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SOLID AND CHILDHOOD TUMOURS

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Contents:

Epidemiology of malignant tumours in the Czech Republic

J. Novák

Introduction

From the perspective of epidemiology, malignant tumours (malignancies - abbreviated MT) constitute a very important group of civilization diseases. Malignant tumours contribute significantly to the mortality of the population in developed countries, including the Czech Republic. One can say that the incidence of malignant tumours in the population rises proportionally to the development of society.

After cardiovascular diseases, which are the most frequent cause of death in our country and worldwide (and are responsible for almost half of all deaths) malignancy is the second leading cause of death in our country. Cancer mortality rate in the Czech population is about 26 %.

Risk factors for cancer development

Tumours arise secondary to genetic changes at the cellular level, which can be caused by external or internal factors. In general, advancing age is one of the major risk factors for adult malignant cancers. Most MTs develop in individuals aged 60 and older. Only some types of cancer (e.g. testicular and cervical cancers) are typically diagnosed in younger age groups. MTs in children and adolescents (0-19 years) comprise less than 1 % of all malignancies. Epidemiological studies from the last four decades have shown that external influences, especially lifestyle factors, play a crucial role in aetiology of malignant cancers. The most important ones include smoking, excessive alcohol consumption, dietary factors, carcinogenic substances, infectious agents, ionizing and UV radiation, etc. Risk factors related to specific types of cancer are described in more detail in corresponding chapters of this publication.

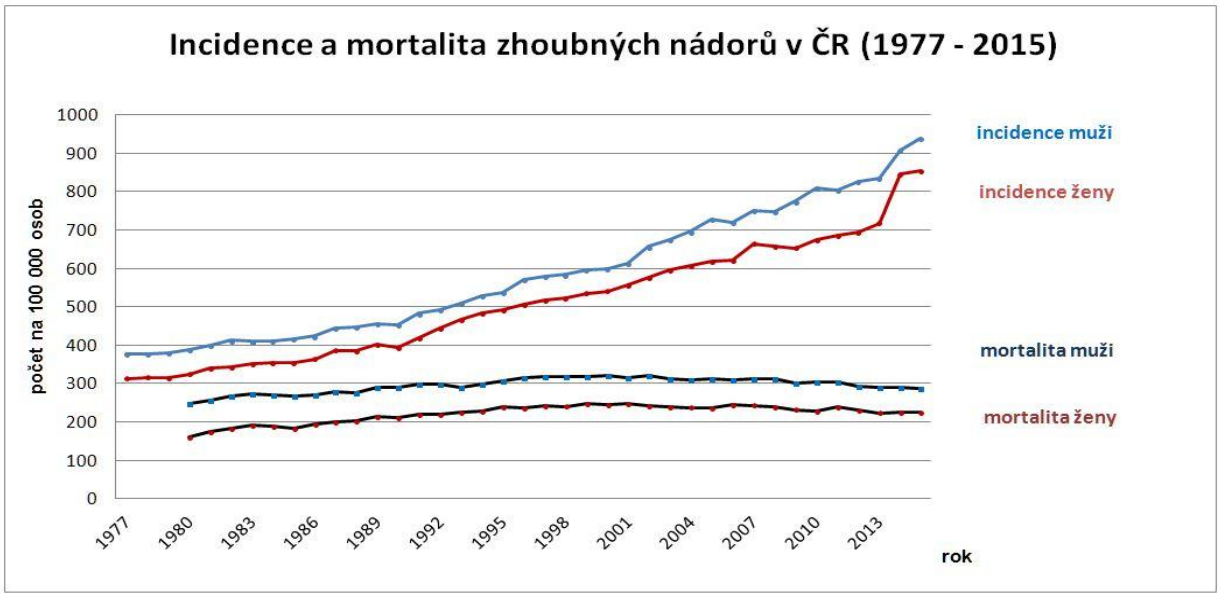
Hereditary forms of malignant cancer represent only about 5 - 10 % of all oncological diseases. The inherited form of the disease should always be considered when we encounter malignant tumour in a patient at a significantly lower age than is usual for the sporadic occurrence of that certain type of tumour.

Malignant tumours in the Czech population

Incidence and mortality

Currently, almost 100 000 malignancies are diagnosed in our country annually. The trend in incidence rates has a steadily increasing character. About 27 000 deaths per year are related to malignant cancer. The mortality rates show rather stagnating or slightly downward trend.

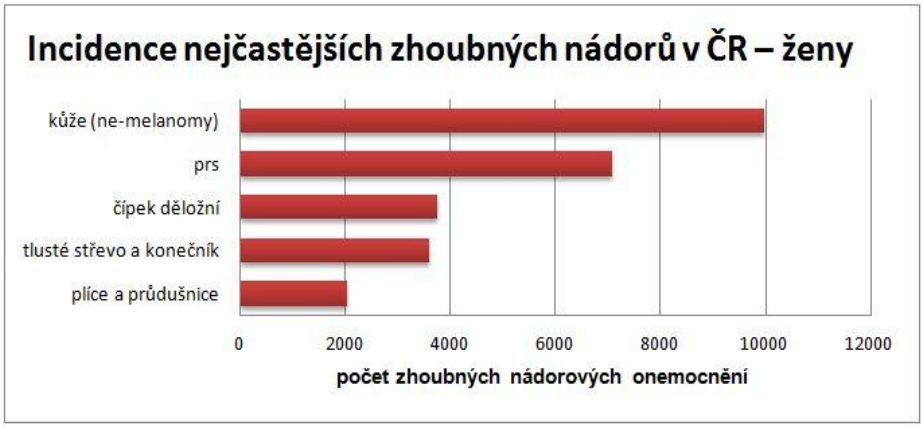
Cancer specific incidence and mortality trends in the Czech Republic are shown in graph 1.



The most prevalent type of malignancy in the population is non-melanoma skin cancer (predominantly basaliomas) and due to its unique characteristics and incidence, it is usually not included in epidemiological analyses. The most common male malignancies are prostate cancer and colorectal tumours. In women, we most frequently encounter breast and cervical tumours (including non-invasive stages), colorectal and lung cancer.

An overview of the most common malignancies in men and women is presented in Figure 2 and

Figure 3.

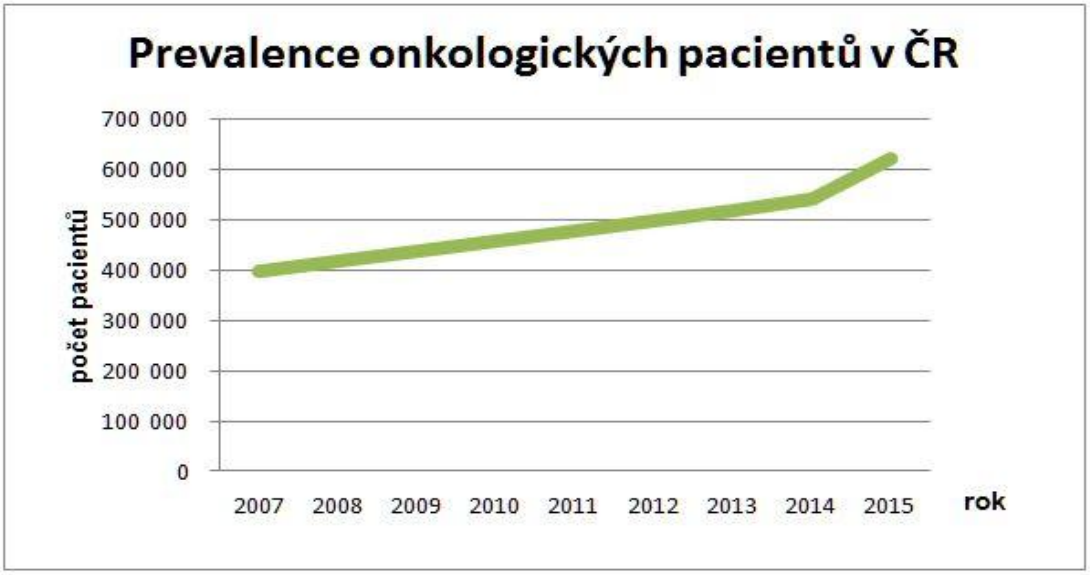


An upward trend in the incidence is noticeable in almost all types of malignancies. An exception, from the long-term perspective, is stomach and, more recently, male lung cancer. Stable incidence rate is observed in Hodgkin's disease. Most of the cancer-related deaths in the population are due to lung tumours, colorectal cancer, pancreatic cancer, and breast cancer in women. Mortality of the most common malignant cancers is shown in Figure 4.

Survival

The survival rate in oncology patients varies considerably, depending on the type of cancer. Five-year survival rates are highest for thyroid cancer (95 %) and testicular cancers (over 90%). The least favourable survival rates are associated with pancreatic, liver, biliary tract and lung cancer (less than 10 %).

Steadily increasing survival rates among oncology patients are reflected by higher prevalence rates, as shown in Figure 5.



International Comparison

Basic epidemiological characteristics of oncology diseases in our country correspond to the situation in other developed countries. The Czech Republic is the world's leading country in the incidence of kidney cancer. Similarly, the incidence of colorectal cancer in our population belongs to the highest in the Europe and worldwide.

The epidemiological data on malignant tumours in our country are available at the National Cancer Registry (NCR), which collects and analyses information from oncology reports. Submitting an oncology report to NCR is mandatory for all physicians involved in the care of an oncology patient.

Useful Links:

All data from the National Oncological Registry of the Czech Republic are available on the website of the Oncology Data Visualization System - https://www.svod.cz/.

Summary tables and overviews from the Czech National Oncology Register are published on the website of the Institute of Health Information and Statistics of the Czech Republic - https://www.uzis.cz/ .

Prevention and Screening of Cancer Diseases

J. Žaloudík

Prevention is an integral part of complex oncology care and fundamentally influences the overall outcomes, as well as cost-effectiveness of cancer treatment. It is important for all doctors to adopt **oncopreventive thinking,** in terms of primary, secondary, tertiary and even quaternary prevention.

Primary prevention aims to reduce the likelihood that an invasive tumour will develop. This is carried out through continuous education against smoking and other toxic substance abuse and the promotion of healthy diets and healthy lifestyle. More specific primary prevention strategies include systematic detection and treatment of precanceroses such as mucosal dysplasia and polyps, urothelial papillomas, suspicious nevi, chronic lesions and inflammations. Another example of primary prevention is the recent introduction of vaccination against viruses associated with certain types of cancer, e.g. human papilloma virus vaccination to prevent cervical cancer or hepatitis B vaccination to reduce the risk of hepatocellular carcinoma by avoiding chronic viral hepatitis and cirrhosis. However, the options of general cancer prevention are rather limited.

Secondary prevention attempts to diagnose an invasive tumour at the earliest and localized stage, that is, at the point when it has not clinically metastasized yet. In fact, early tumour detection provides patients with a chance for long-term cure, mainly by means of surgery and without any significant burden of anti-cancer treatment. Secondary oncological prevention primarily employs non-invasive techniques for the investigation of target tissues and organs. The risk of the most common malignancies increases with age, particularly after fifty years and regular preventive testing is therefore necessary especially in this age group. An active identification of hereditary risks of cancer among relatives or warning signs of cancer (such as the presence of blood in stool) is also an important part of secondary prevention strategies. Targeted screening further includes dermatologic examination, lymph node palpation, standard blood and urine examination, faecal occult blood test or colonoscopy, mammographic and complete gynaecological examination in women, prostate specific antigen (PSA) testing in men, a chest X-ray in smokers or individuals with specific occupational exposure risks. Ultrasound screening of the liver, pancreas and kidneys is commercially available in some institutions, as tumours of these organs typically present with late onset of symptoms usually at an advanced and incurable stage. The responsibility for secondary prevention lies mainly with general practitioners, gynaecologists, urologists and other ambulatory specialists, or specialized oncopreventive workplaces, such as screening mammography or preventive colonoscopy centres.

Tertiary prevention is aimed at early detection of tumour recurrence in cancer survivors. It also comprises screening of treatment-induced toxicities and comprehensive long-term dispensarization of the oncology patient, provided mainly by the oncology centre where the patient was treated, or other specialized outpatient departments. A durable treatment response in cancer survivors also increases chance of developing a second malignancy of other primary tumour that should be identified during the follow-up period. The frequency of second malignancies reaches as much as 15-20% and with the increasing prevalence of cancer diseases in the population, it is becoming a considerable challenge for healthcare system and oncopreventive services.

Quaternary prevention may seem like a paradox, since it addresses cases of advanced and incurable tumours, usually in the fourth clinical stage with metastatic spread. Yet, even in these cases, it is necessary to anticipate the course of disease and, in particular, potential complications of the tumour that may invalidate the patient for the rest of his life, regardless of whether it counts in the order of weeks, months or sometimes even years. Quaternary prevention aims to avoid unnecessary suffering by the virtue of preventing skeletal-related events in high-risk patients, ensuring the derivation of bowel, gall bladder or urinary tract before malignant obstruction appears, or by providing timely analgesic treatment. An integral part of quaternary prevention is an appropriate psychosocial support and ancillary services in order to maintain patient's active lifestyle or, on the contrary, provide palliative sedation at the right point when the patient's discomfort turns into unbearable suffering. While the primary and secondary prevention are generally well-known and broadly applied concepts, tertiary prevention is considered only as a part of oncology routine and quaternary prevention is sometimes confused with passive palliation. However, the ability to prevent problems and complications associated with advanced-stage deadly disease and provide a consistent solution, albeit for a limited time of residual life, is the strongest argument against the introduction of euthanasia. To cite prof. Tannenberger, "eubiosy" - a good living should have a permanent priority over euthanasia - a good death, especially nowadays, when the possibilities of palliative care have remarkably broadened.

Oncopreventive examination can be offered to a healthy individual irrespective of his genetic or occupational risks in the form of a **preventive oncological examination** or via **national screening program**. The essentials of a preventive oncological examination are specified by the Decree of the Ministry of Health of the Czech Republic, namely by Decree No. 70 from the year 2012. The examination is provided by GPs and some outpatient specialists. It is also a commercially available within some complex oncology centres including Masaryk Memorial Cancer Institute in Brno, which pioneered a widely attended program of preventive oncological examinations. A comprehensive oncology check aims to rule out some of the 15 most common malignant tumours that make up 85-

90 % of total tumour incidence. It does not address rare tumours, in which the time of diagnosis usually correlates with the onset of symptoms. The frequency, scope and age limit for preventive screening is adapted to specific hereditary risk factors, if they are present.

Like in other developed countries, the Czech Republic also implemented three national screening programs for early detection of breast, cervical and colorectal tumours. Still, this covers only three particular cancer diagnoses in women and one in men, and it is actually an abridged version of the examinations carried out within the framework of a specialized preventive oncological program. **Mammography screening** in the Czech Republic was introduced in 2002 and it is available to all women from 45 years of age, biannually, in around seventy specialized mammodiagnostic centres evenly distributed across the republic. The target population comprises over two million women. Despite constant efforts to increase participation, the number of women screened annually is around 600 000, i.e. only about 60% of the target population. Thanks to the screening, approximately 3200 out of more than 7000 breast cancers per year are diagnosed in asymptomatic stages, such as Tis and T1 (representing 80 % of all cases). In a non-screened population, T1 and Tis stages constitute only one third of newly diagnosed cases. This corresponds to worse prognosis and quality of life in non-screened patients, as well as higher health care costs. Breast cancer screening has significantly changed the distribution of clinical stages of tumours diagnosed in the last decade, in favour of stage I, and dramatically contributed to reduction of cancer-related mortality. **Screening of cervical cancer** is provided to all women by their gynaecologist and though it has a long-standing tradition, the average participation rate is only about 50%. The incidence of cervical cancer is about six times lower than in breast cancer and the age distribution displays a bimodal pattern**. Screening of colorectal carcinoma** is available to both men and women from the age of 50 either in the form of primary colonoscopy at gastroenterology outpatient clinic or as an annual faecal occult blood testing performed by patients' GP. In the case of positivity, the patient is referred for colonoscopy. Intervals between preventive colonoscopies are adjusted individually according to the findings. If negative, colonoscopy is repeated every ten years, if a polyp or adenoma is detected, the recommended interval varies according to histological characteristics: annual colonoscopy for the case of dysplastic adenoma and five-year interval if the examination reveals an inflammatory polyp. Although ten years of existence of colorectal cancer screening programme has already brought about statistically favourable results, the participation rate is very low, reaching only 20-30 %. The aim of colorectal cancer screening is not only to reduce cancer mortality thanks to early detection, but also to avoid tumour development by removing the adenomas with malignant potential. Colorectal cancer screening thus represents both secondary and primary prevention modality.

To conclude, **preventive methods are an integral part of clinical oncology and early tumour diagnosis is the best guarantee of a successful treatment.**

Organization of oncological care in the Czech Republic

I. Kiss, R. Vyzula

Oncological care in the Czech Republic is implemented at several levels. The basis is represented by primary care provided by **GPs.** If necessary, patients can be further referred to **regional oncology centres (ROC).** Highly specialized care is provided by **complex oncology centres (COC). Since 2017, a concept of National Cancer Centre (NCC) has been introduced.** NCCs are designed as a coordinating scientific and research institution with international cooperation competences throughout the COC network. NCCs serve primarily as national contact points for international cooperation and they are not a substitute for national oncology societies or network of complex oncology centres in terms of competences and policies.

The oncology care system also includes hospice inpatient and outpatient services that are focused on supportive and palliative care for patients in advanced and terminal stages of the disease (http://www.onconet.cz).

Prevention and screening

Secondary cancer prevention, as defined by Section 120 of Act No. 372/2011 Coll. On Health Services, is mainly provided by GPs.

- General preventive examinations are performed every 2 years. They involve a medical history, physical examination and basic laboratory testing.
- Preventive oncology screening programs are focused on colorectal cancer in individuals aged 50 and older (www.kolorektum.cz), and breast cancer in women from 45 years of age (www.mamo.cz).
- Registrant gynaecologists screen for cervical cancer. Every woman older than 15 years is entitled to an annual preventive gynaecological examination in the Czech Republic, which is paid from public health insurance. At the age of 25 years, women start to be actively invited to the screening program by their insurance companies (www.cervix.cz).

