibitors. Currently, other drugs can also be used in the case of progression of the disease - such as everolimus, cabozantinib, axitinib, sorafenib, and recently also nivolumab.

21.8 POST-THERAPEUTIC COMPLICATION

As with other tumors, the treatment complications depend on the treatment modality used and its extent. In almost every case of kidney cancer, the patient undergoes nephrectomy and the solitary kidney can be further damaged by systemic therapy - immunotherapy and biological therapy, which

creates a risk of renal insufficiency. This treatment can also cause leukopenia, thrombopenia or anemia, changes in liver and mineral tests, allergic reactions, hypertension, proteinuria and pneumonia.

Radiotherapy used in the treatment of kidney cancer is always used with palliative intent and therefore complications due to this treatment should not occur at all.

21.9 Follow-up

The follow-up of patients after treatment is permanent. Initially twice a year and later once a year, a follow-up examination, or in the event of complications at any time. In the more advanced stages, controls are more frequent and in generalized diseases are more frequent as required by the patient's condition.

Controls include medical history, physical examination, sampling - erythrocyte sedimentation, complete blood count, biochemistry, urine examination and, at fixed intervals, X-ray of the lungs and abdominal CT, usually 1-2 times a year.

Other examinations such as skeleton scintigraphy and brain CT are indicated according to the patient's condition and complaints.

21.10 Prognosis

Clinical stage and disease grading are critical to patient prognosis. Other factors affecting survival are – general patient status, delayed treatment since the diagnosis, number of metastases and their location, weight loss and previous cytotoxic treatment. In stage I - II, when tumors are limited to the kidney, 5-year survival is about 90 %. Stage III, when tumors do not exceed Gerota's fascia or spread into the vena cava, 5-year survival is between 30-75 %. Stage IV patients, when tumors spread beyond Gerota's fascia, metastases are in more than one lymph node or are distant, 5-year survival rate is only 10 %.

22 MALIGNANT TUMORS OF THE TESTES

Eva Kindlová

22.1 EPIDEMIOLOGY

Testicular germ cell tumors (GCTs) are characterized by a significantly different racial, geographical and age distribution. About 90% of GCTs are found in the white race, 6.6% in blacks and the rest in other races. The highest incidence is in Denmark, the lowest in the Far East; the incidence is increasing in economically developed countries. Approximately half of the cases are diagnosed within a narrow age range of 25–30 years. Occurrence in children and in the older age groups is significantly less represented. Although rare, for the 25–30 age group, GCTs are the most common cancer and account for approximately 1% of all malignant tumors in men.

22.2 ETIOLOGY

Cryptorchidism is an important risk factor for the subsequent development of a testicular tumor. Early orchidopexy is an effective preventive procedure. Pre- and perinatal risks factors are fetal exposure to diethylstilbestrol and premature labor. There are also genetic risk factors in connection with some deviations of somatosexual development, such as: Klinefelter syndrome, some forms of gonadal dysgenesis, etc. The influence of dietary factors - high energy food intake, high amount of saturated fats and cholesterols in diet is also reported.

22.3 SYMPTOMATOLOGY

Although testes are easily accessible for a clinical examination, more than 1/3 of patients come in advanced or disseminated disease stage. The simplest method of cancer detection is a self-investigation, but sufficient training of population is required because nescience of anatomy and patient's shame often cause the diagnosis to be delayed for several months.

Local symptoms:

- painful testicular enlargement or painful testicular resistance,
- pain during rapid growth,
- feeling of heaviness and discomfort in the scrotum.

Locoregional symptoms (usually accompany locally advanced tumor)

- pain in the lower abdomen or groin.

General symptoms (in generalized disease, but may also be part of paraneoplastic syndromes in a localized tumor):

- gynecomastia,
- fatigue, anorexia, fever, cachexia,
- anemia, hypertension, liver dysfunction, hypercalcaemia, amyloidosis
- algic syndrome in skeletal metastases.

22.4 DIAGNOSTICS

It is based on the following examinations:

a) ultrasound examination of the scrotum, groin, mammary gland and cervical and supraclavicular nodes
b) if a testicular tumor is suspected, surgical revision and orchiectomy from the inguinal approach are indicated immediately,
c) Lab testing for values of tumor markers - AFP, beta-HCG, LH, biochemistry and CBC,
d) CT - chest, abdomen, pelvis to exclude metastases in the lungs, lymph nodes of the mediastinum, retroperitoneum, involvement of parenchymatous organs, alternative can be PET / CT
e) Bipedal lymphography for detecting involvement of the lymph nodes of retroperitoneum is a rarely used and obsolete method.
f) Brain CT and skeletal scintigraphy are only indicated when there is a clinical suspicion for metastases at these sites.

22.5 DIFFERENTIAL DIAGNOSTICS

We need to consider inflammation, benign tumors, abscesses, etc.

22.6 PATHOLOGY

Germinal tumors represent 92-96% of testicular cancers. According to the histological type, we classify GCTs into seminomas that originate from partially differentiated seminal canal cells and nonseminomas. Depending on their origin, we further classify nonseminomas into **embryonic carcinomas** - derived from a pluripotent germ cell that is directly transformed into a tumor cell. When the cell is partially differentiated into trophoblastic elements, the tumor is called **choriocarcinoma** or **yolk sac tumor**. Pluripotent germ cell transformation into somatic cells of ectoderm, mesoderm and entoderm is called **teratocarcinoma**. Pure variants containing only one type of tumor tissue are rare. Mixed forms containing different percentages of seminomas and different types of non-seminomas are more common.

In case of mixed non-seminoma, although there is only a minimal proportion of non-seminoma component (eg. 5% of embryonic tumor), treatment and follow-up is always based on non-seminoma component.

CGCs are most commonly found in testes (more than 90%). Extragonadal occurrence is most common in retroperitoneum, mediastinum and pineal gland. In 1-2% CGCs may have bilateral incidence.

Carcinoma in situ is a relatively common finding in CGCs.

Prognostic scheme

Seminomas

Good prognosis - tumor in primary localization, except the lungs, without visceral metastases.
Intermediate prognosis - any primary localization with non-pulmonary visceral metastases.
No poor prognosis.

Nonseminomas

Good prognosis - primary tumor in testis / retroperitoneum (RP) - and without visceral metastases (not including lungs) and the following TM values: AFP <1,000 µg / ml, HCG <5,000 IU / l, LDH <1.5 x N.
Intermediate prognosis - primary tumor in testis / retroperitoneum (RP) - and without visceral meta (not including lungs) and the following TM values: AFP> 1,000 and <10,000 µg / ml, HCG> 5,000 IU / l, LDH <10 x N.
Poor prognosis - primary tumor in mediastinum or visceral metastases other than pulmonary or following TM values: AFP> 10,000 µg / ml, HCG> 50,000 IU / l, LDH> 10 x N.

22.7 THERAPY

Therapeutic modalities

- surgery
- systemic treatment - chemotherapy
- radiotherapy
- palliative, symptomatic treatment

Treatment strategies differ for seminomas and non-seminomas.

Surgery

- the basic treatment procedure is always radical inguinal orchiectomy (IO). In exceptional cases with T1 tumor, procedure saving testes are possible. The procedure should be performed within 24-48 hours after diagnosis.

Radiotherapy

- seminomas and nonseminomas are radiosensitive tumors, therefore the radiation doses used are relatively low - in seminomas 20–30 Gy, in case of recurrence or persistence, then up to 36 Gy; 40 Gy (5 fractions per week, mostly 1.8 Gy per fraction). The extent of irradiation depends on the extent of the disease - paraaortic LN, ipsilateral and paraaortic LN, pelvic and paraaortic LN, mediastinum, other metastatic area (CNS, lungs…).

Systemic treatment

- cryopreservation of semen is always recommended prior to systemic treatment, especially in younger patients. The treatment is always indicated in non-seminomas, the only exception is stage IA and IB when strict monitoring only, is possible.

Cytostatics used: on the basis of platinum (P), etoposide (E), bleomycin (B) - the "gold standard" remains the combination of BEP, or EP.

Other cytostatics used - paclitaxel, carboplatin, gemcitabine, oxaliplatin, vinblastine - are used in relapse of the disease.

Treatment of seminomas

Stage IA (pT1, N0, M0, S0), IB - (pT2-pT4, N0, M0, S0)

- In 15–20% subclinical dissemination is present , usually in retroperitoneum.
- Risk factors include invasion of the rete testis and / or a tumor larger than 4 cm.
- IO and subsequent strict monitoring - recommended for the pT1-3 stages without risk factors.
- IO and adjuvant CHT (preferred method) - 1-2 cycles of carboplatin.
- IO and adjuvant radiotherapy of paraaortic lymph nodes (20 Gy).

Stadium IS

Suspicion for regional node metastases or remote dissemination, not detectable by imaging methods.

- IO and monitoring of tumor markers and repeat CTscan every 2-3 months.
- IO a CHT – 3 cykly BEP,
- IO and radiotherapy of paraaortic lymph nodes (30 Gy).

Stadium IIA – any pT/pTX, pN1, M0, S0

- IO and radiotherapy of paraaortal + ipsilateral iliac nodes (30 Gy),
- IO and curative CHT – 3x BEP nebo 4x EP.

Stadium IIB – any pT/pTX, N2, M0, S0

- IO and radiotherapy of paraaortal + ipsilateral iliac nodes (36 Gy),
- IO and curative CHT – 3x BEP nebo 4x EP.

Stadium IIC – any pT/pTX, N3, M0, S1 a III – pT/pTX, any N, M1a,1b, any S

- Good risk – IO a CHT – 3x BEP or 4x EP,
- Intermediate risk – IO a CHT 4x BEP or 4x VIP (in contraindications of bleomycin).

Treatment of nonseminomas

Stadium IA (pT1, N0, M0,S0), IB (pT2-pT4, N0,M0, S0)

- IO and subsequent strict monitoring - recommended for pT 1 tumors, without RF
- IO a adjuvant CHT (preferred way) - 1-2 x BEP, in Europe, preferred over RPLND (excluding teratomas),
- IO and primary nerve-sparring RPLND, in pN0- monitoring, pN+ - CHT - 2x BEP or 2x EP, monitoring only when a mature teratoma is detected.

Stadium IS

- IO – 3x BEP or 4x EP, after CHT in neg. TM monitoring.

Stadium IIA – any pT/pTX, pN1, M0, S0 a IIB – any pT/pTX, N2, M0, S0

- negative TM – CHT or RPLND,

- Curative CHT – 3x BEP or 4x EP, after CHT and neg. TM and with no residue - monitoring, when residue at CT present - RPLND,
- Primary nerve sparing RPLND: pN0 monitoring, pN1a2 – CHT – 2x EP or 2x BEP, monitoring only in case of teratoma, pN3 – CHT – 4x EP or 3x BEP,
- Positive TM – primary CHT 3x BEP or 4x EP.

Stadium IIC a III

- IIC, IIIA – good risk – 3x BEP or 4x EP,
- IIIB – intermediate risk – 4x BEP or 4x VIP,
- IIIC – poor risk – 4x BEP or 4x VIP.

22.8 Post-treatment complications

Posttreatment complications depend on the type of the treatment.

After CHT, toxic lung injury (bleomycin), impaired renal function or ototoxicity (platinum) and neurotoxicity are common.

Complications after RT are not frequent due to the low dose administered. The problem is that treated are mostly young patients and especially in case of combined treatment,occurence of secondary tumors is possible, in worse case scenario also sterility (hence cryopreservation is performed before the treatment). Other complications may be related to the surgical procedure performed (retrograde ejaculation, etc.).

22.9 Follow-up

It should be permanent and includes clinical examination, laboratory testing for tumor markers, CT scan, ultrasound, PET (necessary especially in case of persistence of the tumor before planned surgery for detection of viable neoplasia).

22.10 Prognosis

A large portion of testicular tumors can be cured permanently. The extent of the disease according to the TNM classification determines the prognosis - it is more favorable in T1-T2 tumors than in T3-4 stages. The presence of peritumoral vascular invasion worsens prognosis as well as histological findings of embryonic carcinoma. In metastatic tumors, the high level of tumor markers and the presence of extra-pulmonary visceral metastases are an unfavorable prognostic factor.

23 PROSTATE CANCER

Eva Kindlová, Renata Soumarová

23.1 EPIDEMIOLOGY

Prostate cancer (PCCAP) is the second most common malignant disease in men. In men over 50, it accounts for approximately 16% of all cancers. Prostate tumors have a significantly differrent racial, geographical and age distribution. PC has the highest incidence in the black population in the US, in the white race the incidence is a half and the lowest incidence can be found in population in the Far East. In 2005, PC was the most frequently diagnosed cancer. This is explained by an aging of population and improved diagnostics methods. On the other hand, mortality in the PC is rising only slightly and in 2005 it even lowered.

23.2 ETIOLOGY

Genetic predispositions are a significant risk factor. Family incidence increases the risk 3x when one family member affected, 5x and 11x in two or more affected family members. Hereditary dependence is autosomally dominant and in these cases PC is diagnosed in a younger age groups. Nutrition and dietary habits also play an important role, with an effect of up to 30-40% being reported. Etiopathogenesis is unknown.

Prostate adenocarcinoma is a hormone-dependent, dependent tumor, but its parts differ in sensitivity to androgens. The basic hormonal stimulus for prostate cell replication is testosterone and even more effective is dihydrotestosterone. DHT is synthesized from testosterone by the enzyme alpha-5-reductase. A large proportion of prostate tumors, which are classified as a localized disease are undervalued and the disease is in reality generalized - most often metastases in the skeleton or lymph nodes are present, less often then mets in soft tissues.

23.3 SYMPTOMATOLOGY

In early stages of the tumor, the patient is asymptomatic, sometimes the first presentation are distant metastases. Local or locoregional symptoms are a sign of an advanced disease.

Locoregional symptoms:

- macroscopic or microscopic hematuria,
- miction problems (both collection and emptying),
- hematospermia,
- erectile dysfunction,
- priapism.

General symptoms may be a symptom of generalized disease, but also part of paraneoplastic syndromes in localized disease:

- algic syndrome in skeletal metastases,
- pathological fractures,
- myelosuppression anemia in skeletal metastases,

- fatigue, anorexia, febrile conditions, cachexia,
- ileous conditions,
- disseminated intravascular coagulation, thrombosis.

23.4 Diagnostics

All examinations and test performed should always be appropriate to the patient's quality of life, survival and associated treatment options. There is no point in burdening the patient with an intensive examination process when it is clear that treatment is no longer possible.

However, it is always necessary to perform **general physical examination**, including per rectum examination (the tumor may be palpable from 0.2 ml), in larger tumors we assess the extent of the disease based on the changes in a gland consistency, borders, consistency, surface smoothness and if the gland is mobile.

Measuring of PSA values (prostate specific antigen) and other examinations - free PSA values, PSA density (ratio of prostate weight to PSA values). Recently, kinetics of serum PSA levels (PSA velocity and doubling time) have also been ascribed great importance. However, PSA is not an unequivocal indicator of prostate cancer - there is no low PSA threshold to rule out the presence of cancer.

Transabdominal ultrasound - prostate size, bladder filling, liver, urinary and renal ducts assessment, lymph node metastases in liver or lymph nodes.

Transrectal ultrasound (TRUS) - evaluates the structure of the gland, but without biopsy it is not possible to clearly distinguish carcinoma from benign hyperplasia; facilitates targeted prostate biopsy, helps to determine clinical T stage - extraprostatic spread, infiltration of seminal vesicles.

Prostate biopsy - performed transrectally under sonographic control.

Re-biopsy is indicated within range of 3–6 months if the first biopsy is negative and there is an increase in PSA value; can be done specifically after MR and ultrasound examination.

Lesser pelvic CT scan does not specify diagnosis, but as well as MRI - may be of importance for the assessment of primary tumor, infiltration of surrounding structures, lymph node finding (definite assessment of LN involvement can only be determined by a pelvic lymphadenectomy).

Scintigraphy of the skeleton, possibly in combination with X-ray for suspected foci, serves to detect skeletal metastases.

Choline PET CT – in case of PSA elevation and in cases of undetectable findings by examinations such as MRI, CT scan or scintigraphy of the skeleton, in suspicion for generalization.

23.5 Differential diagnostics

Due to their symptoms, benign hyperplasia and prostate cancer can often be confused. Also, prostate inflammation can resemble prostate cancer.