Regional Oncology Departments

In regional oncology departments, the diagnostics, treatment and dispensarization is provided mostly on the outpatient basis. Depending on their size and available staff, some of these institutions also have inpatient facilities. These regional oncology departments cooperate with COC in the region. They refer patients to tumour boards and specific treatment modalities or administer conventional chemotherapy regimens (without targeted or costly treatment). They significantly participate in the

dispensarization of all cancer patients, including patients from COC after they accomplished curative treatment.

Complex oncology centres

The most specialized oncological care is centralized in complex oncology centres (COC). Currently, there are 13 COCs in the Czech Republic; some of them comprise several medical facilities. Haematological malignancies are treated in six centres, and all childhood tumours are treated within two specializes centres in Brno and Prague.

COCs are health-care institutions or their associations providing specialized medical care that meets professional criteria declared by the Czech Cancer Society (COS). They have to be equipped by particular facilities:

- at least 2-3 linear accelerators, brachytherapy techniques and other related equipment (Planning (3D) system, dosimetry devices, model laboratory, software for special radiotherapy techniques (IMRT, TBI)
- adequate diagnostic methods that enable accurate identification of specific predictive parameters
- central cytostatic preparation unit, a fully equipped infusion clinic, and on-site ICU

Comprehensive oncology centres provide costly treatment, such as radiotherapy, immunotherapy or targeted agents. This enables concentration of patients suitable for such treatment modalities in high-volume centres, as well as accumulation of specialist physicians cooperating within specific teams and multidisciplinary tumour boards.

Teams that focus on certain types of malignancy develop corresponding diagnostic and therapeutic guidelines, with respect to recommendations of expert societies and internationally recognized best practices. There are, for instance, teams for the treatment of digestive tract tumours, a breast cancer team, a sarcoma team, lung cancer treatment team, etc. Team members are specialist doctors who also coordinate scientific research projects and who participate in multidisciplinary team boards. These usually include a radiologist, a clinical and radiation oncologist, oncosurgeon or oncogynecologists, gastroenterologist and nuclear medicine specialist. The primary goal of these committees is to propose the optimal patient-tailored treatment plan by determining the character and most favourable sequence of specific therapeutic modalities (e.g. surgery, chemotherapy or radiotherapy).

An integral part of each COC is a palliative care team consisting of a palliative medicine physician and pain management specialist, dietitian, physiotherapist, social worker, psychologist and spiritual care practitioner.

Apart from costly therapeutic methods, COCs are also equipped with modern diagnostic technologies, such as PET / CT or PET / MRI. They aim to determine the extent of the illness as accurately as possible, in order to provide an effective treatment plan for the patient.

Another typical feature of high-volume oncology centres is the availability of novel pathology techniques, including molecular diagnostics and predictive tumour screening. These methods are necessary for proper indication of certain targeted treatment, e.g. RAS testing for EGFR inhibitor treatment of metastatic colorectal cancer, HER-2 amplification for antiHER-2 treatment etc. The availability of cytogenetics is also necessary for the detection of hereditary cancer syndromes and further genetic counselling.

For storage of tumour samples, COCs are also equipped with biobanks that contain deep-frozen or otherwise processed tumour tissues and other human biological material, mainly for research purposes. Tumour samples are available for analysis of various biomarkers that may be tested within experimental research trials. In correlation with clinical data, this might facilitate the translation of laboratory findings into clinical practice. Individual biobanks are associated within a national network committed to the preservation of biological material of thousands of patients under standardized and accredited conditions. This national network is a part of pan-European research infrastructure, known as BBMRI (Biobanking and biomolecular resources research infrastructure).

The basics of cancer biology

O. Slabý, M. Svoboda

Introduction

Over the last decades, the knowledge of molecular aspects of cancer pathology has significantly broadened. Numerous molecular changes and damages associated with tumour cell phenotype and behaviour have been described. Although these cellular and molecular processes vary across tumour types, they always yield the same result. In a review by Hanahan and Weinberg published in Cell magazine in 2000, the authors defined six hallmarks of malignant tumour. These properties are applicable to vast majority of tumour diseases irrespective of the particular molecular alterations that caused them.

Carcinogenesis

Carcinogenesis is a highly complex process that involves malignant transformation of cells and subsequent tumour growth. It may be induced by internal (spontaneous mutation, genomic instability) and external factors (chemical, physical and biological) that lead to mutations of DNA encoding oncogenes and tumour suppressor genes. These factors may mutually combine and influence each other and their contribution to carcinogenesis may significantly vary. There is a number of genetic and epigenetic changes that can occur during carcinogenesis. This model of carcinogenesis is applicable to all three overlapping categories of tumour diseases: sporadic (about 70% of cases), familial (15-25%) and hereditary (5-10%). The risk of specific cancer increases from familial to hereditary forms, due to higher penetrance of predisposing genetic mutations at the level of oncogenes and tumour suppressors.

Sporadic tumours, i.e. tumours without any confirmed hereditary background, occur mainly due to carcinogenic exogenous factors. Based on their character, exogenous factors can be classified as **chemical** (eg PAHs, polycyclic aromatic hydrocarbons), **physical** (eg radiation) and **biological** (eg oncogenic viruses such as human papillomavirus) carcinogens. Their common feature is the ability to induce genetic changes that result in activation of oncogenes or inactivation of tumour suppressors. Besides these mutagenic effects, it is necessary to distinguish auxiliary factors, which indirectly promote carcinogenesis by proliferation stimulation or so-called co-carcinogens that directly trigger mutagenic processes, e.g. by induction of certain biotransformation enzymes. Generally, both factors have the ability to influence or potentiate the consequences of DNA damage in favour of malignant transformation. In contrast to carcinogenic factors, chemoprotectants are agents that reduce the risk

of malignant transformation. Correspondingly, **chemoprevention** refers to the use of these substances, both natural and synthetic, in order to prevent the cancer development.

Nonetheless, even in environment free from any carcinogens, **spontaneous mutations** may occur as a result of inaccuracies in DNA replication or impaired DNA-repair mechanisms. Actually, exogenous carcinogens account only for a small proportion of mutations associated with tumour development, and their complete elimination would not significantly decrease the risk of cancer. Spontaneous mutations may accumulate for many years prior to the development of malignancy. The order in which mutations occur may also play an important role in the process of carcinogenesis. This is the reason why many tumours develop typically in higher age, when the lifetime accumulation of genetic changes is sufficient to induce malignant transformation. From the perspective of probability, it can be said that if we live long enough, each of us will develop some type of cancer.

There are also particular mechanisms that can accelerate the process of carcinogenesis. Most tumour cells are characterized by **genomic instability**, which leads to an increase in the mutation rate. Moreover, mutations underlying cancer development provide the affected cells with growth advantage over normal adjacent cells. By natural selection, the cells that carry mutations enhancing proliferation and survival overgrow the others. This process is referred to as **clonal expansion**. Faster proliferation is associated with a higher mutation rate yielding new genome alterations with further selection of the most aggressive sub-clones. Genomic instability together with outbreaks of clonal expansion then culminates in the development of a malignant tumour.

Genes critical for tumour development

There are two main classes of genes that contribute to carcinogenesis: oncogenes and tumour suppressors. Sometimes, a third group of genes involved in DNA repair is recognized, however, from a systematic point of view, these could also be classified as oncogenes or tumour suppressor genes.

Oncogenes

Oncogene is a pathologically activated gene that has undergone a mutation leading either to increased levels of its protein product (oncoprotein) or stimulation of its function. Oncogenic mutations have gain-of-function character (so-called activating mutations), which means that only single allele defect is sufficient to cause tumour. In most cases, mutations of oncogenes occur in somatic cells. The term proto-oncogene refers to a normal, non-mutated form of such a gene. They are involved in regulation of cell proliferation and differentiation. The process of conversion of proto-oncogene to an oncogene is called activation. This happens in three different ways: by structural changes enhancing its activity or causing loss of regulation, secondly, by increasing its amplification without affecting the activity itself, or, thirdly, by chromosomal translocation leading to oncogene

overproduction, or chimeric protein production with increased activity. This could be either tyrosine-kinase receptor activity or increased affinity of transcription factor to a promotor area of a gene. Oncogenes are classified according to the function of their product proteins into five basic categories:

a) oncogenes encoding growth factors,
b) oncogenes encoding growth factor receptors,
c) oncogenes encoding non-receptor protein kinases,
d) oncogenes encoding transcription factors; and
e) oncogenes encoding cell signalling factors (transduction, regulatory factors)

Some of these categories may overlap, e.g. RAF oncogene is a non-receptor kinase as well as cell signalling factor. Classification and examples of significant oncogenes are summarized in Tab. 1.3.1. The role of some oncogenes in carcinogenesis will be discussed in detail in the following chapters.

Tumour suppressor genes

An observation that some types of tumours display different behaviour in hereditary and sporadic forms has promoted the idea of tumour suppressor genes. The explanation for this phenomenon was found in 1971 by Alfred G. Knudson, who formulated the **Knudson two-hit hypothesis.** He studied pediatric patients with retinoblastoma, a tumour originating from precursor nerve cells in the retina, and noted that sporadic form of the tumour develops in approximately 30-month old children, affecting usually only one eye. On the other hand, inherited form of retinoblastoma occurs at earlier age of about 14 months and often in a multiple manner. Supposing that a certain gene is responsible for the tumour, Knudson believed that an individual with a hereditary form of the tumour must have a congenital mutation of at least one allele of that gene. For the development of cancer, a second hit is necessary to inactivate the remaining normal allele of the given gene, whereas, in sporadic form, two mutations are needed to inactivate both alleles. That is why inherited tumours occur at an earlier age. Moreover, since the affected allele is present in all cells of the individual's body, multiple tumours are often observed.

This model described phenotype associated with a tumour suppressor gene for retinoblastoma protein (RB1), although a long time had yet to pass from the formulation of the Knudson hypothesis to the identification and replication of this gene.

A tumour suppressor gene (anti-oncogene) can be defined as a gene whose protein product supresses the development of a tumour and whose inactivation contributes to the process of malignant transformation. Mutations of tumour suppressor genes are recessive, which means that both alleles have to be inactivated in order to render the gene non-functional - so-called **loss of**

heterozygosity (LOH) phenomenon. Tumour suppressor gene products are primarily involved in the cell cycle regulation, apoptosis, or DNA repair mechanisms. By their function, Kenneth Kinzler and Bert Vogelstein classified tumour suppressor genes in 1997 as **gatekeepers** that directly regulate cell growth, and **caretakers** that are responsible for DNA repair. Examples of the most common tumour suppressor genes are summarized in Tab. 1.3.2., many of them will be described in detail together with corresponding malignant diseases in the following chapters.

Types of genetic and epigenetic changes involved in carcinogenesis

Based on previous information concerning factors critical for tumour development, it appears that gene mutations play a crucial role in the pathogenesis of a malignancy. They may occur at the level of individual nucleotides (point mutations) or as extensive chromosomal defects (extensive deletions, amplifications, chromosomal translocation or inversion). The most common types of genetic changes, including examples, are summarized in the tab. 1.4.1.

Although **point mutations** are caused by a change in a single nucleotide base in a sequence of DNA, they can have a significant impact on the encoded protein product. A point mutation can lead to constitutive activation of proto-oncogenes or inactivation of tumour suppressor genes. This type of mutation is most often a result of unrepaired DNA damage inflicted by radiation or chemical agents for example.

Other types of DNA disorders include chromosomal or segmental **deletions** or **amplifications**, resulting in impaired levels of associated protein products. Deletions are more common in solid tumours and their impact on a given gene may varying from a decrease in function to a complete loss of function, depending on the activity of the non-mutated allele. When whole chromosomes are lost or amplified, we speak of **aneuploidy**.

Parts of the DNA may also be rearranged from one chromosome to another (translocation), which can give rise to a fusion gene that combines coding or control sequences of two previously separate genes. Tumour-specific translocations occur mainly in hematopoietic stem cells, sarcomas, but also in prostate cancer, thyroid gland or kidney tumours. The first known fusion gene was detected on Philadelphia chromosome (Ph) in patients with chronic myeloid leukaemia (CML). This chromosome is named after the city where it was first described in 1960 by Peter Nowel and David Hungerford. It contains a balanced translocation between chromosomes 22 and 9 - t (9; 22) (q34; q11) resulting in the BCR-ABL fusion gene.

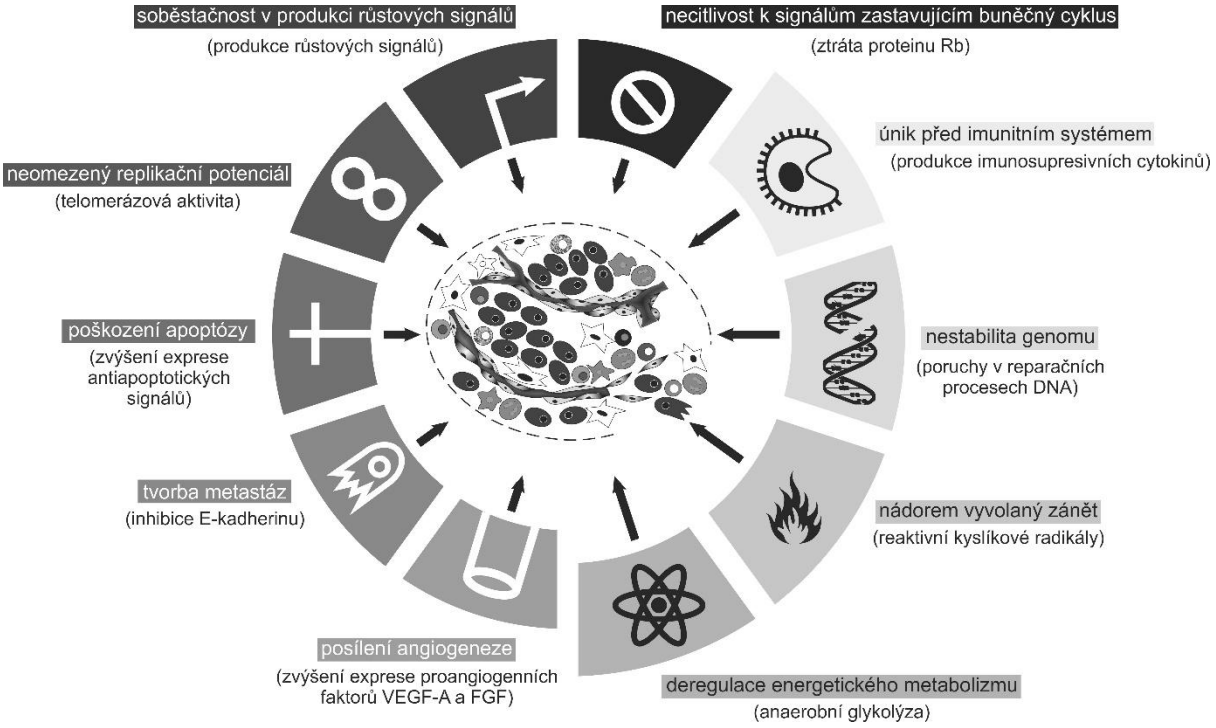
Another significant group of DNA disorders are so-called **epigenetic modifications.** These reversible changes in gene expression are not caused by specific mutations of the DNA sequence, but rather by DNA or histone methylations, such as CpG island methylation. CpG islands are cytosine and guanine

rich DNA regions and the degree of methylation of these islands affects the translocation of adjacent genes - hypermethylation of CpG islets in promoter regions is associated with transcriptional arrest, hypomethylation leads to the opposite. An aberrant hypermethylation and subsequent inactivation of associated tumour suppressor gene plays an important role in carcinogenesis.

Hallmarks underlying the development of cancer

As mentioned earlier, the ground-breaking work in the field of molecular pathology of tumours is represented by the publication from Hanahan and Weinberg in the Cell journal, defining the most common traits typical for malignancies. In an update published in 2011, the authors postulated eight hallmarks that underlie the transformation of normal cells to malignant ones and, additionally, two enabling characteristics that govern the existence of these hallmarks. These are **genome instability** and **tumour inflammation**. Genome instability is a critical component of carcinogenesis, because it accelerates the process of random mutations, including chromosomal aberrations or aneuploidy that facilitate other acquired malignant tumour traits. The inflammation associated with a premalignant lesion or an already existing tumour involves immune system response that can promote neoplastic process through a variety of mechanisms.

Fig. 1 Typical features of malignant tumour (adapted from Hanahan, Weinberg, 2011)



Genome instability and mutations

The genome of our cells is continuously exposed to a variety of mutagens (UV and ionizing radiation, metabolites, reactive oxygen species and other chemicals). Resistance to mutagenic agents is based

on the ability of cells to recognize and repair DNA damage, or to induce senescence (a state when a cell remains metabolically active but does not proliferate) or apoptosis in the case of an extensive damage. There is a number of molecular mechanisms that protect genome stability, such as cell-cycle checkpoints and restriction points, DNA repair mechanisms, or control of mitotic spindle length. If these mechanisms or DNA repair processes are impaired, a cell undergoes senescence or apoptosis due to extensive DNA damage accumulation. However, there might exist specific mutations that favour cell proliferation and result in the evolution of a malignant clone. Corrupted control mechanisms together with increased frequency of mutations caused by genome instability foster the emergence of so-called **driver mutations** that may facilitate further malignant transformation. Genome instability is an important milestone in the pathogenesis of cancer. Genome destabilisation may occur at the level of DNA (due to defective mismatch repair, nucleotide excision repair, excision repair or repair of double-stranded DNA breaks), or chromosomes (chromosomal instability and aneuploidy).

Tumour inflammation

The involvement of inflammation in the pathophysiology of tumour diseases is evidenced by a number of epidemiological studies showing that chronic inflammation is a predisposition to the development of various types of tumours. There are many conditions that trigger chronic inflammation and thereby increase the risk of neoplastic proliferation. They include microbial infections (e.g. *H. pylori infection* is associated with the development of gastric cancer and gastric lymphoma or HBV with hepatocellular carcinoma), autoimmune diseases (such as non-specific intestinal inflammation - Crohn's disease and ulcerative colitis that are associated with a higher risk of colorectal carcinoma), or inflammations of unknown origin (e.g., prostatitis is associated with the development of prostate cancer). Another evidence for the essential role of inflammation in carcinogenesis is the reduction of colorectal cancer risk associated with the use of non-steroidal anti-inflammatory drugs. Inflammation contributes to the growth and progression of cancer by a number of mechanisms that are beyond the scope of this chapter. However, it is of note, that signs of inflammation are present in almost all tumours, including those in which the causal involvement of inflammation in carcinogenesis has not yet been sufficiently proved.

Hallmarks of cancer

In 2000, **Weinberg and Hanahan** postuplated six cancer-associated traits:

a) self-sufficiency in growth signals
b) impaired regulation of the cell cycle
c) unlimited replicative potential
d) evasion of apoptosis

e) sustained angiogenesis

f) tissue invasion and metastasis

These traits of malignant tumours have become broadly accepted and the concept has been widely recognized as the backbone of cancer theory. However, advances in cancer biology over the last few decades made the authors update this crucial paper and in 2011, they presented another four hallmarks:

a) deregulation of cellular metabolic pathway,

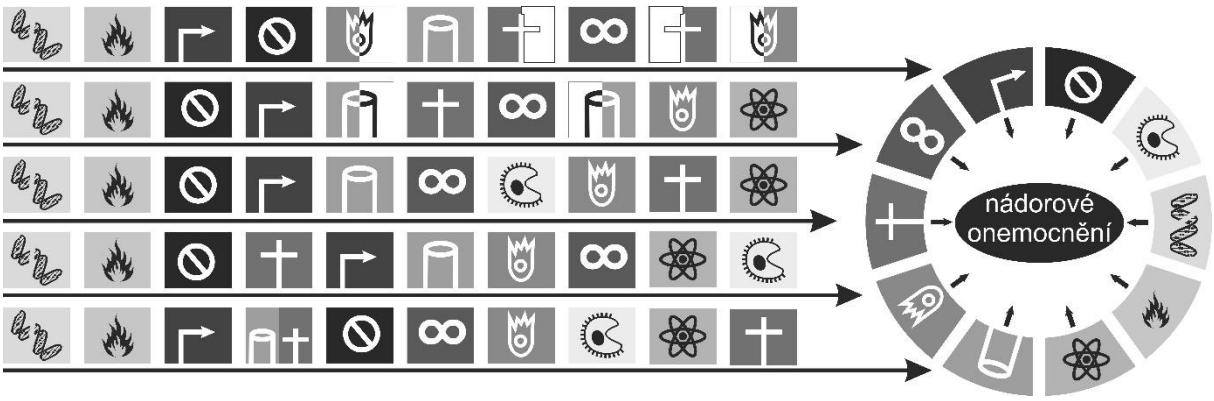
b) immune system evasion,

c) genome instability and mutation,

d) tumour inflammation,

The latter two traits were labelled as "enabling" characteristics (see Figure 1.6.1). Traits designated as deregulation of cellular metabolic pathway and immune system evasion go beyond the scope of this chapter; the other features will be described below. According to the concept of a multi-stage model of carcinogenesis, the successive acquisition of eight cancer hallmarks is fostered by enabling characteristics. The order and the number of mutagenic assaults or specific gene mutations may differ across tumour types.

Fig. 2. The course of carcinogenesis (modified by Hanahan, Weinberg, 2000).



Self-sufficiency in growth signals

Tumour cells use several general mechanisms to sustain chronic proliferation independent from external growth factors. One of them is the production of own growth factors, so-called autocrine signalling (Figure 1.6.3A). Tumour cells can also stimulate their proliferation rate by receptor modulation - either by increased expression or by structural changes that increase affinity for a ligand or enable independent activation (Figure 1.6.3B). Another strategy is deregulation of intracellular signalling pathways. A typical example is the mutation of RAS oncogene that leads to a

constitutive activation of the Ras protein and triggers continuous signalling without any prior stimulation of the associated receptor.

The EGFR (epidermal growth factor receptor)/RAS/RAF pathway depicted in Figure 1.6.4 might serve as a model demonstrating the way how extracellular growth factor signal can be transduced into a cell and regulate gene expression and cell proliferation. This cascade has been a cornerstone of the theory of molecular pathogenesis of cancer. Some of the involved proteins are also therapeutic targets of modern anticancer drugs.

Impaired regulation of the cell cycle

Phases of the cell cycle are regulated by a group of proteins called **cyclins** and associated effector **cyclin-dependent kinases (CDKs)**. The term "cyclin" stems from the fact that its concentration during the cell cycle continuously oscillates because of their changing expression and controlled degradation. Cyclins represent regulatory subunits of the associated CDKs and their pairing with CDKs is highly specific. After the cyclin is bound to CDK, a conformational change occurs in a catalytic subunit of the kinase and its active site is uncovered. Unlike cyclin concentrations, CDK levels remain stable throughout the cell cycle. The cyclin-CDK complexes exert their effect by phosphorylation of serine and threonine on target proteins. Examples of such substrates are condensates, nuclear laminas, the GM 130 protein of Golgi apparatus, the famous transcriptional regulator p53, **retinoblastoma protein (RB)**, transcription factors E2F and SMAD3 (regulatory protein of TGF-β signalling), and many others.

Cyclin-CDK complexes are involved in different phases of the cell cycle and are important regulators of irreversible transitions between these individual phases (Figure 1.6.4). The process of cell division is controlled by a multilevel and redundant system of regulations that maintain tissue homeostasis. An uncontrolled proliferation of tumour cells is usually achieved by a disruption of the system or by inactivation of its key components. For example, mutation of the retinoblastoma tumour suppressor gene disables a key restriction site protein, which has a fundamental role in the development of a number of tumours, such as breast cancer, small cell lung cancer, or bladder carcinoma. Signalling pathways that stimulate cell proliferation lead to an increase in cyclin D synthesis and subsequent activation of CDK4/6 that phosphorylates RB protein and promotes cell cycle progression toward the S-phase. This system is buffered by CDK inhibitors, the p16 and p21 family proteins. Damage to any component of this pathway may result in unlimited tumour growth. For instance, cyclin D encoding genes are amplified in a number of tumours. Activating disorders of the cyclin D / CDK4 / 6 complex are also relatively frequent in many tumours.

Unlimited replicative potential

Every chromosome is terminated by a non-coding repetitive sequence called **telomere** that works as an evolutionary "meter" and its gradual shortening during cell cycles leads to loss of cell's ability to divide. However, some human cells must retain the ability of unlimited division. These are germ cells and some stem cells. For this purpose, such cells express a **telomerase** enzyme (including a human telomerase reverse transcriptase (hTERT) and RNA template) that is able to add *de novo* telomeric repeat sequences to the ends of telomeres. In somatic cells, telomerase is undetectable. On the contrary, approximately 90% of tumours exhibit high telomerase expression, or they are able to synthesize telomere ends by alternative telomere lengthening (ALT), and thus obtain unlimited replicative potential resulting in their continuous proliferation.

Evasion of apoptosis

Apoptosis is a way of actively controlled cell death that comprises serial activation of proteases and endonucleases and final cell destruction with typical morphological changes. There are two major apoptotic pathways: intrinsic and extrinsic. **Intrinsic pathway,** sometimes referred to as mitochondrial, is activated by intracellular stress stimuli such as DNA damage, oxidative stress or oncogene activation. Its regulation is accomplished mainly by Bcl-2 family of more than 20 proteins whose main function is to maintain mitochondrial integrity. In contrast, the **extrinsic pathway** is triggered extracellularly by a family of tumour necrosis factor (TNF) ligands such as TNF-α, TRAIL (TNF-related apoptosis-inducing ligand) or Fas (FASL / CD95L) that bind to the associated transmembrane receptors. Although both of these pathways are triggered by different signals, they can converge and activate non-functional forms of proteases, which in turn lead to progressive proteolytic cell destruction. These proteases, known as **caspases**, function as molecular scissors that cleave intracellular proteins on aspartate residues. They are central effector proteins for both apoptotic pathways.

Tumour cells produce a number of signals (e.g. due to DNA damage or oncogene activation), which would normally lead to induction of apoptosis. However, in the course of carcinogenesis, tumour cells have obtained mutations that allow them not to respond to these signals, escape from the apoptosis, proliferate further and, above all, accumulate other mutations. Evasion of apoptosis is therefore one of the crucial acquired hallmarks of tumour cells. **Extrinsic apoptotic pathway** disruptions include mutations at the level of death receptors such as Fas or TRAIL. **Intrinsic pathway defects**, which are much more common, typically involve mutations that affect the pathway of the **p53 tumour suppressor.** These mutations are the most frequent molecular alterations detected in cancer cells.

Sustained angiogenesis

Tumour growth is strongly dependent on vascular supply. At the beginning of tumorigenesis, the metabolism is mediated by simple diffusion, with the diffusion limit of maximum 100μm, which corresponds to the distance of approximately 10 cells in a row and tumour size of approximately 1-2 mm^3. The angiogenesis is controlled by an array of proangiogenic and antiangiogenic factors. An independent vascular supply has two major impacts on the tumour phenotype:

a) blood flow provides oxygen and nutrients to tumour cells and endothelial cells stimulate tumour growth by secreting growth factors,
b) angiogenesis enables cancer cells to access the circulation, and thus acquire the ability of metastatic spread.

Proliferating tumour cells initially have a "non-angiogenic" phenotype, i.e. they are not capable of creating new blood vessels and thus they have limited possibilities of expansion. A sudden transition to "angiogenic" state, which typically occurs in early phase of carcinogenesis, is referred to as **angiogenic switch**. The basis of this time-restricted event is explained by a hypothesis of equilibrium, which says that the switch is caused by an imbalance between activators and inhibitors of angiogenesis in favour of activating factors. There is a number of mechanisms underlying angiogenic switch, the most important ones include **vascular endothelial growth factor** (VEGF), angiopoietins or basic fibroblast growth factor bFGF (see Angiogenesis Activators). Angiogenesis inhibitors are **thrombospondin-1** (TSP-1), angiostatin or endostatin (see Angiogenesis Inhibitors).

The main trigger for processes leading to the acquisition of an angiogenic phenotype is **hypoxia**, a state of reduced oxygen supply that results in stabilization of **HIF1α** transcription factor (factor 1a-induced hypoxia) which activates expression of particular genes necessary for the adaptation to oxygen deficient environment (e.g. VEGF).

Tissue invasion and metastasis

Tumour dissemination is a complex step-wise process that depends on acquisition of specific malignant traits and is very closely related to angiogenesis or the size of primary tumour mass. The process is driven by the increasing heterogeneity of tumour cell population allowing sequential selection of more aggressive clones capable of metastatic spread. These tumour cells undergo a multi-step process known as **metastatic cascade.** It includes:

a) local infiltration of adjacent tissues
b) transendothelial migration of cancer cells into blood or lymphatic vessel (intravasation), their survival in the circulation
c) escape from the circulatory system (extravasation)
d) subsequent proliferation and formation of metastatic deposit (metastatic colonization) (Fig. 1.6.6.)

Invasiveness and migration

Mechanisms underlying the ability of tumour cells to invade other tissues and migrate to distant sites include:

a) reduction or complete loss of adherence between malignant cells - this is accomplished by, for example, loss of E-cadherin and a conversion of epithelial cell phenotype into mesenchymal, referred to as epithelial-mesenchymal transition (EMT);

b) loss of extracellular matrix attachment mediated by the overexpression of migration-promoting integrins (e.g., avβ3 in malignant melanoma) or suppression of integrins that mediate adhesion to the extracellular matrix and rest cell phase (e.g., α2β1)

c) degradation of the extracellular matrix by proteases such as **matrix metalloproteinase** (MMP) or cathepsins.

Once a tumour cell acquired all these traits, it can leave the primary tumour bed, disrupt the basal membrane and migrate through interstitial layers to the basal membrane of adjacent blood vessels.

Intravasation, transport and extravasation

The process of intravasation encompasses proteolytic disruption of the basal membrane of a vessel (not present in lymphatic vessels) and trans-endothelial spread to the vascular lumen. Since lymphatic capillaries are extensively fenestrated and lack supporting cells (pericytes), many tumours primarily metastasize through lymphatic vessels (**lymphatic spread**) into a regional lymph node, which acts like a filter for tumour cells. However, the affected node may contribute to proliferation and dissemination of tumour cells into other nodes and into the systemic circulation. In advanced stages, the primary tumour undergoes the angiogenic switch and generates its own chaotically arranged vasculature with loose endothelial connections, non-functional pericytes and other pathologic features that lead to their increased permeability and the formation of **haematogenous metastases.** It is estimated that $1cm^3$ of tumour mass sheds several million cells per day into the blood stream, however, only a small fraction (<0.1%) will survive in systemic circulation. The ability to survive depends on whether the cells circulate isolated or in clusters as a part of tumour-associated **microthrombi.** Surface shielding by microthrombi provides tumour cells with protection against physical insults and immune surveillance and facilitates extravasation, i.e. the escape from a vessel lumen into parenchyma favourable for metastatic growth.

Metastatic spread

The ability of cancer cells to grow in a distal site, so-called metastatic colonization or sometimes metastatic virulence, is the last and probably the most demanding part of metastatic dissemination. In contrast to the primary tumour, the microenvironment of the host tissue does not supply

metastatic cancer cells with growth and survival factors that are present in the primary tumour tissue. Without this type of support, metastatic cells remain dormant in a form of small clusters, referred to as **micrometastases**, which can be detected only by microscopy. Generally, an abundant number of micrometastases is required before they eventually outgrow to clinically detectable macrometastases, i.e. lesions larger than a few millimetres. While the earlier steps of the metastatic cascade were highly efficient, metastatic colonization itself is rarely successful and is therefore a limiting step in the whole process. However, the micrometastases remaining in a **dormant state** represent a permanent threat of macroscopic spread, as they might remain dispersed throughout the entire body for many years. In the course of time, cancer cells may adapt to the microenvironment of a new tissue in terms of ECM composition, the presence of growth factors, etc. and begin to proliferate. By selection pressure, sub-clones with mutations that allow for better adaptation to the new microenvironment prevail. Still, if there is a balance between the proliferation and apoptotic death of tumour cells, macrometastases may never occur. The formation of a metastasis is conditioned by another angiogenic switch that would provide cells with adequate vascular supply. Then, newly created macroscopic metastases can further spread and establish so-called metastases of metastases.

Oncological diagnostics: histopathology, cytology, tumour markers

J. Tomášek, P. Fabián

Histological or cytological examination is the basis of an accurate oncological diagnosis. Together with molecular diagnostics, it also assists with cancer risk assessment or prediction of response to specific treatment. Every testing requires appropriate tissue sampling with adequate specimen handling and fixation. An active collaboration between a clinician and a pathologist is crucial for proper histologic evaluation of a tumour, and involves an accurately filled test request with identification of specimen character and location. An oncologist can rarely treat a patient without pathological verification of the malignancy, except for hepatocellular carcinoma, where the diagnosis can be made only based on imaging methods. Clinical diagnosis is also sufficient in patients with advanced cancer and with poor performance status, in whom the anti-cancer treatment could not improve quality of life or prolong survival. Histological verification is often necessary for distinguishing metastatic disease from benign lesions (e.g. pulmonary sarcoidosis, hepatic haemangiomas, or reactive lymphadenopathy). In the case of generalized disease, minimally-invasive procedures, such as needle biopsy is the preferred tissue acquisition method. The specimen has to be representative in terms of volume and viable tumour tissue content. In general, we always prefer histological examination of a tissue to cytological analysis of single cells. On the other hand, tumour cytology is essential in cervical cancer screening, bronchial brushing evaluation, endosonography guided pancreatic fine-needle aspiration, or examination of cancer cells harvested by thoracentesis.

We briefly mention the basics of tumour classification.

Classification of tumours

Tumours are classified according to their histogenetic phenotypes into the following groups:

1) **Epithelial** – tumours derived from epithelial cells. This is the most common subtype.
2) **Mesenchymal** - arising from connective tissue cells, i.e. muscles, cartilage, bones, vessels, etc.
3) **Hematopoietic** tumours, i.e. lymphomas, leukaemia, myeloproliferative and myelodysplastic diseases, histiocytic and dendritic tumours
4) **Neuroectodermal** tumours originate from cells derived from neural crest: glial and ganglion cells, peripheral nerves, paraganglia and melanocytic tumours.
5) **Germ cell tumours** arise from a pluripotent germ cell, capable of differentiating into tumours similar to various developmental stages of somatic tissues (teratoma, embryonal carcinoma, seminoma) or extrasomatic structures (yolk sack tumour, choriocarcinoma).
6) **Mixed tumours** are still recognized as a distinct group of tumours, although the underlying notion of synchronous occurrence of two or more cancer populations within a single tumour

mass is abandoned. In most cases, these tumours have monoclonal origin and comprise multiple cell lines with specific morphological signs that acquired somatic mutations during tumour growth. This group typically includes the above-mentioned teratomas and tumours referred to as carcinosarcomas (which are actually carcinomas with partial sarcomatoid differentiation – morphologically, some tumour cells correspond to carcinoma, while others resemble sarcoma). Another type of mixed tumours encompasses both clonal neoplasia and benign tissue, "passively pulled" into the tumour mass. A typical example is mammary fibroadenoma, where only the stromal component is comprised of malignant cells.

7) Finally, we recognize several **miscellaneous** tumours not classified in previous categories, such as mesothelioma, gestational choriocarcinoma, or tumours derived from the notochord (chordomas).

WHO classification of malignant diseases

WHO, in cooperation with The Union for International Cancer Control (UICC) has developed the International Histological Classification of Tumours, a publication that categorizes site-specific tumours with regard to their histological type. In addition to a unique histological pattern, every new nosological unit has to fulfil several other criteria, such as specific genetic changes and a typical clinical manifestation. Nowadays, the genetic aspect is being increasingly important.