23.6 PATHOLOGY

Histopathologically, more than 95% of prostate cancer found are **adenocarcinomas**, which originates from luminal cells of prostatic acinar cells (acinous, cribriform, solid pattern). It is usually hormone-dependent. On the other hand neuroendocrine cell tumors are primarily hormone resistant. Other variants - squamous cell, intraductal, endometrial, small cell, mesenchymal tumor and lymphomas are rare and usually hormone refractory.

In TNM classification, 4 Mostoffi anaplasia degrees are distinguished, but in practice the Gleason system, which divides tumors based on their anaplasia grade or differentiation into 5 categories is used. More accurate and commonly used is the Gleason score, which is the sum of the two most represented degrees of differentiation. The score can then be from 2 to 10, when GS greater than 7 is considered risky and is associated with poor prognosis and governs the treatment. This usually means use of more treatment modalities, including hormonal treatment.

23.7 THERAPY

Multiple treatment modalities and combinations are used in the treatment of prostate cancer. The choice depends on the progress of the disease, age of the patient, his co-morbidities and last but not least on the patient's wishes. Monitoring or active monitoring, local treatment - surgical treatment, radiotherapy and systemic treatment - hormonal treatment and chemotherapy can all be used.

Monitoring

- **watchful waiting** – the patient's general condition and prognosis of the disease are important factors in deciding about proper protocol choice. Unlike "active surveillance", watchful waiting protocol does not include recommendations for re-biopsies, but only PSA monitoring and a clinical examination every 4-6 months. This strategy is suitable for patients with significant co-morbidities limiting their overall survival rate.
- **active surveillance -** a patient with cT1-2a tumor with low PSA (≤ 10 µg / l), low GS (GS = 6) and smaller tumor size (≤ 2 positive samples) is suitable for active follow-up and delayed local treatment. Treatment should be initiated at first signs of disease activity (eg. GS progression in rebiopsy after 4–6 months at PSA doubling time <3 years, at signs of local progression) or as desired by the patient.

Surgical treatment

- radical prostatectomy (RAPE) - in patients with localized disease, life expectancy of at least 10 years, PSA < 20,
- pelvic lymphadenectomy - recommended in PSA level >10, and GS ≥7,
- widespread pelvic lymphadenectomy (obligatory in moderate risk carcinoma with a risk of lymph node involvement > 5% by nomogram,
- surgical approaches - open , laparoscopic, robotic RAPE are comparable in terms of cancer safety,
- in indicated cases, nerve sparing surgical procedures.

Radiotherapy

- **Curative radiotherapy** with a dose of 76–80 Gy, depending on the size of the irradiated volume. In localized disease - when limited only to the prostate, low PSA and GS <7, only the prostate and seminal vesicle bases can be irradiated (in doses of 20 x 3 Gy or 27 x 2.5 Gy, with 27 x 2.35 Gy - hypofractionation or normo-fractionation 40 x 2 Gy). For radical radiotherapy it is always necessary to use the latest radiotherapy techniques including IGRT.
- **Brachytherapy** - in the form of permanent or temporary implantation, alone or in combination with external RT. The table shows the possible inclusion of BRT into the treatment algorithm in individual risk groups.

	Low risk	**Medium risk**	**High risk**
PSA	0-10 ng/ml	10-20 ng/ml	20 ng/ml and more
T stadium	T+-2a	T2b	T2c-T4
Gleason score	6 and less	7	8 and more
Optimal management	▪ active surveillance ▪ RAPE ▪ External RT ▪ LDR BRT	▪ RAPE ▪ External RT +/- HT ▪ External RT + HDR BRT +/- HT	▪ External RT + HT ▪ RAPE +/- adjuvan or salvage RT +/- HT ▪ External RT + HDR BRT + HT

- **External radiotherapy** - used in locally advanced prostate cancer, when there is an indication for irradiation of pelvic lymph nodes and prostate and seminal vesicles (doses of RT to the area of LN of the lesser pelvis - 25-27 x 1.8 - 2 Gy with concurrent application of higher doses to the prostate) and seminal vesicles 27 x 2.5 Gy and 27 x 2.35 Gy, respectively. RT can be combined with hormone therapy - neoadjuvant, concomitant and adjuvant in patients at moderate and higher risk.

Hormonal treatment

- (androgen deprivation therapy ADT) the aim is to achieve testosterone levels as in castration. It can be used with RT, alone as an adjuvant therapy or in palliative therapy.

Hormonal treatments include:

- agonists - LH-RH analogues of natural gonadotropin-releasing hormone (GnRH) - goserelin (Zoladex), triptorelin (Dipherelin),
- gonadoliberin antagonists (Firmagon),
- antiandrogens - bicalutamide,
- orchiectomy.

Chemotherapy

- docetaxel – a cytostatic promoting the incorporation of tubulin into stable microtubules and preventing microtubule depolymerization which is resulting in a significant decrease in free tubulin and thus disrupting microtubular network within cells, which is essential for vital mitotic and interphase cell functions.

- cabazitaxel – it induces disruption of microtubule network in cells - leads to stabilization of microtubules and consequently to inhibition of mitotic and interphase cell functions.

ARTA (androgen receptor target antigen):

- abiraterone acetate - (Zytiga) – selectively inhibits the enzyme 17α-hydroxylase, this enzyme is required for androgen biosynthesis in testicular, adrenal and prostate tumor tissue,
- enzalutamide - (Xtandi) – is a potent inhibitor of androgen receptor signaling that blocks several steps of the androgen signaling pathway.

Treatment of low-risk (cT1-2a and GS 6 and PSA <10) and moderate risk (cT2b and / or GS 7 and / or PSA 10-20) prostate cancer

Treatment is also chosen according to the preference of the informed patient.

RT - brachytherapy and external radiotherapy, monitoring, active monitoring and surgery (RAPE) are suitable.

Treatment of high-risk prostate cancer (cT2c-3 a/nebo GS 8-10 a/nebo PSA > 20)

RT with neoadjuvant, concomitant or adjuvant hormonal suppression, individually combined external RT with interstitial brachytherapy.

RAPE with extended pelvic lymphadenectomy - the patient must be informed of the high probability of subsequent multimodal treatment depending on definitive histology.

Rarely HT alone - in patients unsuitable for curative treatment

Adjuvant radiotherapy after RAPE – is recommended for patients with risk factors - high GS - more than 7, positive surgical margins, positive seminal vesicles, positive lymph node (s) - hormonal therapy or radiotherapy both possible, the most common is a combination of both.

Treatment of generalized disease

Hormone-sensitive - indicated hormone treatment, early or delayed, continuous or intermittent.
Combination therapy - HT and CHT shows very favorable results.

After some time, the disease becomes castration resistant, which is defined by castration testosterone values (< 50 ng / ml) and one of the following criteria: (biochemical progression: 3 consecutive PSA value increases measured at least one week apart, or radiological progression: occurrence of two or more new bone lesions, or soft tissue progression. All patients have LH RH levels lowered to castration levels by hormone analogues or surgical castration.

Chemotherapy is also used in the treatment - docetaxel, in the second line cabazitaxel. It is also possible to use an androgen biosynthesis inhibitor - abiraterone acetate (Zytiga) or an inhibitor of androgen receptor signaling - enzalutamide (Xtandi).

In cases of skeletal metastases, bisphosphonates can be administered, and in patients with symptomatic bone metastases without known visceral metastases, radium 223 can be used.

In indicated cases it is suitable to use external palliative radiotherapy - in bone metastases or in the CNS involvement.

Very important is symptomatic treatment - analgesic therapy, nutrition, psychological treatment.

23.8 POST-TREATMENT COMPLICATIONS

Post surgery complications - thanks to the advanced surgical techniques the number of stress incontinence decreased to about 5–10%, throat stenosis became very rare. Sometimes, however, depending on anatomical conditions, damage to the peroneal nerve, the lumbosacral plexus or the *femoral nerve* is described.

- Complications after radiotherapy are early - during or shortly after irradiation - dysuric complaints, nocturia, diarrhea, exceptionally hematuria. These complications usually resolve very soon.
- The second group of complications, which mostly progress slowly, are so-called late complications related to the GIT and the urinary tract. The most common is radiation proctitis, manifested by tenesmuses, bleeding, flatulence and radiation cystitis - with hematuria and dysuria. These complications most often arise after a few years of treatment.
- The third group of complications is called very late complications - occurring even decades after treatment , mainly the development of secondary carcinomas.

Hormonal treatment, in addition to the changes in red blood count and liver function tests also causes complications related to its therapeutic effect - ie blocking testosterone and can manifest as increased fatigue, deterioration of sexual functions and libido or gynecomastia.

After chemotherapy treatment paresthesia and changes in blood count may persist for a long time.

23.9 FOLLOW-UP

In only-monitored patients without a treatment, once every 6 months PSA levels are measured and per-rectum examination is performed. Biopsy should be performed once a year to determine if there are new, high GS tumor structures.

Patients after treatment - radical prostatectomy, radical radiotherapy or having hormonal treatment are followed up initially after 3 months - PSA examination, physical examination, including per rectum, later once every six months. In disseminated diseases with hormonal treatment, follow up visits are more often, and depending on the patient's complaints, necessary examinations are performed to ensure that the necessary treatment is started in time.

Also, CBC and LFTs should be monitored in patients with hormonal therapy.

After radical radiotherapy, renal ultrasound check and renal function check (urea, creatinine) are also recommended - because of the risk of fibrosis in the lesser pelvis and associated increased risk of ureteric stenosis with subsequent hydronephrosis and renal insufficiency.

In advanced prostate cancer, as well as during stabilized phase of the disease, examinations are required to check the condition of the skeleton - skeletal scintigraphy, alkaline phosphatase level measuring - usually once a year.

23.10 PROGNOSIS

Prognosis of the disease is dependent on its extent determined by TNM classification, Gleason score (GS), and pre-treatment PSA levels. Patient's general condition and age are also important.

In early stages of the disease, 10-year survival rate is reported to be between 75-93%. In case of generalized disease, survival is usually 18–30 months, but thanks to new preparations it can prolong to up to 5 years.

24 MALIGNANT TUMORS OF THE BLADDER

Eva Kindlová

24.1 EPIDEMIOLOGY

In the Czech Republic, bladder tumors are the 6th most frequent cancer in men and the 13th in women. As in other industrialized countries, the incidence is increasing, while mortality remains practically the same.

24.2 ETIOLOGY

The most prominent etiological factor for urothelial cancer is cigarette smoking. In smokers, the incidence of bladder cancer is 2-4 times higher than in non-smokers and tumors have a lower degree of differentiation. Professional risks include contact with aromatic amine substances in the rubber industry, the textile industry, painters and hairdressers. The most significant risk factor for epidermoid carcinoma is schistosomiasis, as well as chronic irritation such as chronic cystitis, lithiasis or catheter.

24.3 SYMPTOMATOLOGY

Symptoms can be divided into local, locoregional and general.

Local symptoms:

- **microscopic hematuria** occurs in almost all patients, **macroscopic hematuria** – painless and often intermittent is the most common symptom that warns of disease (75-80% of patients),
- **various forms of micturition problems** – dysuria, stranguria or urgency – are more often accompanied by advanced disease than early stages.

Locoregional symptoms – usually present in locally advanced disease:

- **lumbalgia** – pain from ureter obstruction,
- **lymphedema** of the lower extremities in massive lymph node involvement.

General symptoms accompanying advanced or generalized disease:

- fatigue, anorexia, cachexia, anemia,
- algic syndrome in skeletal metastases,
- symptoms from affected organs (CNS, hepatopathy, etc.).

24.4 DIAGNOSTICS

If bladder disease is suspected, the following examinations are required:

- Clinical physical examination
- Urine examination - chemically, bacteriologically and cytologically
- Ultrasonography or CT of the bladder and excretory urography
- Diagnostic cystoscopy, including evaluation of transurethral resection (TUR)

In case of suspicion, it is necessary to perform **transurethral resection of suspect site**, which will determine the histological diagnosis including the depth of infiltration of the bladder wall. Subsequent treatment is then derived from these results. TUR has precisely defined rules – extent, depth of resection performed, sites which can be resected even in the case of non-mucosal mucosal findings – prostatic part of the urethra, so-called random biopsy – multiple biopsies from normal-looking urothelium in case of suspected Tis (tumor in situ), but can be replaced by targeted biopsy using fluorescent cystoscopy with 5-aminolevulinic acid. In indicated cases, a second resection is also performed after 2-6 weeks (in multiple and large-scale tumors, in high grading, or in the absence of detrusor muscle in the sample)

Evaluation of the extent of the disease includes X-ray of the lungs, complete blood count and biochemistry, ultrasounds and CT abdomen. In the case of symptoms or demonstrably advanced disease, which cause suspicion of involvement of other organs, further examinations are necessary to exclude generalization – CT of the lung, CT or MRI of the brain, skeletal scintigraphy, etc.

24.5 Differential diagnostics

It is necessary to exclude:

- chronic inflammation,
- acute inflammation,
- benign tumors (e.g. papillomas),
- hematuria for reasons other than those listed above (post-medication),
- clotting disorders.

24.6 Pathology

A tumor of epithelial origin is typical for the bladder. It is based on the urothelial lining of the bladder. The most common type is urothelial carcinoma (in more than 90%). Significantly less frequent are epidermoid carcinoma (infection is a risk factor here) and adenocarcinoma.

Bladder cancer is divided into **non-invasive** or superficial (does not grow into muscle) and **invasive** or infiltrating (grows into muscle) and it is an important factor when choosing the right treatment.

The panurothelial nature of the disease is typical (occurrence is possible in the upper urinary tract, bladder and urethra) and manifestations of this include multiple findings and frequent recurrence.

24.7 Therapy

Therapy is different depending on whether the tumor infiltrates the bladder muscle or not.

24.7.1 Treatment of non-invasive bladder cancers

Treatment modalities:

- transurethral resection TUR,
- intravesical instillation - cytostatics or immunotherapy,
- cystectomy.

The next course of action, i.e. monitoring or intravesical treatment, depends on the risk of recurrence and progression, which we estimate based on prognostic factors:

- Distinction between Ta (non-invasive papillary carcinoma) and Tis (tumor in situ) T1 (tumor affects subepithelial connective tissue),
- Degree of cell differentiation G1 - 3,
- The frequency of previous relapses,
- Number of tumors, areal extent and presence of accompanying site Tis.

Treatment procedures for non-invasive urothelial carcinoma after TUR

- Only follow-ups – low risk tumors – primary, solitary TaG1 and less than 3 cm,
- Intravesical instillation – in patients with moderate risk tumors – Ta(m) (multiple) G1, TaG2, T1G1-2,
  Cytostatics used - mitomycin-C, epirubicin, or BCG vaccine
- Cystectomy in superficial bladder tumors is considered in patients with high-risk types of these tumors when local or intravesical treatment fails.

24.7.2 Treatment of invasive bladder cancers

Treatment modalities:

- surgery,
- chemotherapy - neoadjuvant and adjuvant,
- radiotherapy,
- combination of modalities.

stage II – tumor affects muscle, negative LU - T2a, b, NO
stage III – tumor affects muscle T3a, b, infiltrates prostate, uterus, vagina T4a, NO

1. radical surgery - treatment of choice is radical cystoprostatectomy with pelvic lymphadenectomy in men, in women cystectomy, hysterectomy with adnexectomy and lymphadenectomy with urine derivation.
2. Systemic treatment
   a. neoadjuvant chemotherapy with cisplatin before cystectomy - the aim is to eradicate potential micrometastases or down-staging. Currently, neoadjuvant chemotherapy is preferred to adjuvant.
   b. adjuvant chemotherapy is considered after cystectomy in locally advanced tumors (pT3, pT4) and in the detection of lymphovascular invasion.

   Cytostatics - cisplatin (DDP), methotrexate (MTX), vinblastine (VBL), doxorubicin (DOXO), gemcitabine (GEM) are used.
3. Multimodal bladder sparing procedure – recently, the use of restorative procedures has been on the rise in oncology. In this case, the maximum TUR is followed by chemoradiotherapy – cisplatin and external radiotherapy up to 45 Gy followed by control cystoscopy. If tumor cells are found, the patient is indicated for surgery. If tumor cells are not found, radiotherapy is finished by going up to a radical dose of 65 Gy and followed by dispenzarization.
4. Radical radiotherapy – in the case of an operable tumor, if the patient is not able to undergo cystectomy (for internal reasons or at his own request), radical radiotherapy up to a total dose of 65 Gy is indicated.

a. External radiotherapy EBRT is used, intensively modulated by IMRT – target volume according to the extent of the disease – bladder area or bladder and regional lymph nodes
b. A 25 -28 fraction mode of 1.8-2 Gy + boost 8-10x 2 Gy is used
c. Fractionation can be shortened in elderly patients, patients in a generally poor condition or patients with a higher amount of comorbidities.

24.7.3 Stage IV - locoregional advanced tumors Tx N1-3, M0

- neoadjuvant chemotherapy,
- radical surgical treatment in operable tumors (radical cystectomy and pelvic lymphadenectomy),
- adjuvant systemic chemotherapy is a considered treatment option, especially if neoadjuvant chemotherapy has not been administered,
- radiotherapy - in the case of a residual tumor after cystectomy, radiotherapy is indicated (if the patient is in good condition).

24.7.4 Treatment of generalized bladder cancer - Tx Nx M1

In the case of good overall condition, the following procedures are possible:

- systemic chemotherapy (cis-platinum, carboplatin, gemcitabine, vinflunine, paclitaxel – immunotherapy) (check point inhibitors – atezolizumab, nivolumab, pembrolizumab),
- surgical treatment – in indicated cases it is possible to use surgery as palliative treatment – removal of metastases causing pressure on organs or pain; possible orthopedic intervention – e.g. in case of spine involvement (stabilization, alleviation of tumor pressure on the spinal cord),
- radiotherapy – indications similar as in surgery, also bladder bleeding and metastases to CNS – external radiotherapy fractionated (most often 5x4 or 10x3 Gy), in some cases stereotactic irradiation may be considered,
- palliative – taking care of patients nutrition and treatment of symptoms such as pain, hematuria (endoscopic coagulation, embolization, radiotherapy) and hydronephrosis

24.8 Post-treatment complications

Complications arise from the treatment – haematuria, dysuria, infection after TUR or intravesical applications, classic postoperative complications and metabolic complications after urinary derivation. After chemotherapy pancytopenia, nausea, fatigue syndrome and paraesthesia. After radiotherapy, we see complications similar to those of lesser pelvis irradiation in prostate cancer (early and late) – see the section on prostate cancer.

24.9 Follow-up

The basis for follow-up of patients with bladder cancer is endo-urological examinations, which are sufficient in case of superficial bladder cancer. Follow-up intravenous urography (IVU) is indicated only in poorly differentiated superficial tumors. First follow-up cystoscopy is indicated in 3 months after TUR and further check-ups depend on findings and prognostic criteria. Regular physical examination, sampling, CT scan of the lesser pelvis and examinations according to the patient's problems.

24.10 PROGNOSIS

The prognosis depends on the stage of the disease. In the case of superficial tumors, the prognosis is favorable. The greatest risk lies in frequent relapses. The need for careful long-term follow-ups is a consequence of the risk of progression of superficial carcinoma from non-invasive to invasive, which significantly worsens the prognosis.

25 PRIMARY MALIGNANT TUMORS OF THE CENTRAL NERVOUS SYSTEM

Svatava Urbanová, Ludmila Loukotková

25.1 EPIDEMIOLOGY

Primary malignant tumors of the brain and spinal cord, i.e. the central nervous system, represent 1–2% of all cancers. In Czech Republic there are about 700 new cases per year. Incidence in the adult population is rising. The incidence curve has two peaks in two different ages. The first is in childhood (under 5 years) and the other is between 60-80 years of life.

25.2 ETIOLOGY

Risk factors are not known. Approximately 5% of tumors are hereditary, mainly in pediatric and younger patients (e.g. neurofibromatosis – occurrence of multiple tumors along nerves and subcutaneous tissue). CNS tumors originate from brain and spinal cord cells, from attached tissues, cerebrospinal envelopes and from the remnants of mesenchymal and epithelial tissue. The largest group among them are tumors from support cells (astroglia, oligodendroglia) – **gliomas**, which account for about 50% of tumors. Another 20% are tumors from the brain and spinal cord, **meningiomas**. These tumors are diverse in their origin, but also in their biological behavior.

25.3 SYMPTOMATOLOGY

Some tumors can be completely asymptomatic and are diagnosed as a random finding, for example, in a CT scan done after a fall or a car accident.

Intracranial hypertension syndrome

Under this term we can imagine a set of problems such as vomiting (mostly without feeling sick, more often in the morning), severe headaches, foggy or double vision, disorders of consciousness ranging from sleepiness to unconsciousness.

Epileptic seizure

Lighter form may be twitching of some limbs or as a state of short-term absence. If the seizure is widespread, it may be accompanied by impaired consciousness, twitching of all limbs, wetting, and severe jaw tightening with the risk of tongue biting.

Site symptoms

They appear to be functional failures of certain parts of the brain that are pressurized or damaged by a growing tumor. Tumors near the movement center can cause varying intensity of movement disorders, ranging from minimal disorders (such as shirt buttoning problems) to severe, in the sense of paralysis throughout the body. Similarly, the center of speech, hearing, sight, etc. may be impaired. A tumor may also manifest itself through a personality change.

25.4 Diagnostics

Any patient with the above-mentioned, even mild symptoms should be examined by a neurologist. Further diagnostic procedures are indicated based on neurological examination. Basic imaging methods with the highest yield include **magnetic resonance imaging**, in case of impossibility of examination or contraindication (e.g. pacemaker), computer tomography is indicated. Based on the results of these examinations, it is possible in most cases to decide on the suitability of the surgical solution. Recently, the importance of positron emission tomography has been increasing. Electroencephalography and ocular background examination to exclude congestion are also part of the comprehensive examination. Stereotactic biopsy is performed in patients with an inoperable tumor to determine the histological type of tumor.

25.5 Differential diagnostics

Diagnostic indecision in brain tumor diseases is not very common. That is, assuming the first contact physician does not underestimate the symptoms indicated by the patient and sends him for a neurological examination where other necessary examinations are ordered.

25.6 Pathology

Primary brain tumors are a very diverse group. Most often arise from cells of supporting brain tissue (neuroglia) – **gliomas**, make up more than 50% of all CNS tumors. According to certain histological signs and disease behaviors, gliomas are simplified into low-grade gliomas and high-grade gliomas, which is important for both the choice of therapy and the assessment of prognosis of the patient.

Glioma with low degree of malignancy (oligodendroglioma, astrocytoma) – grows slowly (years), more often in younger age groups (20-40 years), but its growth is not well limited from surrounding healthy brain tissue and therefore it is often not completely removed in surgery. It may be the same size over years or grow slowly. Over time, genetic mutations may cause the tumor to progress into a more aggressive form of glioma.

Glioma with a high degree of malignancy (anaplastic oligodendroglioma / astrocytoma, glioblastoma) – can arise in two ways. Either natural development through other genetic disorders from low malignant glioma or directly from healthy neuroglia. These highly malignant gliomas are characterized by rapid aggressive growth (weeks or months) with unclear borders, more often affecting older individuals (after 50 years of age). Complete removal is usually impossible. Relapses often occur (regrowth at the site after surgery).

Of frequent brain tumors, **meningiomas** should be mentioned – predominantly benign tumors based on meninges. They are more common in women after 50 years of age. Despite their "benign nature", they can be dangerous due to their growth and pressure on surrounding structures, which can cause major health problems.

Furthermore, cerebrospinal nerve tumors – **neurinomas**, mostly benign. **Pituitary adenomas** manifested by disorders of hormonal function. Tumors of predominantly child age are **meduloblastomas** and **ependymomas** that can spread through cerebrospinal fluid (fluid in the cerebral ventricles and between meninges).

Classification

TNM CLASSIFICATION IS NOT APPLICABLE TO BRAIN TUMORS.
The TNM classification of brain tumors adopted in the 4th edition (1987) was removed in the 5th edition of the TNM classification (1997), as its essential prognostic significance has not been demonstrated. Tumor size (T) has been shown to be much less important than tumor histology and location.

Age, general and neurological status and extent of resection are also considered to be significant prognostic factors. Complete tumor resection, the so-called R0 resection, is prognostically more favourable than R1 resection, where there is a microscopic or macroscopic overlap of the tumor into the resection margin.

25.7 Therapy

The therapy procedure should be based on the decision of multidisciplinary team, which includes a neurosurgeon, neurologist and an oncologist. The basic treatment approach for brain tumors is neurosurgery. Ideally, complete tumor extirpation (R0 operation). Partial operation always has worse treatment results. Inoperable brain tumor must be verified by stereotactic biopsy. On rare occasions, oncological therapy (radiotherapy or chemotherapy) can be indicated in unverified tumors, e.g. at an intolerable risk of performing biopsy puncture in the area of the brain stem, based on a characteristic imaging of the brain by CT and/or MRI.

Radiotherapy is one of the basic treatment methods. It can be used as an adjuvant method after surgery or as a radical method where surgery is not suitable for tumor location, progression or type.

Chemotherapy has a significant therapeutic effect only in some brain tumors (e.g. lymphomas and germinative tumors), in most tumors it is a palliative method. Post-operative application of chemotherapy in pediatric and adolescent patients (PNET tumors, ependymoblastomas or pinealoblastomas) is governed by specialized treatment protocols.

Concomitant chemoradiotherapy is used in therapy, especially in therapy of high-grade gliomas, provided the patient is in good general condition and there is no other contraindication to administration.

Stereotactic radiotherapy (Leksell gamma knife) may be used in the treatment of small tumors or minor postoperative residues (1–3 cm).

25.8 Post-treatment complication

We refer to treatment-related health changes as **early** – during therapy or within 6 months of discontinuation, and **late**, which occur after more than half a year. During treatment, neurological symptomatology may worsen – headache, convulsions, vomiting, sensory disorders or movement disorders. Postirradiation necrosis of brain tissue is one of the most serious late complications.

25.9 Follow-up

An integral part of patient care is regular monitoring after the end of therapy, so that early recurrence of the disease is caught early or possible treatment complications are minimized.

Nuclear magnetic resonance imaging and computer tomography belong once again among basic examination methods, together with neurological and oncological clinical examination. In the first year of follow-up of a patient with a low malignancy tumor, we perform an MRI examination every 6 months, and in tumors with a high degree of malignancy every 3 months. In the second year of patient follow-up, the periods between imaging examinations are doubled.

25.10 PROGNOSIS

Prognostic factors include:

- **Age at the time of diagnosis**

The age under 40 is usually associated with longer survival in the same tumor type than in the elderly.

- **General health status at the time of diagnosis**

Survival duration is significantly negatively influenced by a serious intercurrent illnesses.

- **Histopathological grading**

It significantly affects the prognosis of the disease. In general, tumor malignancy increases with increasing numbers of mitoses, cellular atypia, and the presence of necrosis.

- **Tumor localization and size at the time of diagnosis**

Tumors of the brainstem or regions of functionally significant centers of dominant hemisphere may be inoperable, limited in treatment or may damage vital centers.

26 SECONDARY MALIGNANT TUMORS OF THE CENTRAL NERVOUS SYSTEM

Tomáš Blažek

26.1 EPIDEMIOLOGY

Secondary malignant tumors of the central nervous system occupy a relatively important position within CNS malignancies. The incidence of these neoplasms is up to 10 times higher compared to primary brain tumors. These include metastatic tumors of the brain and cerebral vessels, spinal cord, spinal canal and vertebral bodies. The occurrence of these neoplasms is closely related to the treatment of primary solid tumors. In particular, advances in systemic treatment of solid tumors has improved overall patient survival, however on the other hand, it increases the chances of the surviving patients to develop brain metastases. The occurrence of these tumors related to the age of patients does not reach a specific peak.

26.2 ETIOLOGY

Secondary CNS tumors are formed by metastasizing malignant tumors from other regions. Risk factors include grading, tumor aggressiveness and, in particular, histological tumor type. Breast, lung, melanoma and kidney cancers have a high affinity to metastasize into the CNS, while prostate, pancreatic, biliary tract or liver cancers rarely metastasize into the CNS. The stage of disease and tumor location also play a major role in the development of metastasis. Bulky apical lung tumors or affected supraclavicular lymph nodes in lung tumors are associated with a higher risk of brain metastasis. A specific case is described in bulky esophageal tumors or lung tumors localized paravertebrally which can cause spinal compression through direct ingrowth (per continuitatem) into the body of the vertebral body and thoracic wall. In histological terms, the most frequent metastases are carcinomas of the breast, kidney, melanoma, and lung. Metastases of prostate, breast, lung, and kidney cancers dominate the axial spinal skeleton and dural sac.

Other variants of solid tumors such as colorectal carcinomas, pancreaticobiliary tract tumors or gynecological malignancies tend to establish visceral metastases. CNS or spinal canal involvement is not typical of these tumors, but however cannot be excluded.

26.3 SYMPTOMATOLOGY

The disease is usually manifested by similar clinical symptoms as primary CNS tumors. The course is usually acute, and in terms of neurological complications, it is associated with intracranial hypertension and focal disability.

Collapse states, headache, dizziness, double vision, visual field disturbances, motor affection, disorders of standing and walking, hemiparesis, speech disorders (dysarthria, aphasia) nausea, vomiting, qualitative disturbances of consciousness (confusion, disorientation of time, person, space) and quantitative disturbance of consciousness (somnolence, sopor) may occur.

Often, the first symptoms are **seizures**, most often focal, ie. twitching of specific parts of limbs, short-term loss of consciousness (absence) or with complex symptomatology in the sense of disturbed consciousness accompanied by tonic-clonic seizures with wetting, biting and eventually sinking of the tongue.

Pain is among the first symptoms. In particular, vertebrogenic pain syndrome in metastatic involvement of the spine and spinal canal, it is usually accompanied by numbing pain (neuropathic) which require intense analgesic therapy. When spinal roots are compressed or infiltrated in the lumbar spine, root pain can evolve over the course of a few weeks or more months.

Acute spinal cord compression is one of the urgent states in oncology. A timely diagnosis and strategy of treatment is essential from the point of further progression of the patient. More info below. The clinical picture often is manifested by acute hemiparesis, paraparesis, hemiplegia, paraplegia (disorder of movement of limbs influenced by localized affection).

26.4 Diagnostics

The basis of diagnostics is a full physical examination, including a professional neurological examination, in order to exclude other etiologies other than oncological. Imaging examinations that specify the extent of the disease are crucial. CT scans of the brain, spine and targeted X-ray images are readily fast and available.

The key to a proper diagnosis is a **Brain and Spine MRI,** and it is indispensable for determining a proper treatment strategy. It allows for a detailed examination of the tumour invasion into both soft and hard tissues. In the case of brain tissue, it is able to uncover infiltration of the meninges or even metastatic locales the size of a few millimeters and their relationship with other important structures such as the brain stem , *chiasma opticum*, *nn.optici* and more.

Invasive methods of diagnosis, such as biopsy or excision of a metastatic lesion is not obligatory and depends on several factors. In the case of true metastatic involvement, with risk of deterioration or development of neurological complications after an intervention, the verification process is contraindicated. The indication of any intervention is consulted with a neurosurgeon.

The diagnosis of leptomeningeal involvement must be based not only on MRI findings, but also on cytological examination of cerebrospinal fluid from a lumbar puncture. The complete complex examination also includes an examination of the eye in order to exclude vascular congestion and papilloedema.

26.5 Differential Diagnostics

Often the clinical picture in combination with symptomatology and imaging methods are so convincing that there is no doubt about the diagnosis. Doubts may arise in patients in complete remission after radical treatment of primary oncological disease who show unclear findings on imaging (often in cases of smaller solitary lesions). The differential diagnosis may be non-oncological or oncological. From non-oncological disease, it may possibly be a cerebral vascular accident, AV malformation, aneurysm, neuroinfection (abscess, mycosis, parasite), post traumatic changes, or bleeding into the brain. From oncological possibilities, it may be a primary tumor of the CNS, which can be differentiated by histological verification from a resection or biopsy.

26.6 THERAPY

In therapy, we are able to distinguish between acute phase treatment and treatment after the stabilization of the acute phase.

Acute phase of the disease: is typically characterized by neurological symptoms - seizures, diplopia, visual field disturbances, motor disturbances, disorders of standing or walking, dysarthria, vertigo, nausea, headache, pain, disorders of consciousness… see above for more.