Classification of tumours by their biological behaviour

Tumours can be malignant or benign depending on their behaviour towards the host organism. Their character can be determined based on four major criteria: the level of tumour cell differentiation, tumour growth rate, the behaviour towards surrounding tissues and the ability to metastasize. Benign tumours are well-differentiated (similar to normal cells), grow slowly, are confined to their site of origin and do not establish metastases. For malignant tumours, (with many exceptions) the opposite is true. Tumours with indeterminate histologic pattern that cannot be clearly classified into neither of the categories are referred to as potentially malignant/semi-malignant. An example of these potentially malignant tumours is pheochromocytoma or some borderline melanocytic lesions. A sign of malignant transformation is their ability to establish metastasis.

Estimating the degree of malignancy

A specific tumour type can display a wide range of biological behaviour ranging from very favourable to highly aggressive. Various grading systems are applied to determine the degree of malignancy based on histological features of a tumour. Tumours are graded according to the degree of differentiation, most commonly on three-tier (sarcomas, breast carcinomas, colorectal carcinomas), four-tier (renal tumours) or multi-tier (prostate cancer) scale. Higher score indicates a more

malignant behaviour. Alternatively, a two-tier classification differentiating "low grade" and "high grade" tumours (ovarian carcinomas) has become increasingly used.

Molecular classification of tumours

As mentioned earlier, the identification of tumours based on specific genetic changes is an inherent part of tumour classification, with lymphomas being a typical model. For instance, a tumour from lymphocytes with cyclin D1 gene translocated to the heavy chain of immunoglobulin gene is, by definition, "mantle cell lymphoma".

Nowadays, this concept includes another aspect: various sub-types of cancer are recognized based on specific genetic changes. For example, two types of colorectal adenocarcinoma are distinguished according to the mutational status of RAS oncogenes, which predicts response to treatment with EGFR inhibitors (RAS mutation indicates resistance to the therapy).

Molecular markers used in pathology can be divided into 3 main groups according to their significance:

1) Diagnostic – they are characteristic of a particular tumour type and contribute to the establishment of accurate diagnosis.
2) Prognostic - are used to estimate patients‘ survival.
3) Predictive - predict the response of tumour to a particular type of therapy.

Diagnostic molecular markers

Immunohistochemistry (IHC) plays a crucial role in oncological histopathological diagnostics. Without this method, a proper diagnosis of most soft-tissue tumours or lymphomas would be impossible. We use **lineage-specific markers** that provide information on a histogenetic type of tumours; e.g. cytokeratin expression is characteristic of epithelial tumours. This is essential especially in poorly differentiated neoplasia where morphology is inconclusive and lineage identification is not possible. Another determinant is the expression of **tissue-specific markers**, which associates cancer cells with certain tissues and their tumour derivatives. For example, cytokeratin 20 is characteristic of colorectal, urothelial and Merkel cell carcinomas and is variably expressed in tumours of the stomach and the pancreato-biliary tract. This might help in tumour site localization when analysing tumours of unknown primary. **Tumour-specific antigens** are determinants that often overlap with so-called tumour markers detectable in patient serum. Tumour markers are specific molecules whose aberrant expression is a sign of malignant growth. For instance, alpha-fetoprotein (AFP) is indicative of germinal tumours or hepatocellular carcinoma. **Antigens associated with cell cycle and regulation of apoptosis**, such as RB protein, cyclins, cyclin-dependent kinases and their inhibitors, bcl-2 / bax proteins, caspases, etc. are proteins whose expression is significantly related to malignant

transformation, in both positive and negative way. Their practical diagnostic application is rather limited, though, e.g. the p16 protein is used to differentiate melanomas from their benign counterparts - melanocytic nevi.

Antigens whose expression is changed due to genetic events associated with malignant transformation: most of them result from chromosomal translocations specific for a particular type of tumour, e.g. excessive expression of the anti-apoptotic bcl-2 protein in follicular lymphoma or cyclin D1 protein in mantle cell lymphoma. Chromosomal translocations, characteristic of lymphomas or soft tissue tumours, can be detected directly at the DNA level, particularly by means of interphase fluorescence in situ hybridization or by reverse transcription PCR. These tests are routinely used in order to refine a histomorphological diagnosis or in differential diagnosis of related tumour types (e.g. lymphomas, kidney carcinomas or some sarcomas) or for monitoring of minimal residual disease.

Markers related to immunotherapy

The immune system is a finely balanced mechanism that is responsible for the elimination of foreign pathogens; on the other hand, it must accurately identify normal body cells in order to avoid autoimmune damage to organism‘s own tissues. Normal function of the immune system is controlled by many stimulatory and inhibitory signals and it also plays a crucial role in the carcinogenesis. However, a tumour cell must firstly be recognized by the immune system in order to be destroyed. Tumour cells escape immune surveillance through several mechanisms, either by reduction of their own immunogenicity or by creating an immunosuppressive environment that prevents the immune response from being activated. One of the best-known mechanisms of immune suppression by cancer cells is the activation of immune checkpoints, which have inhibitory effect on T lymphocytes. Currently, the PD-1 (programmed death-1) immunomodulatory receptor found on activated cytotoxic T lymphocytes has a major clinical significance. If a tumour cell produces a PD-L1 ligand that binds to the receptor, it inhibits the T-cell anti-tumour response. Several monoclonal antibodies have been developed to block the interaction between PD-1 on T cells and PD-L1 on tumour cells and thereby re-activate immune system function. In some tumours, the efficacy of immunotherapy has been shown to depend on the **PD-L1 expression** status (e.g. pembrolizumab for the treatment of non-small cell lung carcinoma), in other diagnoses, PD-L1 expression has not been proven as a reliable predictive biomarker (e.g. for nivolumab in the treatment of renal or non-small cell lung carcinoma).

Prognostic molecular markers

These markers are mainly associated with tumour invasiveness and its ability to metastasize and include tumour metalloproteinase expression, proangiogenic factor secretion, or signs of epithelial-mesenchymal transition. Another novel prognostic marker is the presence of cancer stem cells in total tumour cell population. A useful tool for detailed molecular classification of tumours that may appear homogeneous at histopathological examination or by imunophenotyping is **gene expression profiling**. It helps to distinguish several subgroups within one tumour type that may differ both in response to therapy or prognosis (e.g. triple negative breast carcinoma - TNBC). **Proliferation index** is another generally accepted prognostic feature. This index is determined by the number of mitotic figures per microscopic field on a tumour section. It is particularly important in the classification of neuroendocrine tumours or in scoring of GISTs. There are also proliferation-related proteins, which are expressed during active phases of the cell cycle and hence, their expression correlates with tumour growth rate and indirectly also with its aggressiveness. The most common marker of proliferation is the Ki-67 protein. Number of Ki-67-stained cells determines the growth fraction of a total tumour cell population. It is now routinely performed in histologic evaluation of each breast cancer, and is necessary for grading of neuroendocrine and brain tumours.

Predictive molecular markers

There are particular signs that may predict sensitivity of a tumour to a specific treatment. They include either:

1) Positive predictive markers that confirm the expression of target structure for a certain drug (e.g. overexpression of Her-2 protein in breast carcinoma or mutant form of BRAF protein in melanoma) or
2) Negative predictive markers that rule out a possible effect of certain therapy (e.g. RAS mutation in colorectal cancer is indicative of resistance to EGFR inhibitors treatment).

https://atlases.muni.cz/en/index.html
http://ocw.tufts.edu/Course/51/Lecturenotes
http://library.med.utah.edu/WebPath/ORGAN.html

Tumour markers

Tumour markers are substances found in tumour tissue that can be shed to body fluids, or they might be produced directly by the host as a reaction to the presence of a tumour. Detection of markers in tumour tissue is important diagnostic tool. Detection of soluble tumour markers in body fluids is used for diagnostic purposes as well as for monitoring of tumour dynamics. Tumour markers are usually complementary to other diagnostic methods, and are not suitable for preventive screening if

there is no suspicion of cancer. An exception is the examination of prostate specific antigen, which can be used in prostate cancer screening.

Markers are commonly used in differential diagnosis of tumour in a symptomatic patient, for monitoring the effect of anticancer treatment, for the detection of recurrent disease (elevation of markers is often the first sign of cancer relapse) and for staging and prognostication in some types of cancer. It is of note that the elevation of tumour markers may also have a non-cancerous cause (e.g. inflammation, cigarette smoking, etc.) or, on the contrary, the tumour might not release a specific marker and the result might be falsely negative.

Current information on tumour markers can be found at www.cskb.cz (http://www.cskb.cz/res/file/KBM-pdf/2014/2014-1/KBM-2014-1-Dopor-TM-22.pdf)

Table 1: Selected tumour markers

Marker	**Typical malignancies**	**Some of non-malignant causes of elevation**
Carcinomembryonic antigen, CEA	Colorectal carcinoma and other tumours of the digestive tract, breast carcinoma	Inflammatory liver diseases, renal failure, pancreatitis, Crohn's disease, ulcerative colitis, smoking
Ca 19-9	Pancreatic carcinoma, colorectal tumours	Acute and chronic pancreatitis, cirrhosis of the liver, biliary tract disease, renal failure
Ca 72-4	Gastric and oesophageal carcinoma	Benign breast tumours, COPD, nonsteroidal anti-inflammatory drugs, corticosteroids
Alpha-fetoprotein, AFP	Hepatocellular carcinoma, germinal tumours, testicular tumours	Hepatic cirrhosis, hepatitis, inflammatory diseases of the lungs, kidneys, GIT, autoimmune diseases
Ca 15-3	Breast cancer	Liver cirrhosis, benign breast tumours, pneumonitis, ovarian cyst
Human choriogonadotropin, HCG	Testicular tumours, germinal tumours	Pregnancy, renal failure, autoimmune disease
Protic specific antigen, PSA	Prostate cancer	Benign prostatic hyperplasia, prostate inflammation, mechanical prostatic irritation

Chromogranin A	Neuroendocrine tumours	Proton pump inhibitors, chronic gastritis
CYFRA 21-1	Non-small cell lung cancer	Hepatic cirrhosis, systemic connective tissue disease, ovarian cyst, exudates
Ca 125	Ovarian carcinoma	Exsudates, ovarian cysts, liver, gallbladder, pancreatic diseases, pneumonitis, COPD.
HE4	Ovarian carcinoma	Nephropathy, exudations, liver disease
Beta 2 microglobulin	Multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia	Nephropathy, liver disease, chronic inflammation

Some other markers specific of particular tumours include:

Calcitonine - Medullary thyroid carcinoma

Tyreoglobulin - Differentiated Thyroid Carcinomas

Neuron-specific enolase (NSE) - small cell lung carcinoma, neuroendocrine carcinoma, neuroblastomas

Lactate dehydrognase (LDH) - non-specific marker of prognostic significance in malignant melanoma, small cell lung carcinoma, lymphomas, neuroblastoma and other tumours.

Diagnostics in oncology: staging, imaging methods, prognostic and predictive factors

J. Tomášek

Once a tumour is diagnosed, the next step is to determine the extent of the disease, i.e. tumour stage. Precise staging has a significant prognostic value and is critical for planning of treatment strategy, which may differ fundamentally according to the extent of the tumour. A standardized tumour classification system facilitates communication between physicians, enables consistent approach to the treatment of cancer in different stages and comprehensive evaluation of treatment outcomes.

TNM classification

There are several staging systems used in oncology. The most commonly used system is TNM (Tumour, Node, Metastasis) classification developed by the UICC, which covers most solid tumours. The TNM classification evaluates three categories: local tumour extent (T), regional lymph node involvement (N) and presence of distant metastases (M). A simplified principle of TNM classification system is summarized in Table 1.

Table 1 : The principles of TNM classification

T	X	Primary tumour cannot be evaluated
	0	No evidence of primary tumour
	is	Carcinoma in situ
	1-4	Increasing size and / or local extent of primary tumour
N	X	Regional lymph nodes cannot be evaluated
	0	Regional lymph nodes without metastases
	1-3	The number indicates the extent of lymph node involvement. It may be accompanied by letters for further specification, e.g. N1a, N1b, N1c.
M	X	Distant metastases cannot be evaluated
	0	Without distant metastases
	1	Confirmed metastatic spread

There are two types of TNM classifications depending on the way of evaluation:

- **Clinical classification, cTNM,** is based on clinical examination, imaging methods, endoscopy, or perioperative findings.
- **Pathological classification, pTNM,** is established on the basis of postoperative examination of the primary tumour and regional lymph nodes.

After determining TNM parameters, a tumour can be further categorized into clinical stages ranging from I to IV. Each clinical stage involves multiple TNM combinations, which share the same prognosis and require the same treatment approach. For example, in colorectal carcinoma, T1, T2 N1 M0 and T1 N2a M0 tumours are all grouped in IIIA clinical stage.

Modifying symbols used within the TNM classification include:

- **y**: staging was determined following prior treatment, for example, surgical resection specimen after neoadjuvant radiotherapy may be assessed as ypT3, etc.
- **r**: staging of a recurrent tumour after a disease-free period

In some cases, TNM staging is determined with respect to additional parameters, such as tumour markers LD, hCG or AFP in testicular cancer.

Classification of a residual tumour: R - classification

The evaluation of a tumour response to previous treatment is indicated by an R sign. It not only reflects the efficacy of treatment, but also determines the next therapeutic plan.

RX: the presence of residual tumour cannot be evaluated
R0: no residual tumour detected
R1: microscopically proven residual tumour
R2: macroscopically visible residual tumour

Other tumour classification systems:

Besides TNM, gynaecological malignancies (tumours of ovary, cervix, endometrium) can be staged using the FIGO system developed by The International Federation of Gynaecology and Obstetrics. For malignant melanoma, the Clark and Breslow classification is used. Ann Arbor is a special staging system designed for lymphomas.

Classification of patient's performance status

A key factor determining patient prognosis and treatment strategy is his **performance status**, which can be assessed using various classification tools: Karnofsky index, performance status scale defined by WHO or ECOG (Eastern Cooperative Oncology Group).

Imaging methods

Imaging modalities are the mainstay of tumour staging. Generally, imaging can be either structural or functional by its nature. The most commonly used structural imaging methods are CT, X-ray, MRI and mammography. Listing of all conventional radiological methods and their indications is beyond the scope of this text, for detailed information there are cancer-specific diagnostic guidelines that include recommendations of appropriate imaging modalities for each type of tumour. The purpose of imaging in oncology is to detect a primary tumour, assess regional nodal status and detect potential distant metastases. Radiologic assessment is necessary for evaluation of tumour shape, size, vascularization, the amount of necrosis, involvement of surrounding tissue, etc. Sensitivity of imaging modalities such as CT or MRI can be increased by contrast enhancement, i.e. by administering contrast agents either orally prior to examination or intravenously during the examination. Abdominal contrast enhanced ultrasound examination is a useful method for differentiating liver metastases from plain cysts, still, it is not considered a sufficient staging method. Moreover, it is heavily dependent on the experience of an examining physician and the instrumentation. Endosonography examination is an important diagnostic tool for oesophageal, gastric, pancreatic or rectal tumours.

Functional imaging

Nuclear medicine methods help to visualize viable malignant lesions with the use of radionuclides. An isotope is bound to a carrier that is trapped in target organs and emits radiation for a transitional period. This radiation is detected by an external detector (scintigraphy SPECT or PET camera). A complete overview of nuclear medicine methods used in oncology is beyond the scope of this text. The most commonly used modality is bone scintigraphy, which is able to detect skeletal metastases long before there are structural changes apparent on X-ray. A useful diagnostic tool for differentiating malignant from benign lesions is positron emission tomography (PET) that depicts tissues by their biochemical activity, although it lacks precise anatomic localization. This disadvantage is compensated in hybrid PET / CT system that produces exact co-registered images of malignant hypermetabolic lesions. Tracers in nuclear medicine are customized according to the type of tumours. For example, meta-benzoylguanidine (MIBG), which is a structural analogue of noradrenaline, is used to detect pheochromocytomas, paragangliomas and neuroblastomas, octreoscan uses somatostatin analogues for detection of neuroendocrine tumours.

In clinical practice, it is essential to follow standardized diagnostic procedures and protocols designed for each imaging method. Nonetheless, an active communication between a clinician, radiologist or nuclear radiologist is important for successful diagnostics; properly filled referral form should include brief description of a clinical situation and clearly formulated questions.

Evaluation of tumour response following oncological treatment

The assessment of treatment response has to follow certain rules in order to be reproducible and to minimize inter-observer variability. In solid tumours, RECIST (Response Evaluation Criteria in Solid Tumours) or WHO criteria are typically used. These criteria were primarily developed for the purposes of clinical trials, but over time, they have become implemented into common practice. Response evaluation is mostly based on radiologic modalities such as CT and MRI. At baseline imaging, a radiologist identifies all metastases out of which he selects so-called target lesions that are most suitable for repeated measurement. Target lesions are usually up to two metastases per organ and five lesions in total. The remaining metastases are so-called non-target lesions. Their measurement is not necessary, but they should be noted in the course of treatment similarly to non-measurable lesion such as pleural or other effusions. Target lesions are measured in the dimension with the longest diameter, their sum is calculated (LD) and used as a baseline for further treatment response evaluation. Tumour response is classified into four categories: complete response (CR), partial remission (PR), stable disease (SD) or progressive disease (PD).

If we want to monitor a tumour by means of imaging methods, a close cooperation between a clinician and a radiologist is necessary. For example, a radiologist needs to know which examination is considered a baseline, he has to follow the same target lesions throughout the treatment course, and CT scans should be obtained using the same protocol.

Prognostic and predictive factors

Prognostic factors are clinical or biological characteristics that provide information about the probable course of a disease in a non-treated patient. Prognostic factors, for example, help to identify patients with high risk of tumour relapse, which makes them candidates for adjuvant therapy. A negative prognostic factor is, for example, the number of affected regional lymph nodes in breast or colorectal carcinoma, a worse prognosis is also associated with larger tumour size, poor differentiation or the presence of lymphovascular invasion.