The therapy is aimed at alleviating the problematic symptoms, stabilization of the patient and improving the patient's general state so that diagnostic tests can be performed and a further treatment strategy can be planned. The treatment plan is based on anti-edematous therapy in the form of i.v. administration of corticosteroids (Dexamed 8-10 mg) at intervals of 6-8 hours, in combination with a 20% infusion of Mannitol every 12 hours. Concurrently, administration of proton pump inhibitors (Loseprazol, Helicide, ...) is indicated as prophylaxis against the development of gastroduodenal uclers, which may occur with administration of high doses of corticoids. The therapy of seizures is carried out in cooperation with a neurologist, with whom it is possible to prescribe anti-epileptics (valproic acid derivatives) and in strictly indicated cases anticonvulsants (benzodiazepines), which can be administered only with subsequent vital function monitoring, due to the possibility of respiratory depression. Anti-emetic therapy usually consists of prokinetic therapy, such as metoclopramide (Degan, Cerucal) or more effective centrally acting drugs such as - thietylperazine (Torecan).

Acute pain therapy is individualized according to the type of pain and etiology. Mild headaches will respond well to non-steroidal anti-inflammatory drugs (Ibalgin, Indometacin, Novalgin, Algifen, Panadol). In the case of neuropathic pain, usually due to infiltration of nerve roots during metatstatic affection of the spine with compression of the dural sac, it is advised to use combination therapy of non-steroidal anti-inflammatory drugs (Diclofenac, Novalgin) and opioids in the form of tablets or transdermal patches (Palexia tbl., Transtec derm., Fentanyl derm.). Subcutaneous or intravenous administration of opioids is uncommon.

Post stabilization phase and therapeutic balance: after the acute phase calms and passes, it is necessary to evaluate the extent of CNS involvement and also to evaluate the activity of the primary tumor affection. For this purpose, staging examinations are used - MRI of brain and spine, eventually CT, where it is necessary to search and monitor the number of metastatic lesions, their size and location. Primary tumorous disease is examined and re-staged using CT or PET / CT, and diagnostic laboratory tumor markers. When trying to determine the next treatment strategy, it is essential to determine whether the primary malignancy is in remission or rather progressing in other organs outside of the CNS.

The results of individual examinations, the patient's overall performance status and age are important factors in determining the next treatment strategy.

These factors are highlighted in **RPA Criteria** (**R**isk **P**rognostic **A**ssessment), in which patients are divided into 3 groups according to the median of estimated overall survival after treatment. In the 1st group, the median survival was 7.1 months, while in the 3rd group, the survival time of patients is about 2.3 months. Depending on the level of risk and the group to which the patient is assigned, the treatment strategy is chosen, reflecting the optimal treatment modality. The treatment plan must have the maximum benefit for the patient with the lowest possible adverse effects affecting the quality of life. Taking into account the above-mentioned statistical results of patient survival, the chance of cure is very

low. In the vast majority of cases, the treatment is palliative, so it is important that it should not hurt the patient or impair the quality of life in any way.

26.6.1 Therapy of brain metastasis

There are 3 treatment modalities available in the treatment of brain metastases that can be used independently or in a combined fashion. When choosing a particular modality, all factors are evaluated by a so-called multidisciplinary team, which is comprised of a radiation oncologist, neurosurgeon and radiologist.

Surgical resection: the advantage of this modality is maximum tumor removal, with the ability to perform accurate histological examination. An important criteria is a patient's good performance status and ability to under general anesthesia. Resection is optimal for solitary surface deposits with voluminous vasogenic edema or for those causing cerebrospinal fluid blockage. Contraindications to surgery are bulky lesions or, on the contrary, smaller lesions located deep, near important centers, whose damage during resection would cause negative functional results. An independent surgical resection of a locus is never a definitive treatment for a patient, a must **always be supplemented with postoperative radiotherapy** (stereotactic radiation resection or whole brain radiotherapy).

Stereo-radiosurgery (SRS), stereotactic radiotherapy (SRT): is indicated in more cases than when compared to surgery. It allows for treatment of older patients with comorbidities in whom surgical treatment under general anesthesia would be risky. Other indications include minor lesions, deep lesions near risky organs and important centers.

When compared to surgical treatment this method is recommended for **oligo-metastatic affection,** which have $\leq$ 3 lesions. It should always be indicated after resection of the metastasis within the postoperative inpatient irradiation. Stereotactic irradiation is very accurate but technically demanding.

In principle, it is about delivering a very high dose in a short time to a small, well-defined target volume. In the case of SRS, it is in the form of 1 fraction, in the case of SRT 3-5 fractions. See the radiotherapy chapter for more details.

Fixation of the head with a stereotactic frame is necessary to prevent "missed targets" and subsequent irradiation of healthy tissues. In the case of Leksell's gamma knife, this frame is fixed to the skull by screws. In the case of Cyber Knife or Linear Accelerator, a non-invasive fixation with a special thermoplastic mask is used.

Whole Brain Radiotherapy (WBRT): is an effective and proven treatment modality. Together with surgical resection it belongs to historically older modalities compared to SRS and SRT. The irradiation technique is very simple and fast - irradiation of the skull from two opposite fields. It is used especially in patients with worse overall status (low performance status), lower expected overall survival (life expectancy). It is clearly preferred in patients with non-oligometastatic involvement; meaning in all patients contraindicated for surgical resection and in patients with > 4 metastases. A post-operative indication after resection of metastasis has been slowly replaced by stereotactic radiotherapy (SRT). This

is due to lower toxicity of SRT compared to WBRT. Studies have shown a decline in cognitive functions, particularly short-term memory on average 4 months after completion of radiotherapy of the entire neurocranium. If SRT is not possible, then WBRT is always standardly indicated after the operation.

Summary:

- **surgical resection** is preferred for solitary metastases, larger in size, and superficially located. Patients in good overall condition, and able to tolerate surgery. Ideally in patients with better prognosis, as in lung or breast cancer. Radiotherapy (SRT or WBRT) must always be indicated postoperatively,
- **stereo radiosurgery or stereotactic radiotherapy (SRS,SRT**) jis indicated for oligometastatic involvement (<3-4 metastases), in patients unsuitable for surgery, and in lesions located close to important centers. Currently preferred and indicated in postoperative radiotherapy after resection of metastasis. SRT + WBRT is not recommended becasuse of higher toxicity.
- **Whole brain radiotherapy (WBRT)** is the gold standard in patients with multiple metastatic foci, poor overall states, poor overall prognosis and shorter estimated survival times. It is indicated postoperatively if SRT is not possible

The radiation doses applied with WBRT are most often 30 Gy / 10 fractions or 3 Gy eventually 20 Gy / 4-5 fractions, 12 Gy / 2 fractions with a weekly pause between Fraction 1 and Fraction 2. In the case of stereotactic radiation, doses are individually tailored to tumor size, localization and risk organs. Examples of SRS fractionation schemes are 24 Gy / 1 fraction, 18 Gy / 1 fraction and for SRT 3-5 fractions with a dose of 8-10 Gy per fraction.

26.6.2 Systemic therapy of brain metastasis

Treatment of brain metastases with the help of chemotherapy is very difficult to handle and poorly effective. This is due to the low permeability of most chemotherapeutic agents through the blood-brain barrier. As an exception, a combination of carboplatin with etoposide, which is widely used in the treatment of small cell lung cancers, may be used.

This is not the case for targeted therapy and immunotherapy, where results are noticeably better. **Her2-neu positive breast cancers** with metastasis affecting CNS can be treated with lapatinib, which is a dual tyrosine kinase Her2 receptor blocker that freely crosses the blood-brain barrier. The results of new studies show a relatively significant effectiveness of targeted therapy in metastatic **non-small cell lung cancer with ALK + mutation**. Similar results are shown by studies of metastatic **malignant melanoma therapy using immunotherapy**. In both cases (pulmonary carcinoma and melanoma) the patients were not irradiated. Systemic therapy was highly effective. Thus, it can be assumed that for this narrowly specified group of patients, radiotherapy can be omitted at least in the initial phase of the treatment algorithm.

26.6.3 Prophylactic Brain Irradiation

Whole brain radiotherapy is specially indicated in a select group of patients.The treatment aims to reduce respectively prevent the development of metastatic disease in the CNS. It is part of the small cell lung cancer treatment protocol and is also used in hemato-oncology. In the case of small cell lung cancer, it reduces the risk of developing metastases by 50%, and according to some studies by up to 80%, which positively correlates with patient survival. The applied dose is 25 Gy / 10 fractions.

In hemato-oncology, the indications of brain radiation after inductive systemic chemotherapy in the therapy of AML and ALL. The applicated does is approximately form 12-18 Gy 5x a week and 1.5-1.8 Gy per fraction.

26.6.4 Therapy of leptomeningeal metastasis

Metastatic meningeal involvement is less common than focal brain involvement. However, the clinical course of the disease is all the more serious and patients' prognosis worse. It manifests with various symptoms ranging from vision disorders, diplopia and intense headaches, which is poorly responsive to analgesics, to qualitative and quantitative disorders of consciousness. **MRI** is essential in the diagnosis, and is made to show meningeal infiltration. CT is not advantageous in this case. Diagnosis must be confirmed **cytologically** from cerebrospinal fluid. Early therapy is similar to therapy of brain metastasis where antiedematous therapy, analgesics, etc. are indicated. After stabilization of acute symptoms, palliative radiotherapy (WBRT) at 30Gy / 10 fraction is indicated. After the last radiotherapeutic fraction, cerebrospinal fluid is collected once more and evaluated. The next steps depend on the general condition of the patient and cytological findings in cerebrospinal fluid.

In the case of **negative cytological findings and good performance status,** intrathecal administration of chemotherapy (methotrexate) through an implanted Omayo reservoir is indicated. Alternatively it is possible to continue radiotherapy in the craniospinal axis and escalation of dose (boost) to the meningeal infiltration sites. Both options are relatively risky in terms of unwanted side effects. In the case of intrathecal administration, up to 50% of patients are at risk of developing arachnoiditis. Irradiation of the craniospinal axis, on the other hand, is accompanied by myelotoxicity and general worsening of the state of the patient, therefore this variant is preferred in radiosensitive tumors (lymphomas, germinal tumors). In other cases, intrathecal administration of chemotherapy is therefore more preferred.

Worsening of the general condition (CI <60%), positive findings in cerebrospinal fluid or multiple disabilities are important factors of poor prognosis. Further therapy is therefore limited. Usually, the patient can be offered a limited field radiotherapy to the greatest affected area with a dose escalation attempt. In most cases, however, the progression is symptomatic, and supportive therapy is the final step, with the disease progressing rapidly and death following shortly thereafter.

26.7 METASTATIC SPINAL CORD COMPRESSION

Spinal cord compression is one of the acute conditions in oncology. The prognosis of patients with this condition is highly dependent on early recognition of symptoms, accurate diagnosis and initiation of treatment. Time plays a very important role, any delay in starting treatment can lead to fatal consequences.

Etiology

Metastatic spinal cord compression manifests in approximately 5-14% of all cancer patients. It depends on the type of malignancy respectively, histological findings. The most common diagnoses to cause compression include breast carcinomas (29%), lung carcinomas (17%) and prostate carcinomas (14%).

Cord compression can occur due to 2 mechanisms:

- expansion and in growth of metastatic vertebral masses into the dural sac,
- expansion into intervertebral foramina by tumor mass,
- destruction of vertebral bodies by tumor lysis with pathological fractures causing the expansion of fragments into the spinal canal.

All three mechanisms can be combined in the pathogenesis.

Symptomatology

Typical symptoms include pain and irritative neurological symptoms. Symptoms can be expressed individually to varying degrees. The pain is usually localized at the site of the affliction, but infiltration of the lumbo-sacral roots may manifest in the root dermatomes. The intensity of pain varies, from slight post-exertional vertebralgia to severe pain syndromes with a neuropathic component of pain requiring combined analgesia or analgosedation.

Irritative neurological symptoms manifest themselves as paresthesias, dysesthesias, and proprioception disorders. Patients report impairment of stability and confidence when walking (feelings of walking on moss, loss of solid ground under their feet…) Loss of feeling phenomena are typical in the development of paresis or plegias. Generally, the intensity of symptoms and their rate of onset is directly proportional to the volume of metastatic involvement.

Diagnostics

Diagnosis must never be delayed. In spinal compression, "every minute" is valuable. The base for proper diagnosis is an expert neurological examination, which helps to identify the location of the lesion and, above all, is able to distinguish non-malignant causes of the problem.

The gold standard for diagnosis is MRI of spine. Only MRI provides adequate soft tissue resolution and tumor infiltration pictures. If MRI is not possible for reasons other than time (cardiac pacemaker, claustrophobia, obesity), a CT scan with i.v. contrast medium must be made. The finding must always be consulted with a neurosurgeon! (see therapy below). From a neurosurgical point of view, MRI imaging allows for visualization, assessment of the severity of the lesion and determination of technical possibilities in possible surgical intervention.

Prognostic factors related to spinal cord compression

One of the most important prognostic factors is the rate of onset of symptoms. The **time from the first symptoms** of the ailment to the development of motor deficits is the strongest predictive factor in maintaining mobility after oncological respectively neurosurgical treatment..

We are able to divide into 3 groups of patients (Rades et al):

- Group A – loss of mobility within 1–7 days = movement after treatment is 35 %
- Group B – loss of mobility within 8–14 days = movement after treatment is 55 %
- Group C – loss of mobility within > 14 days = movement after treatment is 86 %

As stated above that **rapid diagnosis is essential** to achieve the best treatment results.

Therapy

as mentioned above, time plays a crucial role in therapy. Acute spinal compression is an **urgent** condition and must be **treated within 24 hours at the latest**! As with brain metastases, corticotherapy is of great importance in spinal cord compression. It must be started as soon as possible; as suggested by the first signs and suspicions of such diagnosis. Dexamethasone (Dexona) at a dose of 10 mg i.v. bolus followed by 6-8 mg every 8 hours, with concomitant gastric protection of Proton Pump Inhibitors (loseprazol, omeprazole…). Analgesic therapy is individual according to the intensity of the pain. Mild pains respond well to non-steroidal anti-inflammatory drugs (Diclofenac, Indometacin, Novalgin, Algifen).

Combination therapy with non-steroidal anti-inflammatory drugs (Diclofenac, Novalgin) and opioids in the form of tablets or transdermal patches (Palexia tbl., Transtec derm., Fentanyl derm.) Is required for intense pain with a neuropathic component or for nerve root infiltration. Subcutaneous or intravenous administration of opioids (Morphine) is uncommon.

Each patient must be consulted with a neurosurgeon as part of the diagnostic-therapeutic standpoint.

Surgical Intervention

It should always be preferred in symptomatic patients, meaning those with neurological deficit. Surgical results are clearly better than when compared with independent radiotherapy.

According to a randomized phase III study, Patchel et al showed a significant improvement in motor skills when decompression (laminectomy with resection of TU masses) and postoperative radiotherapy were combined. Surgical treatment is indicated in those with signs of rapid neurological deterioration, localization of the lesion in the upper levels of the cervical spine and in the case of unilateral compression

Radioresistance of tumors (melanoma, renal Ca) is another factor for surgical intervention. Instability of vertebral body and fragments of pathological fractures are high risk factors and may cause the need for surgical intervention and stabilization, even though the patient may be asymptomatic.

Radiotherapy

Radiotherapy as an independent modality of treatment is effective in asymptomatic patients, meaning patients with newly diagnosed metastatic spine involvement without neurological deficit. Both conventional radiotherapeutic techniques and stereotactic irradiation may be applied. Neurosurgical intervention may be omitted in radiosensitive tumors (lymphomas, leukemia, multiple myeloma, germinal tumors) or in patients in whom systemic therapy is planned and life expectancy is > 3 months. The condition is that the neurological deficit must not last longer than 24 hours!

However, if there is a significant worsening of the neurological deficit and pain intensity during radiotherapy, re-consultation of the neurosurgeon and consideration of a surgical intervention may occur. This may be a sign of progression of a radioresistant tumor during treatment.

In all other cases, including contraindications to neurosurgery, multiple disabilities, massive infiltration, poor patient prognosis and marked progression of primary cancer, palliative radiation of symptomatic areas is indicated in order to produce an analgesic effect.

The usual fractionation regimen used in spinal compression therapy is 30 Gy / 10 fraction and 3 Gy. In patients with life expectancies <3 months, doses of 20 Gy / 5 fractions may be administered or 4 Gy or 8 Gy in one session.

26.7.1 Intramedullary spinal cord metastasis (ISCM)

Is a relatively rare group of approximately 1% of intramedullary tumors con-siting of most commonly metastases of lung carcinomas (54%) and breast carcinomas (11%). The most noticeable difference between intramedullary and extramedullary metastases is the high incidence of synchronous brain metastases (41%) in ISCM patients. The diagnostic and therapeutic procedures are the same as in those for acute spinal compression.

26.8 Post-treatment complications

Complications during treatment of secondary CNS tumors are not uncommon. Oncological disease progresses frequently in the form of new metastatic lesions. The blockage of cerebrospinal fluid circulation in tumors obstructing CSF pathways or even bleeding into the ventricular system are clinically serious complications. A ventriculotomy is performed as therapy. Another relatively common complication is an infection in the form of arachnoiditis, occurring in up to 50% of patients receiving intrathecal chemotherapy. Skeletal or brain tissue radionecrosis is a complication of hypofractionated stereotactic radiotherapy (SRT, SRS) regimens. Less common are the general risks of perioperative and postoperative complications.

26.9 Follow Up

The rules of follow-up are closely related to the primary malignancy, respectively evaluation of its activity. When the primary disease is in remission, the focus is on secondary CNS involvement. Similarly as in diagnostics, MRI, CT, and even X-ray are also used for imaging examinations of follow up patients. The basis of indication to re-staging of the disease is the patient's general state, prognosis and. treatment options that could be offered to the patient. If the patient's general condition is poor, the disease progresses and treatment options are limited, then further patient care is symptomatic and re-staging. examinations are indicated only in case of new symptoms and problems.

On the contrary, in patients with oligometastatic involvement after radical treatment of metastases and good general condition with unlimited possibilities of cancer treatment there is a tendency to actively monitor the development of the disease. For this reason, re-staging examinations (MRI, CT) are indicated with the intention of excluding or respectively. catching early progression, in order to initiate another line of treatment.

26.10 Prognosis

The prognosis of secondary CNS tumors is unfavorable. Median survival is between 2-10 months despite intensive treatment. The predictive factors of a good prognosis are as follows:

- Solitary foci affection,
- Tumor with favorable histology – Breast cancer, Lymphomas, Germinal tumors, Prostate Cancers, Lung cancers with positively activated mutations (EGFR +, ALK+),
- In the case of spinal cord compression with a very gradual onset of symptoms that can be neurosurgically removed,
- Primary disease in remission or partial regression.

On the contrary, leptomeningeal metastases, multiple CNS involvement, bones of the spine, acute spinal compression with rapid onset of neurological symptoms within a few days or even hours, are prognostically unfavorable. Histologically, metastases of carcinoma of kidney, lung carcinomas without mutations, and melanoma, are all unfavorable. The overall prognosis is significantly limited by progressive underlying cancer.

27 NON-MELANOMA SKIN CANCER

Jan Dvořák

27.1 EPIDEMIOLOGY

They are the most common malignant tumors. The incidence in 2016 reached 267 new cases per 100,000 persons, 284 in men and 251 in women per 100,000. The highest incidence is in the high age groups. E.g. in women over 80, the incidence is 1,522/100,000 women.

27.2 ETIOLOGY

Significant risk factors for skin cancer are:

a) chemical carcinogens:

- 3,4 benzpyrene,
- polycyclic aromatic hydrocarbons (tar, paraffin oil),
- arsenic,
- tobacco.

b) physical factors:

- UV radiation (component B),
- ionizing radiation (X-ray),
- chronic irritation (fistula, scars, burns, pressure sores, lupus).

c) viral carcinogenesis:

- HPV – 5 (human papilloma virus).

d) endogenous causes:

- genetic predisposition phototype I, II,
- congenital syndromes (xeroderma pigmentosum, nonlinear basalioma syndrome called Gorlin syndrome),
- induced immunosuppression (after transplantation, CLL or AIDS).

27.3 SYMPTOMATOLOGY

Skin affections that do not heal, itch, bleed, increase in size, have a rough, rough surface or scale, should be examined at a dermatological workplace.

27.4 DIAGNOSTICS

The high percentage rate of detection and early diagnosis is possible thanks to the surface localization of skin cancer and good accessibility for examination. Nevertheless, patients, especially the elderly, come in advanced disease stages.

Diagnosis can only be made on the basis of histology. The patient should undergo a basic clinical examination, including a physical examination to rule out another lesion. Complementary examinations such as X-ray of the lungs, US of regional nodes, laboratory examinations are indicated in cases of larger tumors.

27.5 Differential diagnostics

It is necessary to exclude inflammation, abscesses, other skin affections or precanceroses, ie skin changes, which can lead to malignant tumors after some time.

The most common precanceroses are keratoses:

- solar (actinic) keratosis, which occurs in older people on senile degenerated skin, in a place exposed to light - on the face, back of the hand, etc.
- radiation keratosis in the field of chronic X-ray dermatitis,
- thermal keratosis - after burns, in scars,
- keratoses resulting from the action of chemical carcinogens - tar, arsenic, mineral oils,
- leukoplakia that occur on the lip, oral cavity, genital,
- dysplastic nevi (non-cellular),
- condylomata accuminata.

27.6 Pathology

Classification of skin tumors is based on their histological and pathological structure. We divide them according to the structures from which they originate:

Epithelial

- benign - verrucas,
- malignant - basaliomas, spinaliomas, Bowen's disease (chest), Erythroplasia of Queyrat , Paget's disease, keratoacanthoma.

Adnexal

- trichoepithelioma (from hair follicles),
- syringoma (sweat glands)
- cylindroma (from sweat glands or hair follicles).

Mesenchymal

- benign - hemangiomas, fibromas, leiomyomas, lipomas,
- malignant - sarcomas, dermatofibrosarcoma, fibrosarcoma, liposarcoma, Kaposi's sarcoma, malignant fibrotic histiocytoma.

Neuroectodermal

- benign - neurofibroma,
- malignant - neurofibrosarcoma, malignant melanoma, Merkel cell carcinoma.

The most common malignant neoplasms of the skin are epithelial carcinomas: basaliomas and spinaliomas, as well as Merkel cell carcinomas and dermatofibrosarcoma protuberans.

Basal cell carcinoma (basocellular carcinoma) originates from basal cells of the epidermis and from the terminal follicle, accounting for 75-80% of all skin cancers, 85% of which are located in the head and neck area.

Clinically we distinguish superficial basalioma, nodular, scarring, sclerodermiform, ulcus rodens, pigmentary, cystic and hyperkeratotic form. Metastasizes exceptionally, has locally destructive growth.

Spinalioma (squamous cell carcinoma) originates from keratinocytes. It develops intraepithelially and gradually becomes a destructively growing tumor with a tendency to metastasize. Perineural spread is also common. Spinalioma accounts for 20–25% of all skin cancers. It is located most often on the face - on the nose, auricles, cheeks, the back of the hand, as well as the skin and mucous membranes - on the lower lip, on the glans penis, vulva and anus, where the prognosis is much worse. Metastasizes to regional lymph nodes and hematogenously mainly to the lungs.

Dermatofibrosarcoma protuberans is a rare low-grade sarcoma derived from fibroblasts. Very rarely metastasizes. It's radiosensitive.

Merkel cell carcinoma is a rare disease derived from neuroectoderm tissue. It is characterized by aggressive growth with the ability of rapid lymph nodal or distant generalization.

27.7 THERAPY

The high curability rate (up to 97%) of basocellular, squamous cell carcinoma and dermatofibrosarcoma protuberans is due both to the low aggressive nature of growth and to their surface localization facilitating early diagnosis. The aim of treatment is to achieve full local control, good cosmetic effect while maintaining full quality of life. Worse results are seen in Merkel cell carcinoma, where multimodal treatment is always required.

Surgery

- local wide excision with safety edge,
- in cases of lymph nodes involvement (assessed by ultrasound, CT, MRI) their extirpation with histological verification needed.

Radiotherapy is indicated in cases when surgery is not suitable or when there are positive surgical margins (except for Merkel's cancer - even in negative surgical margins, often irradiated together with tumor-draining lymph nodes).
Can be used:

- teletherapy (X-ray, electrons, photons),
- brachytherapy (superficial, interstitial).

Superficial **brachytherapy** has very good results and is used for flat surface lesions preferably on flat terrain. It is performed using so-called **moulage** (Fig. 1, 2), where a special carrier with catheters for the radiation source is placed directly on the tumor. For irradiation Ir^{192} HDR source is most commonly used.

For tumors bigger than 1 mm, we have to choose another method of radiotherapy, either external or interstitial brachytherapy, where the needles or plastic tubes for the radiation source are inserted directly into the tumor (Figs. 3 and 4). The procedure should be performed under general or local anesthesia or analgosedation. The daily dose and fractionation schedule depends on the size of the tumor, its location, histology, age and general condition of the patient.

Both methods, surgery and radiotherapy provide similar treatment outcomes.

Fig 1 Surface Brachytherapy - Moulage

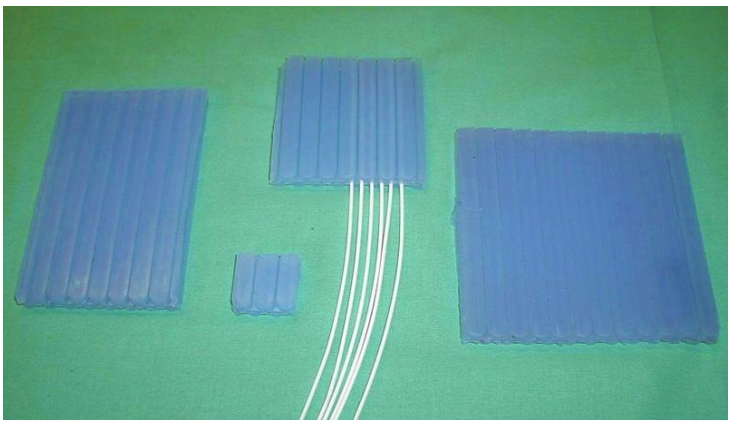


Fig 2 Applying moulage to the arm

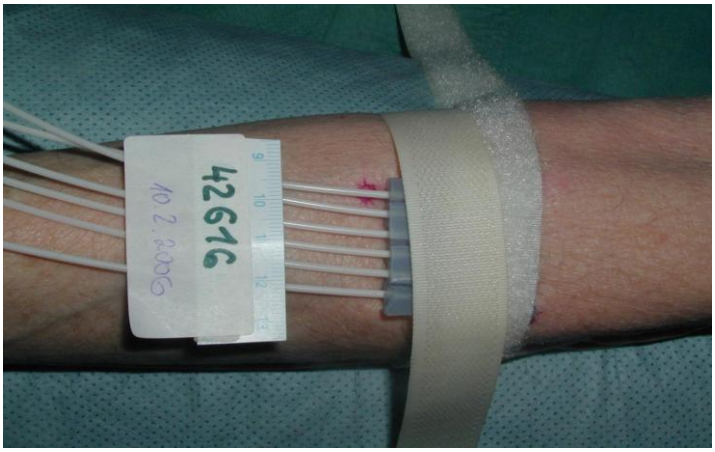
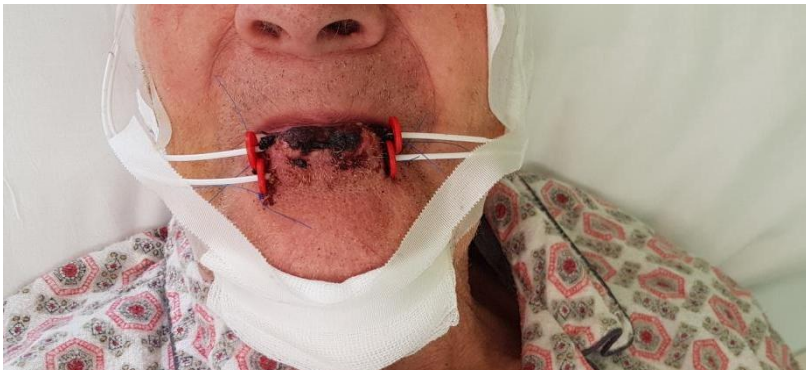


Fig 3 Patient with lower lip tumor

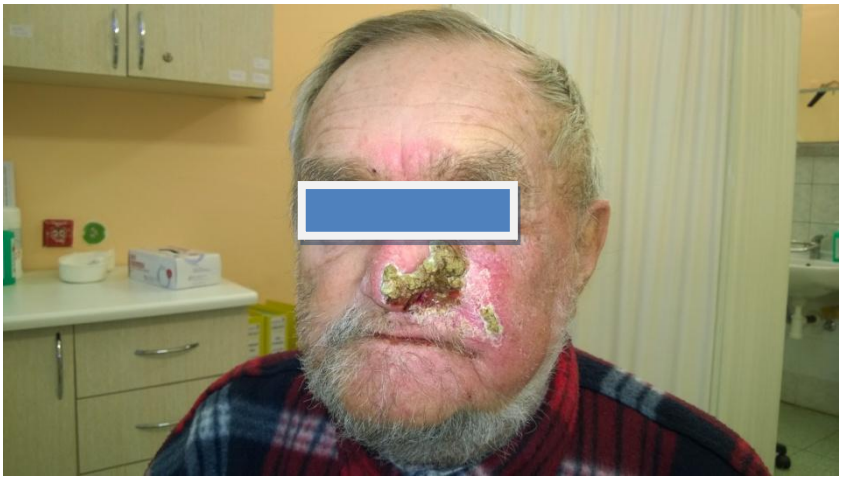
Fig 4 Interstitial application in lip tumor

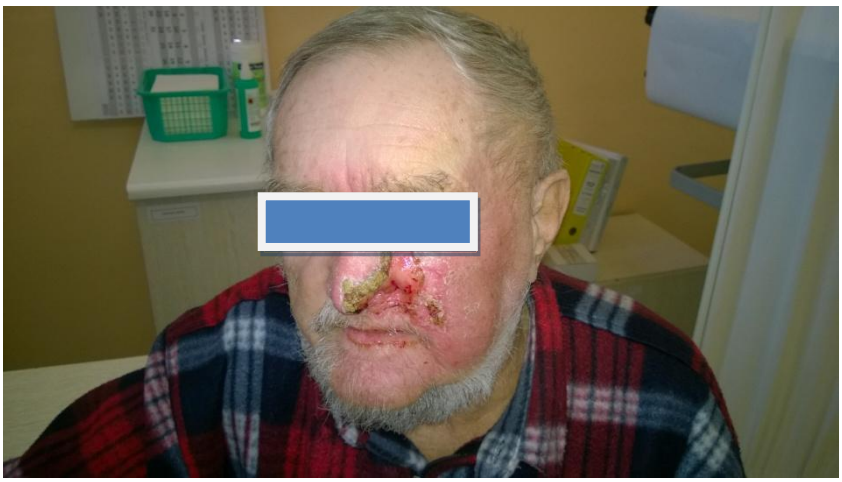


Radiotherapy is preferred in absence of loose skin, in large infiltrating and fixed tumors, in contraindications of anesthesia, or as post-operative irradiation when there are positive margins of the tissue excised (unless reexcision can be performed) and in lymph nodal involvement.

Example of radiotherapy and treatment effect:

1/2017 patient with a 20-year history of repeated resections of spinalioma and basalioma on the face at the start of radiotherapy. In the places of foci - squamous cell and basocellular carcinoma.





Surgery is preferred in young patients, when localization of the tumor is in the hairy part of the head, in recurrence or persistence of the tumor after irradiation, in localization on the eyelids and when the patient has already been irradiated and radiotherapy options are exhausted. The advantage of surgery is a shorter time interval of this therapy.

Other treatment modalities are used more in palliative treatment, after exhaustion of surgery and radiotherapy. Cryotherapy, laser, photodynamic therapy, local chemotherapy - fluorouracil ointment, local ointment with imiquimod.

Another treatment option in palliative therapy is palliative **chemotherapy** in squamous cell cancer, especially in the case of generalized disease. Anti-PD 1 and anti CTLA-4 immunotherapy agents are now undergoing testing for this indication. It is believed that efficacy is similar to that of squamous cell carcinomas at other sites.

In basaliomas without the possibility of local treatment or when generalization is present, it is possible to use biological treatment - vismodegib (inhibitor of the SMO-Hedgehog pathway) with excellent results.

In dermatofibrosarcoma protuberans after failure of local treatment, it is possible to administer imatinib, or palliative chemotherapy.

In Merkel cell carcinoma, systemic treatment by chemotherapy (platinum derivatives, etoposide) or recently, there has been introduced possibility of administration of anti-PDL1 preparation avelumab.