Predictive factors are clinical or biological characteristics that provide information on the chance of tumour response to a specific type of treatment. Some tumour features may have both prognostic and predictive character. For example, hormone receptor positivity in breast cancer is associated with better prognosis, and at the same time, it predicts tumour response to hormone therapy. There are also molecular predictive factors that may have a positive or negative significance. The detection of a target molecule for a certain drug predicts the efficacy of the treatment, e.g. HER-2 protein overexpression in breast cancer is considered a positive predictive factor for trastuzumab treatment). A negative predictive factor indicates resistance to a certain therapy, such as *RAS* positivity in

colorectal carcinoma. Mutated RAS oncogene leads to constitutive activation of EGFR signalling pathway independent of its ligand and thus contraindicate the use of EGFR inhibitors.

Other predictive factors include PD-L1 expression, which is a positive biomarker for pembrolizumab in the treatment of non-small cell lung carcinoma. On the contrary, some other check-point inhibitors have been proven beneficial regardless of tumour PD-L1 expression (e.g. nivolumab in renal or non-small cell lung carcinoma).

Predictive molecular markers can be detected by various methods (proteins by immunohistochemistry, chromosomal translocations and gene amplifications by in situ hybridization, gene mutations by next generation sequencing, etc.). Sometimes a combination of several methods is necessary.

Useful links:

TNM classification is available on the Institute of Health Information and Statistics website: http://www.uzis.cz/publikace/tnm-klasifikace-zhoubnych-novotvaru-7-vydani-original-2011

RECIST criteria are available on the RECIST Working Group website: http://www.eortc.org/recist/

Principles of treatment and tumour response evaluation

P. Grell

The primary goal of oncological therapy is to achieve long-term complete remission of a disease (without macroscopic signs of tumour). However, this is not always possible, especially in patients with advanced disease, or in compromised patients who are unable to undergo aggressive cancer treatment. Oncologic treatment should be considered with the aim of prolonging patient's survival while maintaining or improving their quality of life.

Types of cancer treatment

Oncological care comprises anticancer treatment and supportive care.

Anticancer treatment is aimed at eliminating, reducing, slowing or preventing tumour growth. It encompasses several treatment modalities that can be combined: surgical treatment, radiotherapy and systemic therapy. In general, patients with early-stage cancer can be cured by means of surgery alone, which is the mainstay of anticancer treatment in general, and represents the most effective curative treatment in the majority of solid tumours. At advanced stages, a combination of several modalities (e.g. surgery and subsequent chemotherapy, radiotherapy, hormone therapy or immunotherapy) is usually necessary.

Supportive care is focused on the management of tumour-related complications like dyspnoea, pain, malnutrition, or psychosocial issues. It also aims to alleviate the side effects of cancer treatment itself (nausea and vomiting, haematological toxicity, infectious complications, etc.). Complex supportive care in the context of an advanced cancer is referred to as palliative care.

With respect to the intention of treatment and its role within a comprehensive treatment plan, we recognize following categories:

Curative cancer treatment aims to achieve complete remission of a disease. It encompasses surgical procedures, especially in early-stage cancer, e.g. bowel resection in colorectal carcinoma without lymph node involvement, chemotherapy in the case of highly sensitive tumours such as testicular cancer or haematological malignancies, radiotherapy for prostate tumours, or concomitant chemoradiotherapy for head and neck cancer or cervical cancer.

Non-curative (palliative) cancer treatment is a generic term covering various treatment methods that do not have the potential to achieve a long-term complete cancer remission, but they can reduce the tumour mass, restrict its growth and temporarily prevent it from spreading.

Administration of palliative treatment may prolong patient survival in the range of months or event several years. Tumour shrinkage can relieve symptoms caused by the disease (e.g. pain or dyspnoea), or prevent serious complications (e.g. bowel obstruction or pathologic bone fractures and spinal cord compressions) and thus improve patients' quality of life. When considering palliative systemic therapy, it is important to assess risks and benefits of the treatment and respect patient's attitudes and preferences in the decision-making process.

Adjuvant therapy is administered after surgery or other curative modality. The concept of adjuvant therapy is based on the assumption that a primary tumour can shed tumour cells into blood and lymphatic vessels and thus may give rise to micrometastases and subsequent macroscopic dissemination. The aim of adjuvant therapy is to eradicate micrometastases and thus prevent tumour relapse. Adjuvant therapy is usually used in high-risk tumours, e.g. breast cancer or colorectal cancer with nodal involvement.

Neoadjuvant therapy is administered prior to primary therapy, which is usually a surgery. The aim is to eliminate micrometastases and reduce tumour size in order to minimize the impact of surgical procedure. A typical example is neoadjuvant chemoradiotherapy for advanced rectal or oesophageal cancer or neoadjuvant chemotherapy in breast cancer. In ideal case, a complete tumour response is achieved (verified by a pathologist and indicated as pCR).

Perioperative therapy is a treatment given to a patient prior and after surgery. Actually, it is a combination of neoadjuvant and adjuvant therapy. It is used, for example, in locally advanced gastric cancer.

Induction Therapy is the initial treatment, usually chemotherapy, aimed at tumour cytoreduction or complete tumour elimination. It is always followed by another type of chemotherapy or other treatment modality, most frequently used in haematological malignancies in order to induce remission (eradication) of the disease. Induction therapy is not very common in solid tumours, except for locally advanced head and neck tumours.

Consolidation therapy (intensification therapy): If a tumour remission is achieved by induction therapy, the following treatment given to prevent the disease relapse is referred to as consolidation therapy.

Maintenance therapy is usually a low-dose chemotherapy given to patients with disease remission in order to prolong the disease free interval.

Lines of therapy is a term used in connection with disseminated incurable disease. It refers to a set of certain chemotherapy cycles that are administered to the patient until treatment failure (progression

of the disease) or until its toxicity outweighs possible benefits. First-line therapy is prioritized based on clinical experience and guideline recommendations and after its failure, it is followed by another - second-line treatment etc. The likelihood of a therapeutic response decreases with every other line. In most patients, we eventually reach a point when all possible anticancer treatment options have been exhausted and the patient is afterwards indicated for symptomatic palliative care.

Symptomatic treatment/care: refers to a treatment approach in a patient who exhausted all the possibilities of causal anti-cancer treatment. The aim is to carefully assess and mitigate symptoms caused by an advanced tumour (e.g. pain, shortness of breath, malnutrition, etc.). The scope of symptomatic care largely overlaps with the concept of palliative care. This will be discussed in detail in the chapter "Palliative Care".

Tumour response evaluation

To find out if a treatment is effective, we need to make periodic re-evaluation of tumour size or activity, so-called restaging. An imaging method such as CT, MRI or PET is obtained usually every 3 months during the course of treatment, in order to compare the dynamics of the disease and thereby assess response to treatment. There are several criteria to evaluate tumour response. Basically, if a tumour (or metastasis) increases by more than 20% or a new lesion appears, we speak of **progressive disease (PD)**, which indicates that a change in chemotherapy regimen is required. Tumour size reduction by at least 30% is considered a **partial response (PR).** Other changes in between are classified as **stable disease (SD),** which is often also considered a favourable therapeutic outcome. If all the lesions disappear (which is a rare situation in disseminated solid tumours), it is referred to as **complete response (CR).** In clinical trials and lately also in common clinical practice, we use the so-called Response Evaluation Criteria in Solid Tumours (RECIST). The evaluation is based on imaging methods such as CT or MRI. At baseline imaging, a radiologist identifies all metastases out of which he selects so-called target lesions that are most suitable for repeated measurement. Target lesions are usually up to two metastases per organ and five lesions in total. The remaining metastases are so-called non-target lesions. Their measurement is not necessary, but they should be noted in the course of treatment similarly to non-measurable lesion such as pleural or other effusions. Target lesions are measured in the dimension with the longest diameter, their sum is calculated (LD) and used as a baseline for further treatment response evaluation. Tumour response is classified into four categories: complete response (CR), partial remission (PR), stable disease (SD) or progressive disease (PD).

If we want to monitor a tumour by means of imaging methods, a close cooperation between a clinician and a radiologist is necessary. For example, a radiologist needs to know which examination

is considered a baseline, he has to follow the same target lesions throughout the treatment course, and CT scans should be obtained using the same protocol.

Choosing an optimal treatment plan

Various treatment options are usually prioritized and sequenced according to several factors:

- Histological type of tumour and its localization (e.g. breast cancer, colorectal carcinoma...)
- Tumour differentiation and its proliferation rate (well-differentiated tumour with low proliferation rate, or, on the contrary, poorly-differentiated, aggressive, rapidly growing tumour)
- The extent of a disease, so-called stage (localized disease versus metastatic tumour)
- Sensitivity to a specific type of therapy (there are major differences among tumours in terms of chemosensitivity and radiosensitivity)
- Prognostic and predictive factors (e.g. hormone therapy in oestrogen-receptor-positive tumours, targeted therapy in HER2-positive tumours). Recently, there has been a shift from purely morphological assessment of tumours (according to tumour site and histopathologic appearance) to evaluation based on tumour biological behaviour based on specific genetic characteristics (so-called molecular biomarkers) or the expression of various proteins (receptors). Biological characteristics correlate with the level of chemosensitivity and tumour prognosis (for example, different subtypes of breast cancer might completely differ in sensitivity to therapy and prognosis).
- Patient-specific factors: performance status (PS), other co-morbidities (e.g., cardiac, renal insufficiency, etc.), patient age, personal preferences, social and spiritual factors.

Follow-up (dispensarization)

These are periodic examinations that the patient undergoes after finishing curative treatment. The aim is to detect a possible tumour relapse as early as possible in order to increase chances of repeated cure. Follow-up care includes blood tests, physical exams, imaging methods or other examinations specific for tumour type (mammography in breast cancer, colonoscopy in colorectal carcinoma). Follow-up period usually takes at least 5 years, whereas a relapse usually occurs in first two years after primary therapy. However, a relapse after ten, fifteen or even more years is not an exception.

The role of guidelines

Treatment decision-making in an individual patient often follows tumour-specific general recommendations, so-called guidelines. It is a set of evidence-based treatment algorithms designed for each tumour type and stage. Treatment recommendations are developed by international oncology societies and associations (e.g. European Society for Clinical Oncology, ESMO or American Society for Clinical Oncology, ASCO). Due to rapid advances in treatment options and approaches,

these guidelines are regularly updated. The Czech Republic's guidelines addressing the most common types of solid tumours are published under the title Blue Book of the Czech Cancer Society (available at www.linkos.cz).

An important role in the treatment decision-making process is attributed to multidisciplinary teams. They usually comprise several medical specialists such as oncologist, radiation oncologist, surgeon, radiologist, pathologist or other health-care professionals (psychologist, neurologist etc.) who collectively decide on complicated or otherwise complex cases (for example, rare types of tumours or tumours requiring multi-modal treatment in order to achieve optimal outcomes). The aim of these teams is to improve medical care by providing a complex treatment plan tailored to an individual patient, ensure health-care continuity, centralize costly treatment and complicated cases to centres with adequate expertise and, not at least, to educate individual team members.

Case studies

Multimodal breast cancer treatment

A 67-year-old female patient was diagnosed with T2 N1 M0 breast cancer, i.e. IIB stage. Histologically, it was ductal carcinoma, low differentiated - G3, hormone receptor negative, HER2 positive (immunohistochemically 3+, verified by HER2 gene amplification). The patient was indicated for upfront surgery (partial mastectomy with axillary dissection). Due to tumour size and its biology (an aggressive tumour), the patient received adjuvant chemotherapy (4 cycles of doxorubicin and cyclophosphamide every 3 weeks, followed by 12 cycles of paclitaxel weekly, which means 24 weeks of chemo in total). Afterwards, the patient underwent adjuvant radiotherapy of the whole breast and lymph nodes (for another 5 weeks). Due to HER2 positivity, trastuzumab was also indicated in adjuvant setting, in a 3-week interval for one year. Following this treatment, the patient was further monitored according to guidelines.

Multimodal treatment of colorectal cancer

A 54-year-old patient was diagnosed with a colorectal carcinoma of left colic flexure with two peripherally located hepatic metastases. In particular cases, even a metastatic cancer can be resected. This can significantly improve patient's survival (in contrast to palliative chemotherapy alone) and a small portion of patients can even achieve complete cancer remission. Moreover, there are clinical studies showing that the administration of perioperative chemotherapy might be beneficial in such patients. Therefore, the patient underwent 3 months of chemotherapy (FOLFOX biweekly), followed by resection of the primary tumour and synchronous liver metastasectomy. After the surgery, postoperative chemotherapy was applied for another 3 months. Subsequent CT scans showed no evidence of tumour and the patient was then routinely monitored. However, after two years, he developed unresectable pulmonary and liver metastases, which deemed the patient incurable. He was indicated for palliative chemotherapy with FOLFOX regimen in combination with targeted therapy. After the failure of this first-line therapy (the progression of the disease takes about 10-12 months), he was started on second-line treatment with FOLFIRI regimen (progression free survival in this setting is about 6 months) and the therapy is still ongoing. Afterwards, the options of effective anticancer treatment will be remarkably limited, therefore, we should carefully consider the benefit-risk ratio of every other therapy offered to the patient. In clinical practice, we mostly focus on maintaining a good quality of life through appropriate symptomatic therapy.

Surgical Procedures in Oncology

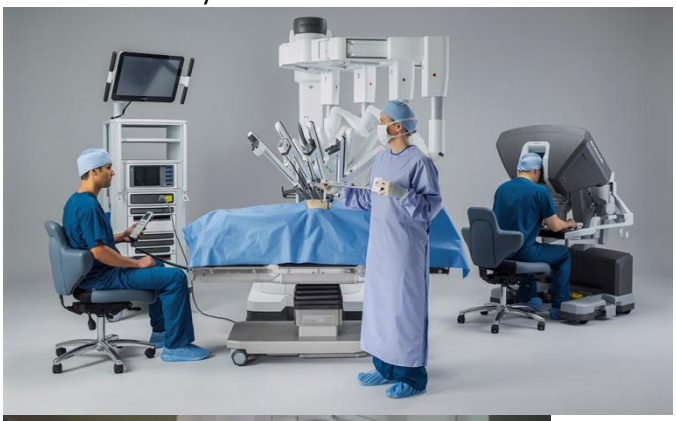
R. Šefr

Introduction

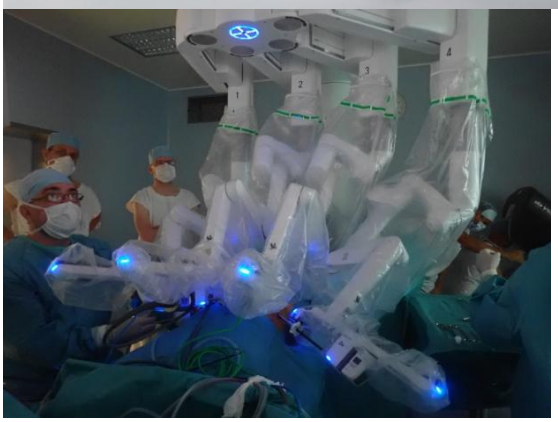
Surgical treatment of solid cancers plays a key role in the management of malignant diseases. In the vast majority of cases, radical surgery is the most effective method of multimodal anti-cancer therapy that gives the patient a chance for complete cure. In early stages of the disease, it is often a definitive procedure that does not require any further oncological therapy.

In the last three decades, the surgical treatment of malignant tumours underwent a turbulent development that has influenced both operational techniques and procedures, and prompted the employment of novel technologies such as mini-invasive approaches, da Vinci robotic system, radionavigated surgery, new ablative techniques, etc. The importance of surgical treatment was augmented by increased detection of early-stage cancers thanks to successful screening programs (breast cancer, colorectal cancer).

Latest Robotic System - daVinci Xi



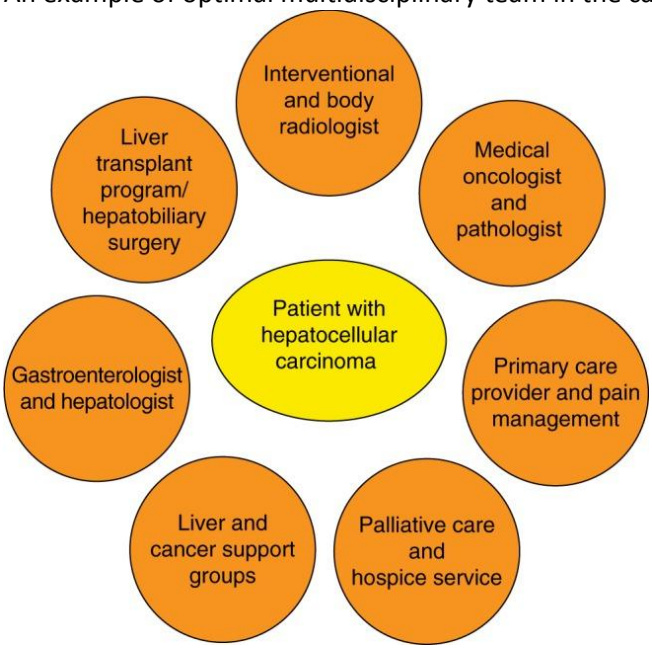
Robotic surgery in progress



Oncosurgery is today a globally recognized, dynamically evolving medical specialty focused on surgical treatment of solid malignant tumours. Oncosurgeron must not only have great expertise in surgical methods, but he also requires practical skills and knowledge of diagnostic methods,

pathological assessment and staging of tumours, as well as basic non-surgical treatment modalities (chemotherapy, targeted therapy, hormonal therapy, immunotherapy, radiotherapy); all of these with a focus on patient-specific and cancer-specific diagnostic and treatment procedures. There has also been a significant progress achieved in the interdisciplinary cooperation among various surgical specialties (e.g. surgery, gynaecology, urology) and, in particular, among oncology experts (clinical oncologist, radiation oncologist, radiologist, gastroenterologist, pathologist, etc.). Multidisciplinary team members vary according to cancer type, which they are concerned with (breast cancer, melanoma, gastrointestinal, urological, gynaecological, etc.). At tumour boards, they discuss each patient's findings and come up with a patient-tailored treatment plan. Tumour boards are an integral part of each Complex Oncology Centre (COC), and they become increasingly prevalent also in smaller district hospitals.