27.8 POST-TREATMENT COMPLICATIONS

Depend on the treatment provided. In connection with radiotherapy, **acute skin reactions** in the form of erythema, rash, dry desquamation, up to wet desquamation (lysis of epithelial cells), rarely also ulcus can occur. Chronic radiation changes include telangiectasias, fibrosis, atrophy, alopecia and rarely radiation ulcus. After surgery, scars occur, often with keloid transformation and with dehiscence, fibrosis of the skin and hypodermis.

Complications of vismodegib treatment are usually mild and non-serious. Undesirable complications of chemotherapy are identical to chemotherapy in other locations. Treatment with avelumab has a similar toxicity profile to other antiPDL1 agents.

27.9 Follow-up

It is permanent in all malignant tumors, with the exception of small solid basaliomas removed radically by surgery. The basis of follow-up is a clinical examination. At a certain interval, blood count and biochemistry, rarely also tumor markers (SCC) measuring (if initially elevated) should be performed. Other examinations include US of the lymph nodes, X-ray of the lungs and US of the liver, CT scan examinations - especially in sarcomas. Visits every 3 months for two years are then gradually prolonging the visits period to up to 1 year. When patient presents with complaints, the examination should be focuses on the symptoms.

27.10 Prognosis

Skin cancers of the basalioma type have a good prognosis because they practically never metastasize. They endanger the patient by local progression and destruction of surrounding tissues. As with other cancers, the patient's prognosis worsens with disease progression. Good illustration shows the table with the probability of local control after radiotherapy .(Tab. 1)

Tab.1 Local control after radiotherapy

Tumor size	Basalioma	Spinalioma
up to 1 cm	97 %	91 %
1 – 5 cm	87 %	76 %
more than 5 cm	87 %	56 %

28 MALIGNANT MELANOMA

Jan Dvořák

28.1 EPIDEMIOLOGY

Currently, malignant melanoma is considered a tumor with a fast growing incidence. Geographically, the highest prevalence of malignant melanoma is among the Nordic Caucasian population living in countries with high sunshine (Australia, New Zealand, South America). In 2016, the incidence of invasive melanoma in the Czech Republic was 24.69 per 100 000 inhabitants. In men, the incidence is slightly higher than in women. The incidence of malignant melanoma is shifting to younger age groups and its incidence at prepubertal age is no exception.

28.2 ETIOLOGY

The cause of malignant transformation of melanocytes is unknown. It may be spontaneous, especially when the tumor is present at rare anatomical locations. But, most skin melanomas and probably also ocular forms of melanoma are caused by UV-induced changes in predisposed individuals. The greatest risk is in the population with skin phototype I, II.

Excessive exposure to UV radiation, received in a short period of time (beware of sunburn with solar dermatitis), is considered the most dangerous.

Genetic factors are also important in its pathogenesis. Several hereditary syndromes, such as familial atypical multiple mole (FAMMM) dysplastic nevi syndrome, xeroderma pigmentosum, are also playing roles in melanoma development. Approximately 5–10% of melanomas occur in families with genetic predispositions.

Other predisposing factors are: presence of large congenital nevi, drug-induced immunosuppression, or HIV disease.

28.3 SYMPTOMATOLOGY

Most patients present with complaints that the pigment nevus has become larger, it is bleeding, discolored, itchy or flaky.

The ABCDE criteria are set to identify suspicious lesions:

Asymetrie – irregular asymmetric shape
Bordeline – border irregularity, crimped edges with projections and notches
Colour – irregular speckled discoloration
Diameter – diameter over 5 mm and continuous enlargement
Evolvement – tendency to melanoma development

28.4 DIAGNOSTICS

Primary skin melanoma is in most cases diagnosed clinically, visually, but long-term experience and practice is required. Classical or computer dermatoscopy can also be used in differential diagnosis.

The clinical examination must include palpation of lymph nodes areas (groin, axilla, clavicle and cervical lymph nodes), or ultrasound examination. Histological examination is required when complete lesion removal (not biopsy) is required.

Staging examinations include X-ray of the lungs, ultrasound of the liver, CT of the chest, abdomen and lesser pelvis. Based on the symptoms, examinations may also include bone (scintigraphy), brain (CT, MR), FDG CT / PET, blood count and biochemistry testing.

28.5 Differential diagnostics

It is necessary to exclude benign lesions such as verruca, fibroma, hemangiomas, onychomycoses as well as other malignant skin tumors (spinaliomas, basaliomas).

28.6 Pathology

Malignant melanoma is a melanocyte-based neuroectodermal tumor. Theoretically it can arise in any tissue. In the vast majority of cases it occurs on the skin, in the tissue of the eye and rarely on the mucous membranes. The most common form is skin melanoma. Nowadays, it is essential to investigate the presence of activation mutation BRAF 600 to decide on further treatment options.

From clinical and pathological point of view melanomas can be divided into several types:

Superficial spreading melanoma (SSM) - represents about 58% of all. It is the most common form with the highest causal effect of UV radiation. Grows slowly, occurs most often on the trunk and limbs. **Nodular malignant melanoma** (NMM) is present in about 21%. From the beginning it is a vertically growing tumor with a high probability of metastases.

Lentigo maligna (LMM) represents about 9% of all melanomas. It is a slowly growing form, often located on the face, and especially found in old age groups.

Acrolentiginous malignant melanoma (ALM) is a special form of melanoma that occurs on the distal parts of the finger, usually subungally. It causes considerable diagnostic problems because it can be mistaken for subungual hematoma or onychomycosis. It also occurs on the palms and soles of the lower limbs.

Mucosal melanomas account for less than 1%. UV rays are not involved, the incidence is the same for all races. They occur in the vagina, perianally, orally, in paranasal sinuses, etc. Usually they are diagnosed late, which worsens their prognosis.

Eye melanomas are the most common intraocular tumors in adults. They may originate from various intraocular structures, from choroid, cilia or iris.

28.7 Extent of the disease

TNM classification version 8 was issued in 2017 and is currently used. It is relatively complex and biochemical criteria such as LDH levels are also included in the stage assessment.

However, following criteria are still used when assessing tumor size by a pathologist: invasion depth through histological skin layers (Clark I-V) and vertical tumor thickness in mm (Breslow).

Prognostic risk factor is the presence of ulceration, angioinvasion, lymphangioinvasion, high mitotic activity and elevated LDH levels.

28.8 THERAPY

Surgery - early total excision with sufficient edges of healthy tissue is the only curative treatment method. Currently, there exist a recommendation - excision with a 1 cm edge of healthy tissue for T1 and T2 and a 2-3 cm edge for T3 and T4. The excision depth should be at least equal to the melanoma height (up to the muscle fascia). If the tumor has not been excised "in toto", insufficient safety margin was not respected, or surgical incision has passed through the tumor, re-excision is recommended. Re-excision should be performed within 4 weeks of the primary procedure. In case of metastatic involvement of regional nodes, lymph nodes block dissection is indicated.

Sentinel node method is used to detect clinically undetectable metastases. It follows the assumption that in lymphatic metastases, lymph nodes are drained via the lymph from the primary tumor site to a tumor-draining nodes present in a relevant regional area and where metastases are most likely to be detected. If this sentinel node is affected, exenteration of the relevant tumor-draining area is considered. If not affected, the tumor has not yet metastasized and exenteration is not performed.

Adjuvant therapy: Immunotherapy with interferon alpha is used. It is used in clinical stage IIB - IIIC according to AJCC classification 2011. However, its effectiveness is questionable, since it does not improve OS (overall survival). Currently, promising data for adjuvant combined administration of **BRAF / MEK inhibitors** dabrafenib / trametinib in patients with BRAF V 600 activation mutation or immunotherapy with anti PD antibodies nivolumab or pembrolizumab in patients with BRAF negative tumor are already available.

In cases of positive lymph nodes, **adjuvant radiotherapy** is indicated.

Palliative treatment is indicated for generalized or recurrent disease. Nowadays, new treatments methods are prefered and chemotherapy use is declining.

Tumors with BRAF and V600 mutations can be treated with **BRAF inhibitors:** vemurafenib, dabrafenib, optionally by combining the **BRAF inhibitor with the MEK inhibitor** dabrafenib / trametinib, or vemurafenib / cobimetinib. In addition, patients with generalized malignant melanoma can be treated by **immunotherapy** with ipilimumab (**anti-CTLA-4 receptor antibody**) or with **anti PD antibodies**: nivolumab, pembrolizumab.

It is also possible to use **radiotherapy**, especially in lymph node involvement or when metastases are present (to the bone, brain, etc.).

Intralesional treatment with Talimogene laherparepvec (T-VEC) is an interesting option for local affections or recurrent lymph nodal disease.

28.9 POST-TREATMENT COMPLICATIONS

Depend on the type of treatment performed. After surgery, keloid scars and dehiscence may develop. Acute skin reactions may occur after radiotherapy: erythema, rash, edema, lysis of epithel, or chronic changes such as: fibrosis, telangiectasias, lymphedema. Immunotherapy is associated with high temperature, flu-like symptoms, mucosal toxicity (colitis, enteritis) and other immunological problems. Significant photoprotection is required when using BRAF inhibitors.

28.10 FOLLOW-UP

It is permanent and includes clinical and physical examination of scars, regional lymph nodes, lung X-ray, liver ultrasonography. Further examinations are indicated based on the patient's symptomatology. Visits are regular - once every 3 months, after 2 years then twice a year.

28.11 PROGNOSIS

It depends on the time of diagnosis and the size of the tumor. When the tumor is removed in the radial spread phase, metastatic process is practically prevented and these patients are cured by simple excision. The vast majority of cases can be detected through education and prevention, and most skin melanoma deaths are completely unnecessary.

For isolated primary malignant melanoma, is a number of prognostic factors: age, associated internal diseases, Clark's stage (skin invasion level), vertical tumor thickness (histopathological measurement of maximum tumor thickness in mm- Breslow's stage), ulceration, angioinvasion, lymphangioinvasion, and mitotic activity.

28.12 PREVENTION

It is related to population education - information about harmful effects of UV radiation and necessity to use creams with high UV protective factors, especially for phototypes I and II. The so-called tertiary prevention is also important, ie permanent follow-up of patients who have already been treated for melanoma in order to prevent or detect progression of the disease on time.

29 SARCOMAS

Marián Liberko

29.1 EPIDEMIOLOGY

Soft tissue sarcomas form a heterogeneous group with more than 80 histological types. Most sarcomas are based on soft tissues 75%, gastrointestinal stromal tumors account for 15% and bone sarcomas 10%. The most common are liposarcomas and leiomyosarcomas. Overall, these are rare cancers, which account for less than 1% of malignant tumors in adults, but are very common in children and account for about 10% of all pediatric malignancies - ranking third after haematological malignancies and CNS tumors. Predilection area are limbs - almost 50%, most often in the thigh area. Sarcomas occur on the trunk and retroperitoneum in 40% of cases and in the head and neck area in 10%. Sarcomas metastasize predominantly hematogenously to the lungs; lymphogenic metastasis is rarer. Synchronous metastases occur in 20–25% of patients.

29.2 ETIOLOGY

Sarcomas are tumors of mesenchymal origin. The cause of malignant transformation of mesenchymal cells is unknown. Congenital genetic abnormalities or deletions of key genes such as p53 in Li-Fraumeni syndrome may be involved in pathogenesis. Many sarcomas exhibit specific chromosomal rearrangements and mutations that are detectable by molecular-biological methods and allow for further subcategorization of sarcomas. Another risk factor is ionizing radiation. Therapeutic irradiation can lead to secondary malignancies of both bone sarcomas and soft tissue sarcomas.

29.3 SYMPTOMATOLOGY

Symptoms of the disease are influenced by the location and size of the tumor. When tumor is localized on limbs, there is palpable resistance. Other manifestations are pain, especially nocturnal in bone sarcomas, limitation of limb movement or pathological fracture in bone involvement. In tumors on the trunk and retroperitoneum, symptoms are often minimal or nonspecific. With slow growth, the surrounding tissues and organs have long adapted to expansion. Thus, even large tumors can be an accidental findings during examinations for other diseases. The most commonly reported symptoms are pressure, abdominal pain, abdominal tension, emptying disorders, back pain and weight loss. In gastrointestinal stromal tumors, the first manifestation may be blood in stool, hematemesis, abdominal pain or acute abdomen.

29.4 DIAGNOSTICS

Numerous examinations are used in the diagnosis of soft tissue sarcomas. Ultrasound examination can be considered to be a basic diagnostic method, which can already lead to a suspicion of a tumor. CT scan, or better yet, MRI, provides better information on the extent of the disease and the relationship of tumor site and surrounding structures. Histological examination provides additional information necessary for the choice of treatment. Further distinction of individual subtypes is possible by means of immunohistochemical examination and molecular biology methods. If malignancy is confirmed, staging

examinations are indicated to determine the extent of the disease and to select the optimal treatment procedure - skeletal scintigraphy or PET / CT. However, there is no specific marker for sarcomas that would allow monitoring of response to treatment and possible relapse of the disease after treatment is over.

29.5 THERAPY

The treatment of sarcomas, as well as other malignancies, takes place via multidisciplinary teams. All oncological treatment modalities (surgery, radiotherapy, brachytherapy, chemotherapy, biological therapy, hormonal therapy and hyperthermia) may be used, depending on histology, extent of the disease (staging) and patient's condition.

Surgical procedure

The quality of the operation is crucial for the patient's further fate. The goal is to achieve R0 resection, i.e. with histologically negative edges. There are three basic types of resection: marginal excision, broad local excision and radical resection.

In **marginal excision**, the tumor is removed only with its pseudocapsule at high risk of leaving a subclinical microscopic residue. Resection margins are smaller than 1 cm. The risk of local recurrence in this case is 80%. In the case of re-resection, a residual tumor was described in 50% of cases.

In **broad local excision**, the tumor is removed with more than 1 cm border of healthy tissue within one muscle compartment. The risk of local recurrence varies between 30% and 60%. This method of excision can provide effective local control of superficial limb tumors.

Radical resection removes the tumor with the entire muscle compartment in one block up to the insertions and in the fascial boundaries. The risk of local recurrence is described as 10–20%. Often, the neurovascular bundles and affected part of the bone must also be removed. Replacement of nerve and bone grafts is a part of this resection. Large defects can be replaced by stalk lobes or loose tissue transplants. A conservative, limb-saving approach is always preferred. Amputation is acceptable only in the case of irreversible damage to the limb and neurovascular bundles by the tumor, which, despite the performance of the limb sparing performance, would result in no limb function. Contrast clips should be placed in the tumor site area for radiotherapy planning purposes.

Surgery in addition to resection of the primary tumor is also indicated in the context of metastasectomy of lung metastases - the oligometastatic disease; either alone or in combination with non-adjuvant or adjuvant systemic treatment. Combination therapy extends the symptom-free period and overall survival. There is less evidence for liver metastectomy.

External radiotherapy

It is applied in the form of preoperative, intraoperative or postoperative, alone or in combination with systemic treatment. Sarcomas are among the more radioresistant diseases requiring application of high doses of radiation, which is often limited by the presence of risk organs near the irradiated volume.

Pre-operative radiotherapy is an option with the aim of reducing the size of the primary tumor, improving operability and “sterilizing edges”. The advantage of preoperative radiotherapy is lower

overall dose (45–50 Gy) and also the presence of the tumor itself, which to a certain extent pushes neighboring radiosensitive structures further away. After surgery, radiotherapy is indicated for deep-seated tumor in biologically younger patients, R1 resection, marginal resection, high grade tumor and tumor size above 5 cm. Doses administered postoperatively are higher (60-65 Gy) and the irradiated volume is larger, because of postoperative changes and scars.

Brachytherapy

Brachytherapy is another option used in the treatment of sarcomas. It can be administered alone or in combination with external radiotherapy to increase dose delivered to the tumor site, or to treat recurrent tumors in an already irradiated volume. Treatment with interstitial brachytherapy may be initiated in a relatively short period of time after surgery, as opposed to external radiotherapy, which may be initiated only after the resection wound has healed, meaning in 3-4 weeks. The principle is based on the introduction of plastic catheters into the tumor bed during surgery and subsequent postoperative irradiation of the bed in the form of interstitial brachytherapy using the afterloading technique.

Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) allows single-dose irradiation of the target volume with a high dose while leaving critical healthy tissues intact as much as possible. Pre- or post-operatively, the dose may be supplemented by external irradiation. Dose escalation increases the possibility of local control. Mobile X-ray irradiators or a linear accelerators (mobile linear accelerators are used or patient is transported to the irradiation facility) are used to perform the IORT. The disadvantage is the necessity of single application and difficult determination of radiation dose. IORT is mainly used in retroperitoneal sarcomas.