An example of optimal multidisciplinary team in the case of a patient with liver tumour



Main roles of surgical specialties in oncology

- Preoperative diagnosis and staging of the disease
- Strategy and timing of surgical treatment
- Locoregional therapy
- Surgical treatment with systemic impact
- Auxiliary method for providing non-surgical therapy or nutrition
- Treatment of complications of illness and treatment

Preoperative diagnostics and staging of the disease

Detailed and accurate diagnosis of a disease is crucial for prospective care planning. This includes mainly determination of tumour stage and the extent of tumour spread, which requires collaboration of a number of specialists.

There are no universal diagnostic imaging guidelines for all malignancies, e.g. CT and endoscopic ultrasound (EUS) are suitable for the assessment of oesophageal carcinoma, whereas in case of rectal carcinoma, MRI is currently a gold standard. Similarly, when a breast cancer is suspected, ultrasound and mammography are the methods of choice.

The positron emission tomography (PET), usually combined with computed tomography (CT), is suitable for identification of solitary malignant lesions and to rule out cancer dissemination, for example into lymph nodes, brain, lung, liver, etc. Other imaging methods (such as bone scintigraphy) are indicated with respect to presumed type of tumour spread (e.g., breast cancer, prostate cancer) in order to provide information on the extent of disease.

Overall, modern imaging methods are nowadays an irreplaceable aid in preoperative staging of a tumour. They provide clues for further planning of ancillary diagnostic procedures or surgical strategies.

Another step in the diagnostic algorithm includes the collection of tumour samples (biopsy) and their histopathological examination. Tumour samples can be obtained by an open biopsy (excision biopsy), CT or ultrasound-guided percutaneous fine-needle aspiration biopsy, or during an endoscopic examination (bronchoscopy, gastroscopy, colonoscopy etc.). These diagnostic procedures provide a comprehensive pre-operative evaluation of malignant lesions regarding its topography (tumour relationship to anatomical landmarks) and behaviour (tumour type, aggressiveness, proliferation rate and many other biological characteristics).

A tumour is then clinically classified according to the TNM system (Tumour, Nodal spread, distant Metastases). The combination of values in each category determines a tumour stage (I-IV). Tumour-specific staging is issued in a tabular manner, whereas stage I indicates an early detection of a disease, while stage IV refers to an advanced disseminated tumour.

Despite the advances in diagnostic procedures and equipment, a physical examination of a patient remains the mainstay of diagnostics. This includes the evaluation of patient's overall health condition, which helps to predict his or her ability to undergo surgery and possible postoperative complications.

At a preoperative patient appointment, a surgeon should have enough time to respond to patient concerns regarding the extent of surgery, its method (minimally-invasive or open) or any equally effective non-surgical alternatives. A thorough physical examination is necessary to evaluate local findings in accessible tumours, such as melanoma, breast cancer, abdominal tumour or sarcoma of the extremities. In correlation with previous examinations and tumour stage, this gives a surgeon the idea of the type and the extent of operation. A typical example is rectal carcinoma, especially in its proximal part, which is palpable at digital rectal examination. A surgeon might evaluate tumour distance from the sphincter, but also the extent of the tumour, its mobility or fixation to the surrounding tissues, and hence decide on the feasibility of a so-called sphincter preserving operation. He communicates his assumption to the patient, who also has to be warned that a final decision regarding the character of procedure is always made during the course of surgery itself. Similarly, a patient with a breast cancer should be thoroughly informed about the extent of surgical intervention, its cosmetic effects and possible involvement of a cosmetic surgeon in order to achieve the most acceptable aesthetic outcomes.

Strategy and timing of surgical treatment

The greatest responsibility of an oncologist is to choose the right type and extent of surgical procedure with respect to individual patient's needs and biological behaviour and stage of the tumour. It is also necessary to take account of other non-surgical treatment options (e.g. neoadjuvant chemotherapy), especially in locally advanced tumours. A surgeon must also have sufficient knowledge and practical experience and skills necessary for the operation itself.

Timing of an operation is very important. A majority of oncological patients undergo an elective surgery, that is, planned in advance and preceded by an internal medicine and anaesthesiologist consultation. On the contrary, there are cases when a patient has to be operated due to an urgent medical condition, without any delay. This is most commonly because of an acute abdomen resulting from gastrointestinal and intra-abdominal bleeding (less common), bowel perforation or malignant bowel obstruction (frequent). These clinical situations that may occur as a result of a malignant disease or as an adverse effect of anti-cancer treatment are discussed below.

According to the intent of a surgery, it can be **radical** - with curative potential, **prophylactic** or **palliative.** The purpose of a curative surgery is to attempt a so-called **R0 resection** (complete removal of the tumour with healthy-tissue margins). R0 type of resection has not only macroscopic, but also histopathologically confirmed negative margins. The size of recommended safety margins varies according to the type, stage and location of the tumour, and is based on robust clinical experience

evidenced by numerous studies. Achieving a R0 resection with a sufficient safety margin is essential for preventing local tumour recurrence.

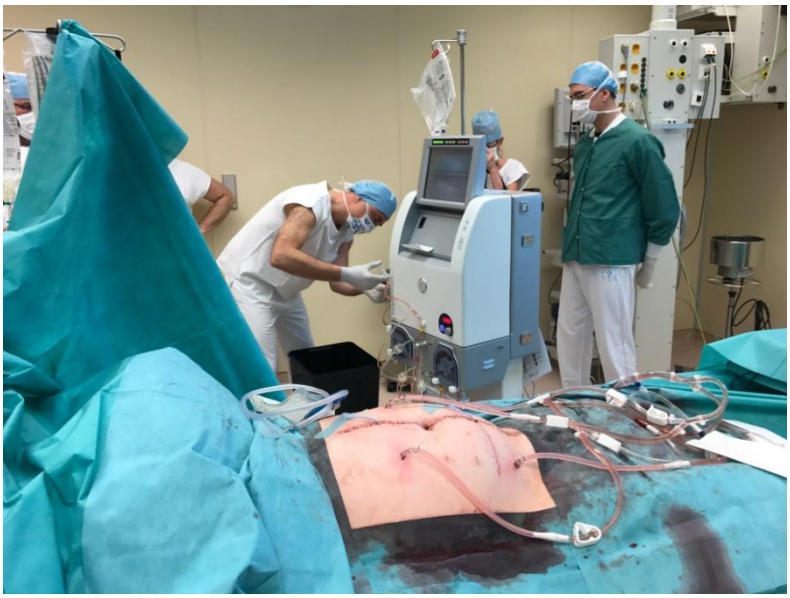
Unfortunately, this is not always possible due to anatomical location of a tumour (e.g. in the case of pancreas) or mutilating functional (e.g. lower rectal carcinoma) or cosmetic (breast carcinoma) impact of the surgery. Again, this depends on the type of tumour, its aggressiveness, patient previous medical history and his preferences.

In the case of microscopic evidence of tumour cells in resection margins, we speak of **R1 resection.** A tumour tissue macroscopically visible at the resection margin is referred to as **R2 resection** .

The goal of **prophylactic surgery** is to remove a tissue or organ susceptible to malignancy. This kind of operation is usually indicated on the basis of a molecular genetic examination in correlation with clinical findings and patient's informed consent. Typical example is subcutaneous mastectomy in BRCA 1 and 2 positive patients, thyroidectomy in MEN II syndrome or colectomy in Lynch syndrome.

The aim of **palliative surgery** is to improve patient's quality of life by alleviating or eliminating tumour-related symptoms and thereby indirectly extend his overall survival. The tumour itself is usually left in situ or only reduced in size. An example of palliative surgical treatment is a so-called debulking surgery in gynaecological tumours, when the tumour is not completely removed, but its mass is substantially reduced, so that the patient can undergo subsequent systemic treatment. Another example is a by-passing of a malignant bowel obstruction (e.g. by gastro-enteroanastomosis or ileo-transverso-anastomosis) in order to avoid a bowel diversion surgery or to facilitate patient's nutrition. Cytoreductive procedures also include a so-called hyperthermic intraperitoneal chemoperfusion (HIPEC), which augments the effect of a debulking surgery by a 30-90 minute rinse of abdominal cavity with a cytostatic agent. The local effect of chemotherapy is increased by heating of administered solution to approximately 42 ° C. The method has proved to be particularly effective in the treatment of malignant mesothelioma and peritoneal pseudomyxoma, however, it has been increasingly used in other diagnoses, such as ovarian and colorectal carcinoma, gastric cancer, etc.

Hyperthermal intraperitoneal chemoperfusion (HIPEC) and RAND perfusion device in the background.



Prior to surgery, each patient is carefully examined by an internist and anaesthesiologist. The initial pre-operative assessment addresses patient's overall health status and his co-morbidities with regard to surgery-specific characteristics, its risk-to-benefit ratio, etc. In addition, psychological and nutritional preparation of the patient is crucial for a favourable outcome of the surgery. Supposing a colostomy is indicated, a specially trained nurse assists in its planning and localization. The post-operative care continues even after patient's discharge from hospital. One should also take notice of social circumstances, e.g. whether the patient is able to take care of himself or he needs a special assistance, which can be arranged in advance by a social worker.

Prior to surgery, the patient is fully informed about the procedure and he gives an "informed consent" to it. The exception for obtaining an informed consent is an emergency (so-called vital indication surgery), when immediate treatment is needed in order to prevent serious health complications (e.g. an acute abdomen).

Locoregional therapy

It is a domain of all surgical specialties and the most important task of surgery in general. Locoregional therapy from the surgical perspective means the removal of a tumour and corresponding tumour-draining lymph nodes.

Oncosurgery techniques follow specific precautions in order to avoid tumour spread during the surgery:

- Resection with an adequate safety margin
- mobilization of structures and tissues with respect to the anatomy of surrounding tissues
- prevention of tumour capsule disruption or direct tumour incision
- early ligation of the vascular supply of the tumour

- no touch technique
- en-bloc tumour resection (so-called multivisceral resection of locally advanced tumours),
- anatomically oriented dissection of regional lymph nodes or sentinel node mapping in particular cases
- respect to patient's quality of life and functional or cosmetic outcomes of the operation

All of these recommendations may be difficult to implement in case of advanced tumours, reoperations, or in anatomically unfavourable settings.

The most common procedures in cancer surgery and metastasectomy

- excision - skin tumours (basalioma, melanoma)
- extirpation – capsuled subcutaneous or retroperitoneal tumours
- resection – cancer of lungs, gastrointestinal tract, parenchymatous organs
- amputation - tumours of extremities (melanoma, sarcoma).

The most common types of surgery by tumour site:

- skin – excision, sentinel biopsy (in malignant melanoma)
- breast – partial or simplex mastectomy, sentinel node biopsy or axillary dissection, radical mastectomy
- lungs - segmental lung resection, lobectomy, pneumonectomy
- digestive system – oesophageal resection, partial or total gastrectomy, colectomy, rectal amputation, etc.
- liver – anatomical or extra-anatomic liver resection
- pancreas - pancreatoduodenectomy, left pancreatectomy, total pancreatectomy.

The most common types of surgical procedures in secondary malignant tumours

Surgery of distant metastases is a very common surgical procedure in oncology centres. It mainly concerns the liver and lung operations, less frequently it involves surgery of bile ducts, pancreas, small intestine or brain metastases.

The most common primary tumours, for which a metastasectomy is indicated are colorectal cancer, gastrointestinal stromal tumours, kidney cancer, soft tissue sarcomas, malignant melanoma. Rarely, resection of metastases of breast, stomach and pancreatic carcinoma is performed. Operations at organs afflicted by metastatic disease do not actually differ from the primary tumour surgery.

Prerequisites for a curative operation are :

- the primary tumour or its relapse is radically resectable,
- it is possible to completely remove all metastases at a tolerable risk-benefit ratio,
- there are no equally effective alternatives to surgery,
- patient informed consent with the proposed procedure.

Surgical treatment with systemic impact

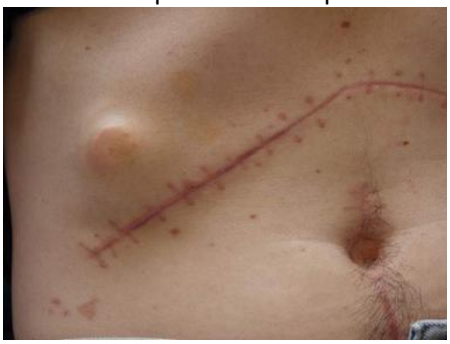
This is a type of surgery, rather uncommon in the clinical practice, which can influence the overall patient's status. Most commonly, it involves removal of glands with hormonal activity, such as thyroid gland, parathyroid gland, pancreas or adrenal gland. An appropriate substitution therapy is always required afterwards.

Surgery as an auxiliary method

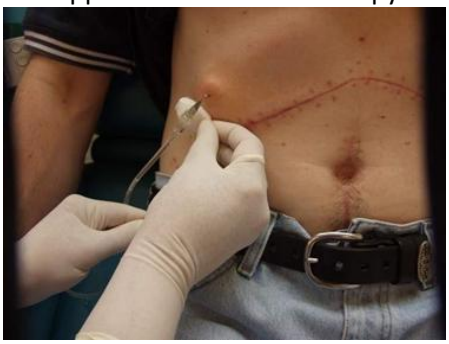
The implantation of permanent central venous catheters and intravenous ports for the application of chemotherapy and other medications is an indispensable surgical procedure. A port is a device made of an inert material that is placed into pectoral subcutaneous tissue, while its catheter is inserted into adjacent venous system, usually the subclavian vein. Medications can be injected through the skin into a portal (reservoir compartment) using a special needle. Alternatively, peripherally inserted central catheters (PICC) or PICC ports (which are a combination of both previously mentioned options) may be used.

Less often, there are ports used to provide locoregional treatment, e.g. an arterial port system inserted to hepatic artery for regional chemotherapy of the liver.

Intraarterial port into a. hepatic



the application of chemotherapy with a Huber needle



Surgeons often assist to radiotherapist by operative placement of clips into the tumour bed (most commonly sarcoma) for subsequent radiotherapy planning. This method helps to reduce the risk of local recurrence of the tumour. In appropriately equipped hospitals, radiotherapy can also be applied during a surgery directly to the tumour bed with the same objective (e.g. in pancreatic cancer, rectum).

Another important role of surgery is to providing access routes for enteral or gastric feeding in patients with insufficient or absent oral food intake. This applies, for example, to patients with an advanced oesophageal or gastric tumours, who might benefit from nutritional gastrostomy and jejunostomy, respectively. Besides these palliative indications, this procedures can be utilised prior to oncological treatment (neoadjuvant) in order to provide adequate nutrition before a major curative surgery.

Dealing with complications of illness and treatment

Complications requiring consultation or intervention from a surgeon are very common in oncological patients, though they are not always related to the underlying disease. The most common complications in oncology patients include:

Intestinal obstruction - a very common and serious cause of morbidity and mortality among cancer patients. Decisions on the timing, extent or feasibility of an operation are often difficult, especially in advanced intra-abdominal tumours or after a number of previous abdominal operations. For example, in advanced or recurrent ovarian cancer, approximately two-thirds of patients will experience at least one episode of intestinal obstruction. Similarly, almost all patients with peritoneal carcinomatosis suffer from complications of impaired peristalsis, which are usually inoperable. Besides ovarian carcinoma, colorectal and gastric carcinoma are the most frequent causes of ileus. This type of intestinal obstruction develops and progresses rather slowly and unless a perforation or intestinal rupture occurs as result of massive bowel dilatation, the indication of surgery is usually not urgent.

In these patients, it may be necessary to establish a stoma (colostomy or ileostomy) or surgical gastrostomy for decompression and relief from profuse vomiting. In some cases, it is possible to bypass the obstruction by performing an anastomosis of intact intestinal loops. Mortality and morbidity associated with malignant bowel obstruction is up to 10% and 30%, respectively, and an average overall survival is around six months.

On the other hand, one third of bowel obstructions are caused by benign conditions (adhesions, hernias), or they are only pseudo-obstructions without true mechanical blockage (e.g. due to radiation-induced colitis or intestinal paralysis resulting from chemotherapy-induced enteritis, opioid analgesics overdose, long-term immobility, electrolyte imbalance, etc.). These emergencies require early diagnosis and the therapy has to be causal. It is especially important to distinguish ileus from pseudo-obstruction, which does not necessitate surgical intervention.

Bleeding - It can occur as a complication of a surgery or a biopsy, or due to bleeding disorders (secondary due to anticoagulants, thrombocytopenia and coagulopathies). A common cause of post-operative bleeding is a ligature rupture (e.g. in liver resection) or erosion of operation wounds, e.g. after partial mastectomy. Most haemorrhages can be managed by administration of haemostyptics, fresh frozen plasma or by local interventions (wound injection, endoscopic treatment of gastric bleeding). Massive bleeding requires an urgent surgical revision.

Gastrointestinal perforation - may occur in any stage of cancer, even as an initial presenting symptom. Perforation of intestinal loops into peritoneal cavity or adjacent tissues and organs

(broncho-oesophageal, recto-vaginal fistula, etc.) results in an acute abdomen. Differential diagnoses include benign conditions such as peptic ulcer, diverticulitis or appendicitis that might often occur in oncology patients as well.

Other oncologic emergencies that require surgeon consultations are biliary obstruction, superior vena cava syndrome, pericardial tamponade, or septic states.

Conclusion

In conclusion, it should be emphasized that surgical specialties represent one of four main pillars of anti-tumour treatment (radiodiagnostics, oncosurgery, clinical oncology, radiation oncology). Their importance will increase with the rising incidence of malignancies and thanks to continuous professional advances in oncosurgery and postgraduate education programs.

Radiotherapy

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Radiotherapy (RT) is a method that uses ionizing radiation to treat cancer, as well as particular non-cancerous diseases. It constitutes an important part of therapeutic procedures in oncology; 50-70% of patients undergo radiotherapy in the course of their disease. This specialty deals with the whole range of systemic tumour-related conditions, therefore a term **radiation oncology** is more appropriate.