Chemotherapy

Sarcomas are generally classified as chemoresistant tumors. Chemotherapy can be indicated in adjuvant, non-adjuvant and palliative administration. The most effective cytostatics are anthracyclines (doxorubicin, epirubicin), ifosfamide, with less response dacarbazine, gemcitabine and taxanes. Possibility of administration is monotherapy or combination.

Adjuvant chemotherapy

The aim is to improve local control and extend the time to disease relapse. In adjuvant administration, chemotherapy may be considered for high-grade tumors greater than 5 cm in depth, in younger patients and in chemosensitive histological types (liposarcoma, synovial sarcoma and partially leiomyosarcoma). Clear-cell sarcoma and alveolar sarcoma are considered chemoresistant.

Neoadjuvant chemotherapy

It can facilitate tumor operability, allow for conservative solutions without mutilating consequences and reduce the risk of dissemination. At the same time it may identify patients who could benefit from adjuvant therapy, based on the tumor response. The percentage of tumor necrosis found after neoadjuvant treatment is considered to be an independent predictive factor in soft tissue sarcomas.

Palliative chemotherapy

Used for metastatic diseases, which are most often the lungs. Prognosis of generalized sarcomas is poor. The aim is to slow progression of the disease and alleviate the symptomatology of metastatic spread.

Most commonly, doxorubicin or ifosfamide are used as monotherapy. Combined regimens lead to prolonged asymptomatic period but do not prolong overall survival.

Biological treatment

A tyrosine kinase inhibitor, pazopanib, is available for the treatment of selected subtypes of soft tissue sarcomas (except liposarcoma). It is indicated in the 2nd line of metastatic disease with improved symptom-free period and overall survival against chemotherapy. A novelty is monoclonal antibody: anti-PDGFR alpha - olaratumab.

29.6 Other types of sarcomas

Gastrointestinal stromal tumor (GIST) – the most common type of sarcoma with a significantly better prognosis compared to soft tissue and bone sarcomas. Its typical attribute is expression of the CD 117 marker. The most common sites are the stomach, duodenum, jejunum, ileum, colon and rectum. Basic treatment is surgical resection with the aim of R0 resection. Possible adjuvant therapy is indicated according to the presence of risk factors in the histological preparation. In case of metastatic disease, palliative treatment is indicated. GISTs are completely chemoresistant tumors. In their treatment, both adjuvant and palliative, targeted treatment with a tyrosine kinase inhibitor – imatinib – is used.

Bone tumors – very rare in adulthood. High grade osteosarcomas and chondrosarcomas; in these cases, multimodal treatment of a chemotherapy, surgery and radiotherapy is utilized. A specific type is Ewing's sarcoma, which is most common during puberty; however, it can be encountered later in life. It is a bone tumor with a pronounced extraoseal component and early hematogenous dissemination to the lungs and bone marrow. Treatment is multimodal according to international protocols and combines induction chemotherapy, surgery, radiotherapy and consolidation chemotherapy.

29.7 Post-treatment complications

Acute side effects are most often wet desquamation of the skin in irradiated fields. Late adverse effects of radiation after conservative surgery may significantly affect function of the preserved limb. These include limiting the extent of movement due to fibrosis, muscle and joint contractures, edema, chronic pain and bone fractures. Long-term rehabilitation is required after the end of treatment. Risk of developing secondary malignancies is particularly high in children treated for soft tissue sarcomas with expected long-term survival. The most common secondary malignancies include osteosarcomas, brain tumors and leukemia.

29.8 Follow-up

The aim of post-treatment follow-up is to detect any recurrence of the disease in time to the extent that subsequent intervention may have a curable effect. A follow-up examination should take place every 3 months for at least 3 years. Regular monitoring of the primary focus site using imaging methods is necessary to detect very frequent locoregional recurrence. Part of the follow-up is also examination to assess the presence of metastases. The risk is highest for the first 2–3 years after treatment of the primary tumor.

29.9 PROGNOSIS

Five-year overall survival is 50–60%. The main prognostic factors are tumor size, placement depth in relation to superficial fascia, presence of metastases in distant organs, degree of differentiation and radicality of surgery. Adverse factors include higher age and poor general condition of the patient. Response to preoperative treatment in advanced forms and the duration of asymptomatic period for relapse are also of prognostic importance. Even after radical tumor removal, distant metastases occur in 50% of cases within 5 years. In primary inoperable and metastatic forms, only 10–30% of patients experience a response to combination therapy, resulting in a low 5-year survival rate of 8%.

30 MALIGNANT TUMORS OF THE CERVIX

Martina Kubecová, Klaudia Reginášová

30.1 EPIDEMIOLOGY

There are large regional differences in the incidence of this tumor. It is highest in South America, the lowest in Israel, Finland, Luxembourg and Ireland (less than 5 per 100,000 women). In the Czech Republic, 15 new cases / 100,000 women were recorded in 2016. We are even able to recognize large differences within the country. The mortality rate for this cancer is low, in the Czech Republic in 2016 it was calculated to be 6.9 / 100,000 women. The problem is the diagnosis of early stages. In the Czech Republic, only 50% of cases were diagnosed in stages I and II, while in other EU countries the number is around 75%. The highest incidence is seen in women between the ages of 40 and 49. Screening for cervical cancer is extremely important for diagnosis of early stages. As of 2008, cervical cancer screening has been occurring in the Czech Republic, offered to women during gynecological examinations, the process includes cytological collection once a year, aimed at detecting precancerous lesions and early stages of the tumor.

30.2 ETIOLOGY

The role of human papillomaviruses (HPV), particularly HPV 16 and 18, in the development of cervical cancer has been confirmed. Factors contributing to the transmission of these viruses include promiscuity, early commencement of sexual life and poor personal hygiene. Smoking also plays an important role. Vaccination plays an important role in preventing HPV-associated tumors and is recommended in girls between 13-14, around 1 year before commencement of sexual activities.

30.3 SYMPTOMATOLOGY

The most common symptoms which cause a woman to come to the doctor include vaginal bleeding, especially after intercourse, and discharge. Abdominal and sacral pain with weight loss occurs in more advanced stages. Uremia caused by blockage of ureters by the pelvic tumor is a symptom of very advanced tumors.

30.4 DIAGNOSTICS

The basis of proper diagnosis is a gynecological examination (vaginal and rectal) and collection of cytology. Histological verification by biopsy or endocervical curettage is required. Basic staging examinations include lung X-ray, ultrasound examination of kidneys and lower pelvis, vaginal ultrasound and pelvic magnetic resonance imaging. CT examination of abdomen/pelvis and PET, and sometimes. cystoscopy or rectoscopy are indicated in more advanced tumors. Magnetic resonance imaging is extremely important in the early stages when there is uncertainty as to whether the tumor is confined to only the cervix or invading the parameteria. In squamous cell carcinoma, a tumor marker SCC is also examined for.

30.5 Differential Diagnostics

It is necessary to distinguish the possible infiltration of another malignant tumor (uterine carcinoma or rectal carcinoma) into the cervix.

30.6 Pathology

In the beginning, there are changes in the cervical epithelium, such as dysplasia, which we call CIN (cervical intraepithelial neoplasia). We distinguish 3 levels: CIN I - mild, CIN II - moderate, CIN III - severe. Cancer can develop directly (without dysplasia), and dysplasia does not have to turn into cancer. The term carcinoma in situ refers to a stage where the malignant tumor has not yet broken through the basal membrane.

Invasive carcinoma is histologically 90% squamous cell, 9% adenocarcinoma and 1% other subtypes of malignant tumors (undifferentiated carcinoma, sarcoma, neuroendocrine carcinoma, etc.). The tumor may have a different degree of differentiation, which is designated by so-called tumor grading (G1 - well differentiated, G2 - moderately differentiated, G3 - slightly differentiated, undifferentiated). Prognostically worse tumors are less differentiated.

The tumor may grow on the surface of the cervix (exophytic) or within the cervix (endophytic). Endophytic growth usually allows for the disease to be detected at a more advanced stage because it is asymptomatic for longer periods of time.

30.7 Therapy

Depends on the stage of the disease.

Stage I - the tumor is limited to the uterine cervix.

Stage I tumors may be microscopic (referred to as Ia1 and Ia2), but also very bulky, for example in excess of 4 cm in length (labeled Ib3 according to the new classification as of 2018). Surgical treatment is the treatment method of choice. Microscopic tumors can be resolved by conization (excision of the cervix while saving the body of the uterus), which allows for possible subsequent pregnancies. In older women and larger stage I tumors, a hysterectomy is performed with resection of borders, with removal of uterine vessels, bilateral adnexectomy and lymphadenectomy. Postoperative irradiation is sometimes necessary.

Stage II - the tumor spreads from the cervix to the parametria: IIb (not up to the pelvic wall) or to the upper third of the vagina - IIa.

Surgical treatment can only be used in stage IIa if the tumor affects only the upper third of the vagina and when the upper third of the vagina is also resected in addition to the cervix. For other tumors, radiotherapy (RT) enhanced by chemotherapy is indicated.

Stage III - the tumor spreads from the cervix to the pelvic wall or into the lower two-thirds of the vagina, or causes hydronephrosis (blockage of the ureter and preventing urine outflow from the kidney). The method of treatment choice is radiotherapy potentiated by chemotherapy.

Stage Iva - the tumor grows into the bladder or rectum. The method of treatment choice is radiotherapy, often only palliative.

Stage IVb - the tumor produces distant metastasis. The treatment is most often only palliative.

In the early stages of disease, the results of radiotherapy and surgery are the same, however radiotherapy has more complications.

Radiotherapy is always used in combination, for example as **external radiotherapy** and brachytherapy. We irradiate the area of the lower pelvis, which includes the uterus with the tumor, as well as the lymph nodes (nodes of the pelvis). Irradiation is performed in linear accelerators utilizing high energy braking radiation, and using the multiple field technique (most often called IMRT), where we try to salvage as much healthy tissue as possible (Fig. 1). The dose of radiation to a lower pelvis does not usually exceed 45 Gy applied over 5 weeks, irradiating daily in small doses (1.8–2 Gy).

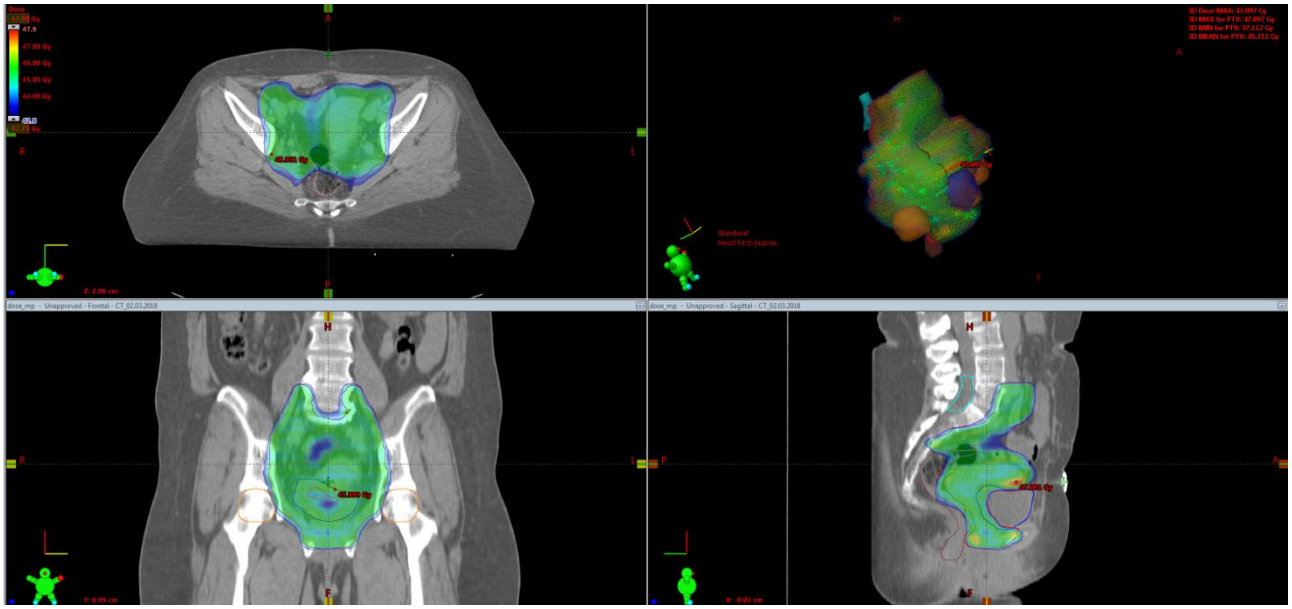


Figure 1 Irradiation of the lower pelvis using IMRT technique

Brachytherapy (BT) is irreplaceable in the radical treatment of cervical cancer because it allows us to apply a high dose of radiation (up to 85-90 Gy) directly into the tumor without damaging the surrounding healthy tissues. BT applicators are inserted directly into the vagina, cervix and uterine body, known as uterovaginal BT (intracavitary). We use Ir 192 (gamma emitter) with high dose rate (HDR) as a radiation source. If BT cannot be performed for any reason, the chances of tumor curability are significantly reduced. Postoperative irradiation involves vaginal (intracavitary) BT, where the applicator is inserted into the vagina, which ends as blind scar.

Chemotherapy is a complementary method used in cervical cancer. It is used as

- Concomitant, ie potentiation of RT, most often cisplatin once a week,
- Neo-adjuvant: preoperative, for large so-called bulky tumor Ib2 (tumor > 4 cm) or IIa, when ifosphamide and cisplatin are most commonly administered - 3 series at an interval of 10 days followed by surgery. The goal is to reduce the tumor and improve operability.

- Palliative: in recurrent and metastatic tumors, most commonly cisplatin and paclitaxel, ifosfamide.

Biological therapy is used in cervical cancer in combination with chemotherapy for metastatic disease. The preparation avastin (bevacizumab) - VEGF inhibitor (vascular endothelial growth factor), acting on newly formed vasculature, is used.

30.8 Post treatment complications

Critical organs for radiotherapy are loops of the small intestine, rectum and bladder.

Acute complications may be seen after irradiation, occurring a few weeks after stopping RT.

- GIT: diarrhea, flatulence, bleeding (rarely),
- urological tract: dysuria, polakisuria, hematuria (rarely),
- skin, mucosa: erythema, exanthema, edema, epitheliolysis.

Delayed complications may be seen 6 or more months after stopping RT, and are usually incurable:

- GIT: enteritis, proctocolitis, proctitis, bleeding, intestinal stenosis, ulceration, fistula (rectovaginal),
- urological tract: stenosis of the ureters and urethra, cystitis, incontinence, hydronephrosis, ulceration, fistula (cystovaginal),
- skin and mucosa: dryness, hyperpigmentation, depilation, telangiectasia, fibrosis, necrosis, stenosis of vagina or even blockage

30.9 Follow Up

Regular and lifelong; 1st and 2nd year, follow up is performed every 3 months, 3rd to 5th year every 6 months, then once a year. We always perform a gynecological examination, and in certain intervals renal ultrasound, blood count and biochemistry, ultrasound of lower pelvis, X-ray of lungs, SCC (Tumor marker specific for squamous cell carcinoma), and eventually CT or MRI

30.10 Prognosis

The main prognostic features include the size of the tumor itself and lymph node involvement. Prognosis is worsened by: high grading, histological type - adenocarcinoma, endophytic growth, secondary anemia, worse general state of the patient, etc.

5- Year survival: St. I – 90 %, St. II - 60 – 75 %, St. III - 25 – 48 %, St. IV - 5 - 10%.

31 MALIGNANT TUMORS OF THE UTERUS

Martina Kubecová, Klaudia Reginášová

31.1 Epidemiology

It is the most common gynecological tumor and the second most common tumor in women (after breast cancer, not including skin tumors). The incidence is particularly high in developed countries, estimated to be around 20–35 new cases per 100,000 women. In the Czech Republic, the incidence was 36/100 000 women in 2016, while mortality was comparatively low, 8/100 000. Most patients are postmenopausal (75%).

31.2 Etiology

Risk factors for endometrial cancer include obesity, diabetes mellitus, hypertension, family history, infertility, nulliparity, Stein-Leventhal syndrome, estrogen exposure, and high animal fat intake.