By the intent, it can divided into **curative (radical)** and **palliative radiotherapy**. The goal of radical radiotherapy is to eradicate the tumour and cure the patient. Radiotherapy is a method of choice in treatment of particular types of cancer or might be an equally effective alternative to a surgical (often mutilating) procedure. The main objective of palliative radiotherapy is to control symptoms of an advanced cancer (e.g. pain management or reduction of the risk of pathological fractures). With regard to the extent of disease and patient's prognosis, it may also be used to prevent local recurrence of the tumour and thus influence overall survival.

Depending on the location of the radiation source, radiotherapy is divided into **external beam radiotherapy (TRT)** and **brachytherapy (BRT)**. In external beam radiation therapy (also known as teleradiotherapy - TRT), the source is located outside the body and directs the radiation at the tumour "through the patient's skin". In brachytherapy, the radiation source is placed in close proximity of the tumour, directly into the organ affected by the tumour, or to tumour bed.

In the context of other treatment modalities, radiotherapy can be used before the surgery (**preoperative - neoadjuvant RT**), in order to reduce the tumour size by so-called "downsizing" or "downstaging", e.g., in rectal cancer; during the surgery (**intraoperative radiotherapy**, e.g. breast cancer or soft tissue sarcomas) or after surgery, for example after partial mastectomy. The post-operative extent of tumour determines whether the irradiation targets residual microscopic disease - **adjuvant radiotherapy** or whether it used to treat macroscopic residual tumour, with either curative or palliative intent.

From a technical point of view, there are many different types of radiotherapy. **Conformal radiotherapy (3D-CRT)** is a technique in which radiation field is adapted to the irregular shape of the target volume (tumour, tumour bed, etc.). **Intensity modulated radiotherapy (IMRT)** is an advanced type of conformal radiotherapy technique, which not only adjusts the radiation field according to the shape of the target volume, but also modulates the intensity of each beamlet. IMRT provides more accurate dose distribution to the target volume with respect to its irregular shape. This minimizes the

amount of radiation received by surrounding normal tissues, particularly in the case of concave-shaped target volumes. Such sparing of critical structures also allows dose escalation to the target volume. In intensity-modulated radiotherapy, the linac gantry may be static and the patient is irradiated from a limited number of fixed angles or the gantry may rotate around the patient. **Volumetric modulated arc therapy (VMAT)** is currently the most advanced radiation technique. It combines the IMRT principle with the possibility to modulate the rotational speed of the gantry, dose intensity of each beam and orientation of a multi-leaf collimator, thus shortens the time of irradiation while increasing its accuracy. The technique of **4D-radiotherapy (4DRT)** allows to track the motion of target volume in the course of irradiation (it reflects patient's position, physiological movements of the organs etc.) and it synchronizes radiation with these movements. **Image-guided radiotherapy (IGRT)** uses advanced imaging technology to monitor target volume changes throughout the radiotherapy. Imaging systems enable to detect and compensate for possible target volume changes in time and thus achieve higher accuracy of every radiotherapy fraction. Precise dose administration is a key to successful radiation treatment. The rationale behind **stereotactic irradiation** (SRS, SRT, SBRT) is that it uses high-energy radiation beams directed to a small target volume with a very high precision. This method can be used to treat malignant lesions in the lungs, liver, abdominal cavity, pelvis or skeleton. Modern linear accelerators allow the application of ablative radiation doses without any risk of missing the target or damage to surrounding sensitive tissue. A great advantage of this method is its non-invasive character, no requirement of anaesthesia and the possibility of outpatient administration. Radiation doses used in SBRT have a biological effect comparable to surgical treatment, hence, it is often referred to as **radiosurgery**.

Radiobiology

Ionizing radiation might induce damage to tumour microenvironment and surrounding tissues. Absorption of radiation energy leads to ionization of biological structures, particularly DNA molecules. Ionization can damage cellular structures also indirectly, by creating highly reactive free radicals from water molecules. Both events result in single-strand and double-strand DNA breaks, which are more difficult to repair. Radiation-induced damage leads to the activation of many signalling pathways, genes, and cell cycle control proteins. This may result in:

a) successful repair process and cell cycle maintenance,
b) incorrectly repaired DNA damage which induces apoptosis or mitotic death,
c) incorrectly repaired damage which leads to mutations not recognized by the cell

It was found that sub-lethal or lethal cell damage and DNA repair mechanisms are different in tumour and healthy tissues. Based on this distinction, **fractionation** was introduced, i.e. splitting of

the total radiation dose into series of smaller doses (fractions). Fractionation enables repair of affected healthy tissues in between the fractions. Various fractionation schemes have been designed in order to achieve highest possible tumour response with acceptable toxicity to healthy tissues. Advances in technology have allowed more accurate targeting of radiation while increasing the dose intensity per fraction (radiosurgery). This primarily leads to microvascular damage with subsequent necrosis.

Adverse effects of radiotherapy

Adverse effects vary in their character, extent and incidence, depending on several factors: radiation dose, volume of irradiated tissue, technique, type of radiation, its energy, individual patient's sensitivity to ionizing radiation or the application of radiosensitizing agents (particular cytostatics, biological treatment).

Systemic (general) reaction to radiation occurs especially in the case of larger target volumes. Most common symptoms include fatigue, loss of appetite, nausea, vomiting, or cognitive changes. Patients often compare these non-specific symptoms of so-called post-radiation syndrome to a hangover. The mechanism underlying early post-radiation changes has not been sufficiently elucidated yet. It is hypothesized that irradiation probably causes irritation of certain tissue receptors or structures that results in the above-mentioned symptoms. In the case of more extensive skeletal irradiation, a decline in blood count usually occurs.

Local reactions to radiation are limited to the irradiated area, and the most common are listed in table 1.

In practice, early, late and very late side effects are distinguished. They differ not only in the time of onset, but also in the underlying mechanism and subsequent reaction of tissues (Figure 1 a-d, 2 a-b, 3 a-b, 4).

Acute (early) side effects occur during the course of radiotherapy and persist for several weeks after the treatment (usually up to three months). They are more pronounced in tissues with rapidly proliferating cells, such as epithelium of the skin, mucosa, or hematopoietic system. The acute reaction results from a damage to a radiosensitive stem cell that impairs its further division and maturation into differentiated cells. Acute reaction is reversible and its intensity and course depends on the rate of stem cell repopulation and epithelial regeneration.

Late (chronic) adverse effects develop months or even years after the exposure to radiotherapy. They primarily afflict tissues with low cellular turnover, such as subcutaneous tissue, lungs, kidney, brain, heart, bones or muscles. These tissues contain stem cells as well, but their rate of proliferation is low and cell maturation is very slow. Stem cell damage incurred by radiotherapy manifests within

weeks or months following the treatment, because these cells have a long cell cycle and the damage is revealed only at their division. Changes vary from atrophy and necrosis to fibrosis or microvascular damage. Chronic changes are irreversible, their onset may be sudden or gradual and their development cannot be predicted based on the intensity of acute changes.

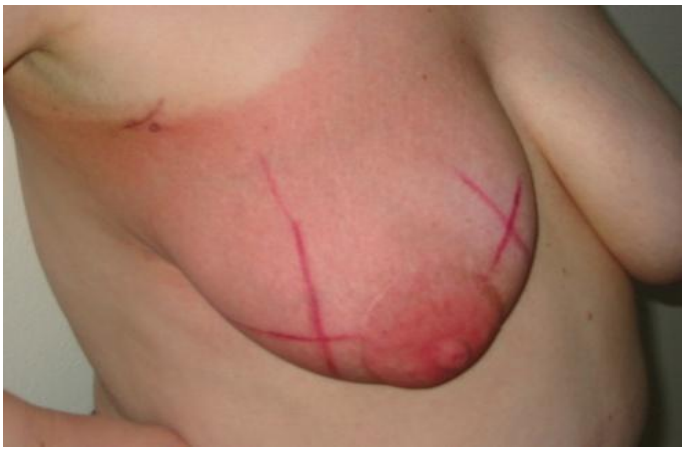
Very late changes develop in the order of years following the treatment and they are caused by radiation-induced mutations. Somatic mutations often result in secondary malignancies. The incidence has a bimodal distribution, the first peak occurs by the third year after radiation exposure and typically involves haematological malignancies. The second peak occurs ten or more years following radiotherapy and it is predominantly associated with solid tumours. Germinal mutations increase the risk of genetic disorders with different phenotype changes, therefore, radiation therapy should be carefully considered in childhood and fertile-aged patients.

Tab. 1 Selected manifestations of radiation toxicity

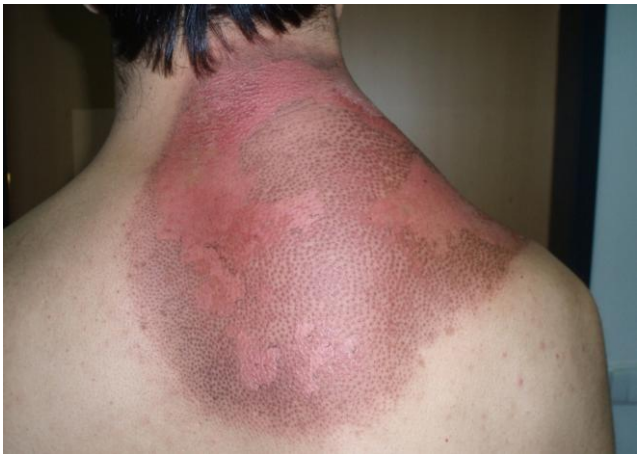
Location	Acute changes	Chronic changes
Skin	Radiodermatitis: Grade 1 - erythema, G2 - dry desquamation, G3 - moist desquamation	Atrophy, fibrosis, depigmentation, hyperpigmentation, telangiectasia, epilation, alopecia
The oral cavity	Mucositis: G1- erythema, oedema, G2- fibrin patches, G3 - ulcers	Atrophy, fibrosis, swallowing difficulties, xerostomia
Lung	Radiation pneumonitis	Pulmonary fibrosis
Gut, rectum	Oedema, mucosal congestion, dysmicrobia, increased peristalsis, diarrhoea, tenesmus	Peristalsis impairment, incontinence, stenosis, fistula, ulcer, enterorhagia
Bladder	Oedema, cystitis	Fibrosis, telangiectasia, reduction of bladder capacity and micturition disorders, haematuria
Brain	Oedema, leukoencephalopathy	Oedema, necrosis, cognitive decline, pituitary function disorders

Fig. 1: Acute skin reactions

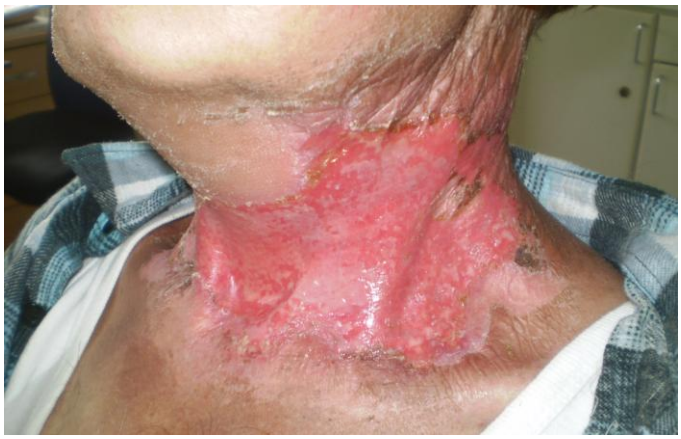
a) Grade 1 - erythema



b) Grade 2 - erythema with dry desquamation



c) Grade 3 – moist desquamation with incipient reepithelization



d) Acute reactions of skin appendages - hair loss in the irradiated field

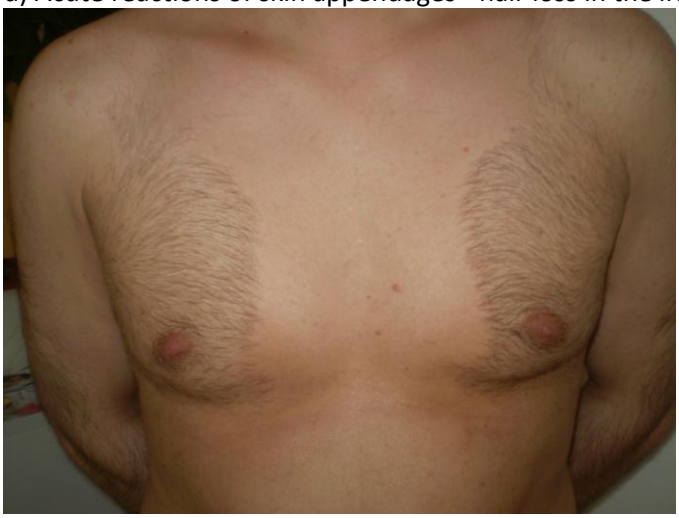


Fig. 2: Acute mucosal reaction - erythema and patchy ulceration with fibrinous pseudomembranes

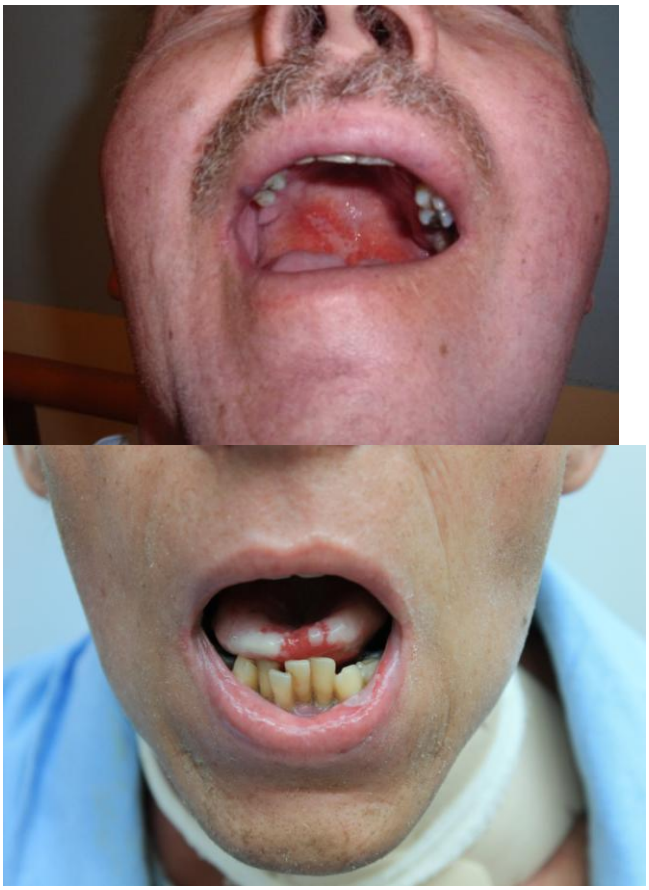
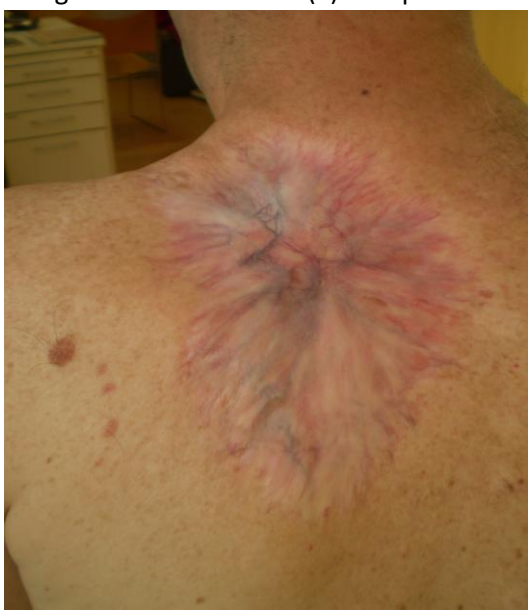
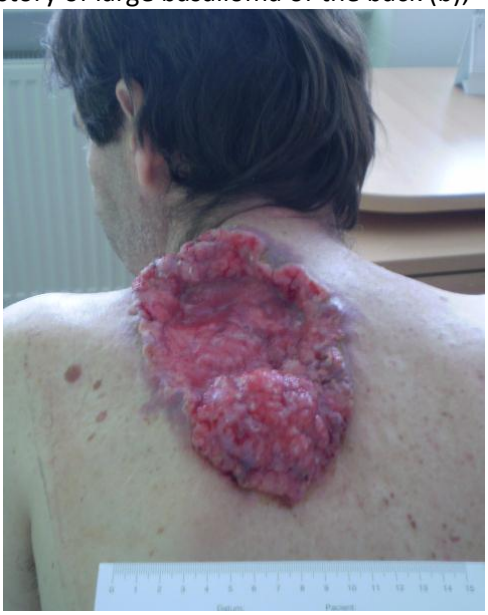


Fig. 3: Late, chronic skin changes
Teleangiectasis and fibrosis (a) in a patient with a history of large basalioma of the back (b);

a) 

b) 

Postiradiation ulcer

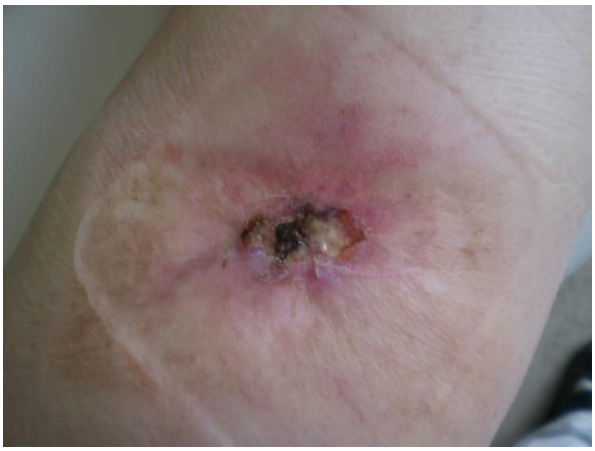
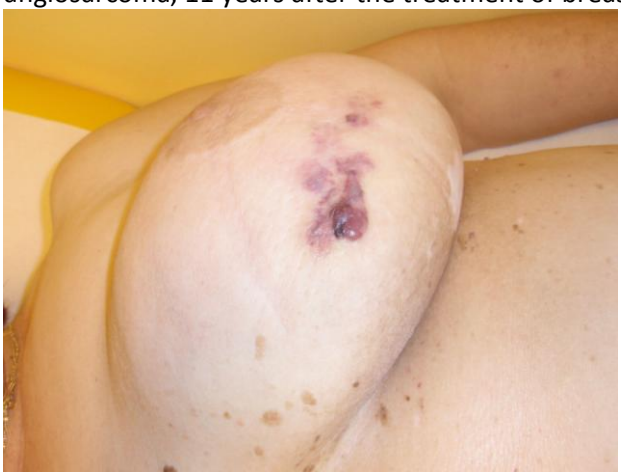


Fig. 4: Very late radiation-induced changes - a secondary malignancy in the irradiated field - angiosarcoma, 11 years after the treatment of breast cancer



Radiation sources in radiotherapy

Radiotherapy uses mainly high-energy photon and electron radiation. There are several other types of radiation used rather experimentally - accelerated protons, light ions, neutrons –so-called hadron therapy.