31.3 Symptomatology

The most common symptom is vaginal bleeding during menopause. Bleeding may be caused by endometrial cancer in 1/3rd of the cases, myoma in the next 1/3rd and unknown cause in final 1/3rd (it is probably a hormonal imbalance). Other symptoms such as abdominal pain, back pain, disorders of urinations and weight loss are signs of advanced disease.

31.4 Diagnostics

The basis of proper diagnosis is a gynecological examination (vaginal and rectal). Histological verification by endocervical curettage or hysteroscopy is required. Basic staging examinations include X-ray of the lungs and ultrasound examination of the kidneys and lower pelvis. Special importance is given to vaginal ultrasound examination, which shows us not only the size of the uterus and its relationship to the surrounding structures, but also the height and homogeneity of the endometrium, and depth of tumor penetration into the uterine wall, etc. Additional examinations include CT scan of the abdomen and lower pelvis, magnetic resonance imaging, and PET, etc.

31.5 Differential Diagnostics

It is necessary to distinguish the infiltration of another tumor in the uterus, such as cervical cancer, bladder cancer or rectal cancer.

31.6 Pathology

90% of these are adenocarcinomas (endometrioid, clear-cell, serous papillary, etc.), and 2-4% are sarcomas (leiomyosarcoma, endometrial stromal sarcoma, etc.), which are prognostically unfavorable. In

addition, adenoacanthomas may arise from squamous metaplasia. Tumor differentiation is based on grading (G1, G2, G3), and is of great importance in the prognosis of the disease.

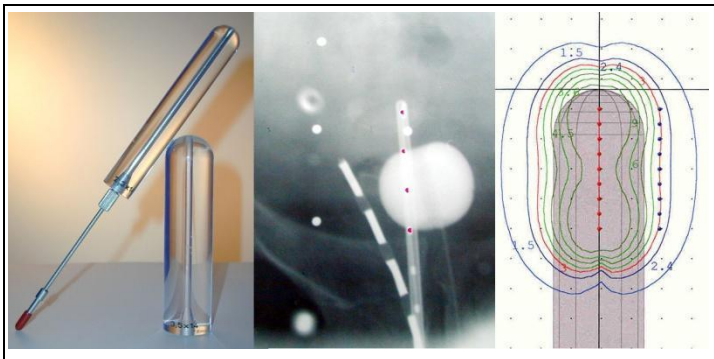
31.7 THERAPY

Therapy depends on the stage of the disease. The method of treatment choice is **surgical** intervention in stages I - III. The extent of the procedure depends on the extent of involvement (depth of tumor growth in the uterine body), tumor differentiation and lymph node involvement. Most often hysterectomy with bilateral adnexectomy is performed. Lymphadenectomy is indicated in more advanced and less differentiated tumors. Omentectomy is indicated in serous papillary carcinoma. We must not forget that the lymph nodes of the uterus not only drain into the lower pelvic nodes but also paraaortic lymph nodes.

Depending on the extent of the surgical findings, **postoperative adjuvant radiotherapy** (RT) is indicated in some cases.

Post-operative RT can be combined, ie tele-therapy and brachytherapy (BT), or independent vaginal BT can be used, which is administered by insertion of the applicator for BT into the vagina and subsequent irradiation of the upper third to half the vagina. (Fig. 1)

Figure 1 Adjuvant brachy radiotherapy in Uterine cancer



A B C

a) applicator for vaginal HDR brachy radiotherapy - linear emittor

b) image of the applicator with source mockup, with rectal marker and contrast filled bladder

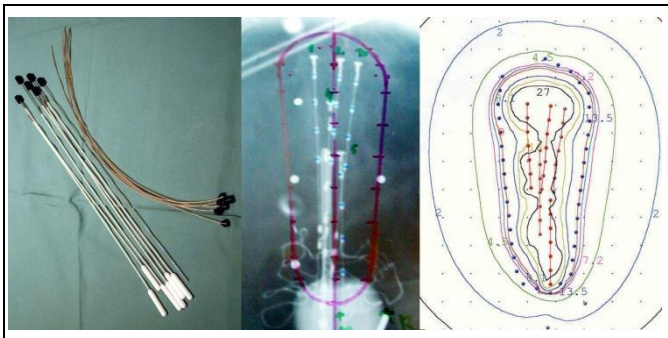
c) isodose plan

For external irradiation, high-energy X radiation of linear accelerators is used. Irradiated areas include drainage lymph nodes, the dose does not exceed 45 Gy for 5 weeks, multi-field technique (most commonly called IMRT) is used.

Independent Radiotherapy is indicated in the case of advanced disease, or if the patient is contraindicated for surgery due to internal medicine criteria. In advanced diseases, we use combination therapy: teletherapy and brachy radiotherapy (uterovaginal). In early stages, endometrial cancer can be cured by independent uterovaginal brachytherapy. There are several possible techniques that may be used. The most successful way in irradiating the uterus by the so-called Heyman tamponade (Figure 2), when the uterus is filled (under general anesthesia or analgosedation) with the brachytherapy applicators. The disadvantage is that we require high-quality X-ray imaging of the application, which is nearly impossible in obese women, who also happen to be most likely to suffer from endometrial cancer. Therefore, the most commonly used method is the Y probe (Figure 3), where the brachytherapy applicator is inserted into each of the corners of the uterus and joined into a Y-shape in the cervix. This

application also gives a very good dose distribution. The simplest method is utilization of a linear emitter (Figure 4a) where a simple applicator (probe) is inserted into the uterus. This method can be used for radical brachytherapy in the case of a small uterus or as a palliative method.

Figure 2 Brachy Radiotherapy used in inoperable uterine cancer



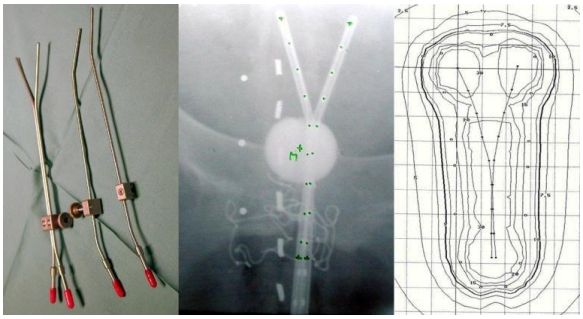
A B C

a) applicator for HDR brachy radiotherapy – Heyman's tamponade

b) image of the applicator with source mockup, with rectal marker and contrast filled bladder,

c) isodose plan

Figure 3 Brachy Radiotherapy used in inoperable uterine cancer



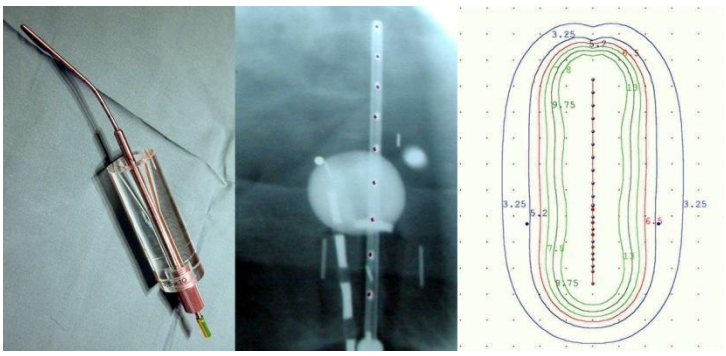
A B C

a) applicator for HDR brachy radiotherapy – Y probe,

b) image of applicator with source implants, rectal marker and urinary bladder filling with contrast,

c) isodose plan

Figure 4 Brachy Radiotherapy used in inoperable uterine cancer



A B C

a) applicator for HDR brachy radiotherapy,

b) image of the applicator with source mockup, with rectal marker and contrast filled bladder,

c) isodose plan.

Chemotherapy is used only in very advanced tumors, in younger patients, in massive lymph node involvement and especially in serous papillary carcinoma. The combination of carboplatin and paclitaxel is most commonly used.

Hormonal therapy is particularly important as a palliative method. Up to 33% of patients respond to hormonal therapy with gestagens at the time of metastatic spread. In particular, pulmonary metastases of mature endometrial cancer respond very well to this type of therapy and often with a long-term effect.

31.8 POST-TREATMENT COMPLICATIONS

Are identical to those found in cervical cancer.

31.9 FOLLOW UP

Regular, lifelong; 1st and 2nd year checkups every 3 months, 3rd to 5th year every 6 months, then once a year. We always perform gynecological examination, at a certain intervals also renal ultrasound, biochemistry panel, ultrasound of lesser pelvis, vaginal ultrasound, lung X-ray, Ca 125 level measuring (marker often indicating disease progression).

31.10 PROGNOSIS

Significant prognostic factors include the depth of uterine wall penetration, grading and lymph node involvement. Five-year survival varies greatly in stage I. In stage Ia, when the tumor affects only the endometrium or extends superficially into the myometrium and is well differentiated (G1), survival rates reach 98%. Survival decreases to 87-90% if the tumor is moderately differentiated or grows to serosa. 3 grade further reduces survival to 70-78%. In stage II, when the tumor grows into the cervix, the five-year survival rate is 65%. In pT3, when the tumor grows outside of the uterus, the survival rate is 15–30% and only 5% when it infiltrates into the rectum or bladder. 5-year survival of patients treated with independent radiotherapy stages I/ II reaches 74-78%.

32 OVARIAN CANCER

Martina Kubecová, Klaudia Reginá̋čová

32.1 EPIDEMIOLOGY

It is the second most common malignant gynecological cancer, incidence in 2016 reached 18 new cases per 100,000 women in the Czech Republic. Unfortunately, the disease has a very high mortality rate, almost 12/100 000 women. The highest incidence is in western countries, the lowest in Japan. Most often occurs in the 6th decade.

32.2 ETIOLOGY

Its etiology is not known, but ovarian cancer is more common in women who have not given birth and in women with fewer pregnancies. It is often associated with breast cancer and in 5–10% genetic-familial factors are involved. Genetic predisposition is proved mainly in high grade serous ovarian carcinoma (BRCA mutation I or II), therefore a large part of the patients with confirmed diagnosis of ovarian cancer is send for a genetic examination.

32.3 SYMPTOMATOLOGY

Early stages are completely asymptomatic. In up to 70% of cases, the tumor is only symptomatic in very advanced stages (IIIc). Symptoms occur due to the compression of abdominal organs by the tumor and by a growing ascites. However, the main presentations are digestive problems, nausea, vomiting, passage disorders, abdominal enlargement, pain, weight loss, etc.

32.4 DIAGNOSTICS

Diagnostic process is very difficult due to the anatomical location of ovaries inside the abdominal cavity. Early stages can be diagnosed by ultrasound examination. Other basic examinations include gynecological examination (vaginal and rectal), vaginal ultrasound examination, CT-scan of the abdomen and lesser pelvis and measurement of levels of tumor markers, especially Ca 125. This marker is elevated in 95% of malignant ovarian epithelial tumors. In mucinous carcinoma, Ca 19-9 is elevated, in granulosa cell tumors, beta-HCG and alpha-fetoprotein levels rise. Other staging examinations include lung X-ray. Laparotomy with subsequent histological verification is a diagnostic but also a therapeutic process.

32.5 DIFFERENTIAL DIAGNOSTICS

It is necessary to distinguish benign tumors and ovarian cysts, endometriosis and in advanced tumor exclude its origin from the gastrointestinal tract. In breast cancer, metastatic spread to ovaries should be considered.

32.6 PATHOLOGY

90% epithelial tumors (coelomic epithelium):

- Serous,
- Mucinous,
- Endometrioid,
- From clear cells (mesonephroid),
- Brenner's tumor,
- Mixed epithelial,
- Undifferentiated.

10% other:

- Dysgerminomas,
- Granulosa cell tumors
- Teratomas,
- Embryonic carcinomas,
- Choriocarcinomas and others

Histogenetic classification by tumor origin:

- **From coelomic epithelium**: epithelial, undifferentiated, carcinosarcomas,
- **From germ cells**: teratomas, germinomas, embryonic carcinomas, choriocarcinomas,
- **From gonadal stromal cells:** from granulosa cells,
- **From non-specific mesenchymal cells**: lipomas, fibromas, leiomyomas, angiomas, lymphomas, sarcomas.

32.7 THERAPY

The method of choice is **surgery**. Only rarely in very advanced diseases with wide metastatic spread such as to the liver or CNS and in patients in very poor general condition it is possible not to perform laparotomy and diagnose the disease by biopsy, extremely rarely cytologically from ascites. In these patients palliative (most commonly chemotherapy) or symptomatic treatment is initiated. In a small percentage of patients with such an advanced tumor, response to chemotherapy is a significant regression of the disease. In these cases, chemotherapy can be considered a neoadjuvant treatment and radical laparotomy is indicated.

Basic surgical procedure include lavage of the abdominal cavity, when present, evacuation of ascites, hysterectomy, bilateral adnexectomy, uterine tube removal, omentectomy, commonly appendectomy, and in some cases also lymphadenectomy (pelvic, paraaortic lymph nodes). The effort is always zero macroscopic residual disease, which doubles overall survival and is the most important for disease prognosis.

Debulking surgery (surgery reducing tumor mass - cytoreductive) is also of the great importance because subsequent treatment is then often more effective. In primary inoperable tumors, where only explorative laparotomy with histology is performed, successful systemic chemotherapy is followed by so-called interval debulking surgery - an operation that in the second phase removes the remaining tumor including ovaries, uterus, omentum, etc.

Chemotherapy (CHT) is a systemic treatment method based on platinum derivatives and taxanes. The combination of carboplatin and paclitaxel is most commonly used. It is given as one day infusions at regular three-week intervals. It can be administered as adjuvant (postoperative), neoadjuvant (preoperative) or palliative method. Other cytostatics may be used but are less effective. Cytostatics can also be applied directly to the abdominal cavity.

Radiotherapy (RT) is only used in individual cases. Whole abdomen radiotherapy (WART technique) is indicated, when the treatment is limited by a radiation dose - maximum of 30 Gy with covering the liver and kidneys. RT is indicated, especially in cases of microscopic disease, in tumors smaller than 2 cm and more commonly in mature tumors (G1).

Palliatively we can irradiate, for example, tumor recurrence in the lesser pelvis, paraaortic lymph nodes and other metastases.

Hormonal therapy is hardly used, although 50% of the tumors are positive for estrogen and progesterone receptors. The effect of hormone therapy is small, maximum 5–15%, it is used only as a palliative treatment (tamoxifen - antiestrogen, aromatase inhibitors, Megace - Medroxyprogesterone acetate - gestagen - it only has a supporting effect).

Targeted treatment has become increasingly important in recent years. Treatment with bevacizumab increases time to relapse, but unfortunately has no impact on overall survival. In BRCA positive patients, the addition of PARP inhibitors (olaparib) to treatment of relapsing disease significantly prolongs overall survival. PARP inhibitors interfere with cellular repair processes and interfere with the DNA strand breaks repair process.

32.8 Post-treatment complications

Perioperative and postoperative complications consist of bleeding, intestinal perforation, complicated and prolonged healing, postoperative adhesions with intestinal passage disorders, etc. CHT has typical side effects - nausea, vomiting, alopecia, haematological toxicity up to febrile neutropenia, neurotoxicity, etc., RT of the whole abdomen can also be accompanied by nausea, vomiting, diarrhea, severe anorexia and passage disorders. Chronic complications also occur - especially passage disorders due to a bowel stenosis.

32.9 Follow-up

Is regular and lifelong - 1st and 2nd year visits every 3 months, 3rd to 5th year every 6 months onwards once a year. Gynecological examination, blood sampling for Ca 125 levels should always be performed, at certain intervals then also abdominal CT scan, ultrasound, biochemistry testing, X-ray of the lungs, or metabolic PET / CT.

32.10 PROGNOSIS

Prognostic factors include: extent of disease, tumor residue after surgery, tumor grading, histological subtype, patient's age.

There are three prognosis groups:

1. stage I, II, tumor completely radically removed, eventually with a microscopic residue,
2. stage I, II, minimal tumor residue (less than 2 cm),
3. bulky tumor, st. III, IV.

Five-year survival rate: within prognosis groups there are major differences in survival. For example in stage I, stage Ia (tumor within one ovary) having a survival rate of 90%, Ib (tumor inside both ovaries) of only 65% and Ic (tumor on the surface of the ovary, tumor ruptured or ascites present) only 57%. For stage II survival is 45% and for stage III, which is very advanced, 5-year survival is reported to be relatively high, up to 20-40%, in stage IV where distant metastases are present (eg liver, lung, bone, CNS) etc.) then only 5%.