The primary and most widely used radiation source for external beam radiotherapy is **linear accelerator** (Figure 5), which produces both braking and electromagnetic radiation of different energies. The accelerator head is equipped with a collimator that filters the radiation beam to a desired shape. There are also devices with a multileaf microcollimator (with very fine plates) that are used for stereotactic radiotherapy and radiosurgery. Modern accelerators are able to monitor patient's position by real-time CT scanning during the course of radiotherapy (image-guided radiotherapy, IGRT). **Cyberknife®** (Figure 6) is a radiosurgery device, which has the linear accelerator mounted on a robotic arm. This enables highly accurate targeting of radiation. **Tomotherapy** combines a CT scanning technology with a rotating linear accelerator gantry (Figure 7). Prior to the

treatment, a CT scan of a target volume is provided and the radiation is delivered to it in a layer-by-layer manner. **Cobalt therapy** uses the radioisotope cobalt-60 as a radiation source emitting gamma rays with energies of 1.17 MeV and 1.33 MeV with a half-life of 5.3 years, so the source needs to be replaced every five years. However, cobalt therapy is nowadays considered obsolete and is being replaced by modern technologies, with the exception of **Leksell gamma knife** (LGN), which uses up to 201 cobalt-60 sources arranged in a hemispheric manner in the head of the device. **X-ray irradiation devices** are based on an X-ray tube principle. The maximum radiation dose is delivered to the skin surface area. Its absorption in bone tissue is also specifically high, which makes it suitable for treatment of skin tumours and palliative radiotherapy of skeletal metastases. **Heavy particle therapy - so-called hadron therapy** requires very large accelerators (e.g., synchrotron, cyclotron) to produce heavy energetic particles (protons, ions – e.g. carbon, helium). The energy emitted by these particles increases while they penetrate the tissue and reaches its peak (so-called Bragg peak) just neat the end of its range. This can reduce the radiation burden to healthy tissues surrounding the tumour and increase the dose to the target volume. This advantage is, however, rarely taken into practice.

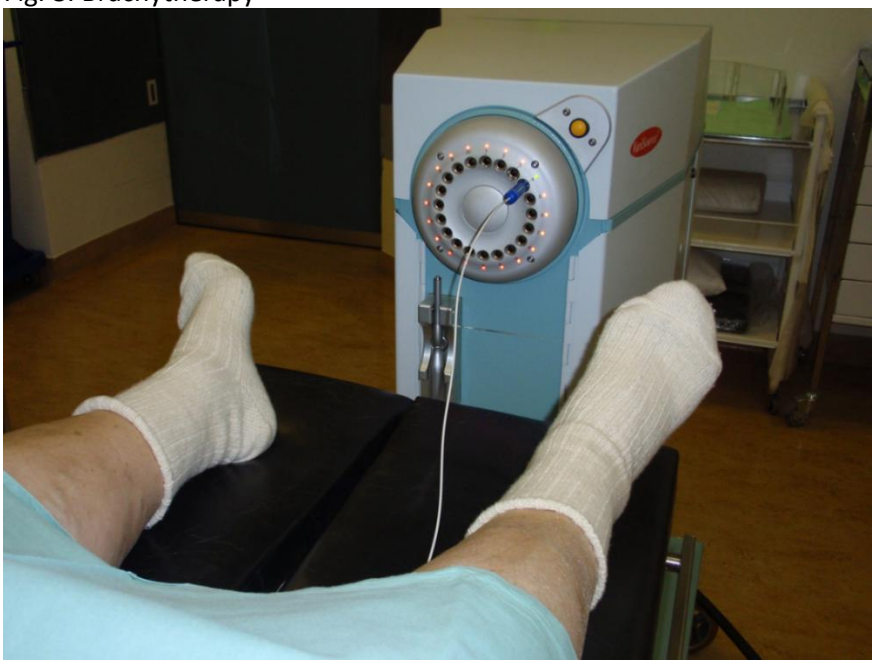
In cancer treatment, we use only a few natural and artificial **radionuclide sources**, either in a sealed or an unsealed form. **Brachytherapy** (Figure 8) uses sealed irradiation sources that are inserted directly to the tumour vicinity (intracavitary, intraluminal, interstitial placement) or into tumour bed. The rate of radiation emission to the environment is very fast, which minimizes the exposure of healthy tissues. The placement of radiation source to the target area can be either permanent or temporary. The procedure usually involves so-called afterloading technique, in which inactive applicators are firstly inserted into the target area and afterwards loaded with radiation sources. Brachytherapy varies by dose rate delivered to the tumour, **HDR (high dose rate) devices** are characterized by high-intensity radiation and shorter irradiation time. In permanent brachytherapy, gold, iodine or palladium isotopes are used in the form of seeds (e.g. in prostate cancer).

Fig. 5: Linear accelerator

Fig. 6: CyberKnife - a robotic irradiator

Fig. 7: Tomography

Fig. 8: Brachytherapy



Medical use of radiotherapy

Radiotherapy together with surgery is a basic method of local tumour management. It might be used in the treatment of both cancerous and non-cancerous diseases.

Malignant skin tumours

Basal cell carcinoma (basalioma) - radiotherapy is an equivalent alternative to surgical extirpation with basically identical therapeutic results. In the case of tumour recurrence after surgery, it is advisable to consider treatment with radiotherapy (and vice versa).

Squamous cell carcinoma (spinalioma) - the method of choice is radical surgery, radiotherapy is preferred in inoperable tumours. In some cases (e.g. in positive surgical margins), adjuvant radiotherapy is indicated. The total dose is usually applied in 10-17 fractions using an X-ray or electron beam accelerator, or, alternatively, by brachytherapy.

Tumours of the central nervous system

High-grade gliomas (G3 astrocytoma and glioblastoma) - the treatment method of choice is neurosurgery. Concomitant chemoradiotherapy (radiotherapy with simultaneous administration of temozolomide) is indicated in adjuvant settings.

Low-grade gliomas - astrocytomas, oligodendrogliomas. A radical neurosurgical resection is crucial in this type of tumours. Irradiation is indicated in the case of inoperable tumour recurrence or subtotal resection.

Meningeomas - the primary treatment is surgical resection. Stereotactic radiotherapy or radiosurgery may be indicated in treatment of inoperable tumours or as an alternative to a high-risk surgery.

Stereotactic radiotherapy (SRT) uses accelerated fractionation schemes (e.g. 5 x 5Gy with a linear accelerator). In stereotactic radiosurgery (SRS), a single dose of radiation is applied to the tumour (total dose of 12-18Gy with a gamma knife).

Other CNS tumours suitable for radiotherapy are pinealocytomas, pinelablastomas, germinomas, choroid plexus tumours, craniopharyngeoma, pituitary tumours, vestibular schwannomas etc.

Malignant head and neck tumours (tumours of the oral and paranasal cavity, thyroid and salivary gland tumours, oropharyngeal, hypopharyngeal, nasopharyngeal, laryngeal tumours)

Early-stage tumours are usually managed by single treatment modality – either surgery or radiotherapy. Advanced cancers are treated with radical surgery followed by postoperative radiotherapy. In certain patients, a non-surgical approach is preferred, while salvage surgery is spared for recurrent cancer. To date, concomitant chemoradiotherapy is most frequently used to treat locally advanced inoperable tumours, since it was proven more effective than sequential treatment.

Thyroid cancer is managed by the administration of radioactive iodine therapy or postoperative external beam radiotherapy (medullary carcinoma and iodine negative tumours).

Malignant gastrointestinal tract tumours (GIT)

Malignant tumours of the oesophagus and stomach - the method of choice is a radical surgery followed by adjuvant radiotherapy (or chemoradiotherapy). In the case of borderline operability,

surgery is preceded by neoadjuvant chemoradiotherapy. Depending on the clinical scenario, the patient may undergo definitive chemoradiotherapy or palliative irradiation of malignant stenosis.

Rectal carcinoma – surgery is the primary curative treatment, the role of radiotherapy is mainly neoadjuvant (preoperative) or adjuvant (postoperative). The aim of a prolonged five-week chemoradiotherapy is tumour downstaging, which increases the chances of sphincter-preserving surgery.

Anal carcinoma - squamous cell carcinoma is primarily treated by concomitant chemoradiotherapy. It usually does not compromise sphincter function and has comparable therapeutic outcomes as a radical surgery.

Gallbladder, biliary tract and pancreatic carcinoma – currently, curative surgery is the gold standard of treatment. With regard to the high incidence of local recurrences, adjuvant radiotherapy appears beneficial. Radiotherapy has its role in palliative care as well.

Bronchogenic carcinomas and mediastinal tumours

Non-small cell lung carcinoma - radiotherapy (together with sequential or concomitant chemotherapy) is a preferred treatment method in advanced inoperable tumours. Besides external irradiation, intraluminal brachytherapy is used for alleviation of malignant bronchial obstruction. Radiotherapy is also indicated in superior vena cava syndrome and Pancoast tumour. Smaller tumours might be managed by stereotactic radiotherapy.

Small cell lung carcinoma - systemic chemotherapy is the method of choice, followed by consolidation radiotherapy in extensive-stage cancer. Prophylactic irradiation of the brain is sometimes indicated to minimize the incidence of brain metastases.

Breast cancer

Radiotherapy of the whole breast, chest wall, lymphatics or tumour bed boost is indicated according to the local extent of the disease, character of the surgical procedure and other prognostic factors. It usually takes from five to seven weeks. Brachytherapy can be used for irradiation of the tumour bed.

Malignant gynaecological tumours

Malignant tumours of the vulva and vagina – surgery is the primary treatment method. Irradiation may be indicated as adjuvant, curative or neoadjuvant therapy. Brachytherapy is commonly used in vaginal cancer.

Cervical cancer – early-stage tumours are treated by radical surgery and subsequent adjuvant radiotherapy. In advanced stages (from stage IIB - infiltration of the parametrium), curative concomitant chemoradiotherapy (external beam radiotherapy + cisplatin + brachytherapy by utero-vaginal application - UVAG) is indicated.

Uterine cancer - the method of choice is a surgery followed either by adjuvant radiotherapy (vaginal cuff brachytherapy or a combination of BRT with external beam radiotherapy) or active surveillance.

Cancers of male reproductive system

Penile carcinomas - most patients are treated by surgery. External beam radiotherapy or brachytherapy (skin surface or interstitial applications) are also involved in the treatment, possibly also in combination.

Prostate cancer - according to clinical stage, PSA and Gleason Score (GS), patients can be divided into prognostic groups with low, moderate, high and very high risk of tumour relapse and progression. In a localized prostate cancer, radical prostatectomy, curative radiotherapy or watchful waiting can be considered. In locally advanced prostate cancer, radiotherapy and hormonal treatment are preferred.

Testicular cancer - In seminomas, inguinal orchiectomy is the standard treatment approach. Retroperitoneal radiotherapy (of para-aortal lymphatic nodes) might be considered as an adjuvant treatment. In non-seminomas, radiotherapy is usually indicated as a palliative treatment or in adjuvant setting after chemotherapy.

Renal cancer – clear cell carcinoma is generally a radioresistant tumour, however, sometimes irradiation can be used as a palliative treatment method in skeletal, brain, or other metastases.

Bladder cancer - radical cystectomy is the standard procedure in infiltrating tumours, post-operative irradiation might be of benefit in particular patients. Curative chemoradiotherapy is indicated in inoperable tumours or as a palliative method.

Lymphoproliferative diseases

Hodgkin disease – early and intermediate stages are treated with chemotherapy followed by involved field radiotherapy (irradiation of initially affected and / or residual lymph nodes) with a dose of 20-30Gy. The treatment of advanced stages is predominantly based on chemotherapy.

Non-Hodgkin lymphomas

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL / SLL); Follicular lymphoma - the treatment of choice in the early stages is the involved field radiotherapy, advanced stages are managed by chemotherapy.

Marginal Zone Lymphomas (MZL) - treatment of nodal MZL is similar to the therapy of follicular lymphomas. Radiotherapy is essential in MALT (mucosa-associated lymphoid tissue) lymphomas; in early-stages of the disease, it has a curative potential (e.g. in gastric MALToma). Advanced stages require additional chemotherapy administration.

Diffuse large B-cell lymphoma (DLBCL)

Patients with localized disease are treated by chemotherapy in combination with IF radiotherapy. Advanced stages are treated with chemotherapy alone.

Mycosis fungoides (and Sézary syndrome) is a highly radiosensitive disease. In the case of an extensive disease, a so-called **total skin electron beam irradiation (TSEBI)** is indicated.

Solitary plasmocytoma – irradiation is the mainstay of therapy.

Multiple myeloma - patients are preferably treated with systemic therapy. Radiotherapy is used in palliating local symptoms, especially in pain management or to prevent pathological fractures of osteolytic lesions of the axial skeleton.

Leukaemia - is primarily a radiosensitive disease, yet, irradiation might be sometimes used as an auxiliary method to chemotherapy. It can also be beneficial in local management of symptomatic leukemic infiltrates. Prophylactic irradiation of the skull and the medulla is performed in acute lymphoblastic leukaemia (ALL) and less commonly in acute myeloid leukaemia (AML).

Total Body Irradiation (TBI) is used as a preparative procedure for bone marrow transplantation (total dose of 10Gy is applied in 5 fractions over 3 days or , alternatively, 4.0Gy are delivered as a single-dose, whereas the lethal radiation dose is believed to be 4.5Gy).

Soft tissue sarcomas and malignant bone tumours

Soft tissue sarcomas are treated mainly by surgery. Radiotherapy can be sometimes used as an adjuvant method in order to decrease the risk of a local recurrence. Brachytherapy of the tumour bed is often indicated in combination with external beam radiotherapy.

Osteosarcoma – these bone tumours usually require multimodal treatment. Initial chemotherapy is followed by surgery supposing a radical resection is possible. Otherwise, radiotherapy is indicated.

Chondrosarcoma – surgery is the only curative treatment, all other modalities are used only for palliative purposes. Generally, primary bone tumours of adulthood are radioresistant.

Childhood tumours

The therapeutic strategy in childhood cancers is based on their high sensitivity to treatment (both chemo- and radiotherapy). Radiotherapy is an important part of the multimodal treatment of childhood malignancies.

Leukaemia - Prophylactic irradiation of leptomeninges often follows the induction therapy of acute leukaemia (ALL), in order to eradicate micrometastases. Scrotal irradiation is performed in ALL patients with testicular involvement, who achieved cancer remission after induction treatment, or in patients with testicular relapse of the disease.

Central nervous system tumours – neurosurgery is the treatment of choice. Alternatively, chemotherapy and sequential irradiation can be used in residual or metastatic tumour management.

Embryonal tumours (primitive neuroectodermal tumours – PNET, medulloblastomas) In these tumours, the entire cranio-spinal axis must be irradiated (from skull to S2 vertebra) due to the high risk of cancer dissemination through the cerebrospinal fluid.

Radiotherapy is also commonly used in the treatment of craniopharyngeoma, pineal tumours, ependymomas, and retinoblastomas.

Neuroblastoma - the basis of treatment is a surgery along with conventional or intensive chemotherapy. Radiotherapy of high-risk neuroblastomas is a substantial part of the treatment protocol.

Nephroblastoma (Wilms tumour) – a combination of surgery, chemotherapy and radiotherapy is usually applied. Radiotherapy is indicated postoperatively. Unlike Grawitz tumour, Wilms tumour is radiosensitive.

Soft tissue sarcomas in children are more chemo- and radiosensitive in contrast to their adulthood counterparts. Radiotherapy is usually delivered concurrently with chemotherapy.

Ewing sarcoma – the treatment protocol includes a surgery accompanied by neoadjuvant chemotherapy or chemoradiotherapy. Radiotherapy might also be used postoperatively after non-radial resections. Radiotherapy alone may be indicated also in the case of inoperable tumour, or if the surgical procedure is considered mutilating. Unlike osteosarcoma, this tumour is radiosensitive.

Emergencies in oncology

Acute radiotherapy (up to 48 hours) is indicated in patients with impending **complete spinal cord compression** who are unable to undergo surgery. It is also used in management of acute **superior vena cava syndrome.** In the case of **pathological fractures** of long bones, osteosynthesis should be considered in the first place.

Radiotherapy of non-cancerous diseases

Calcanear spurs, arthrosis and epicondylitis are the most common diagnoses that might benefit from radiotherapy, especially if all orthopaedic and lifestyle interventions have been exhausted. However, irradiation is not suitable for young patients. Radiotherapy can also be used in treatment of **Dupuytren's contracture** and **induratio penis plastica - Peyronie's disease** and **acute superficial thrombophlebitis**.

Systemic anticancer treatment

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Introduction

Systemic therapy in oncology comprises a wide range of drugs with various mechanism of action. Currently available types of pharmacotherapy used in cancer management include **chemotherapy**, **hormone therapy**, **targeted therapy** and **immunotherapy**. Chemotherapy and targeted therapy directly affect the metabolism of tumour cells and their proliferation. Targeted treatment interferes with a specific molecule (receptor) in a tumour cell and blocks cellular signal transmission. Immunotherapy influences tumour cells indirectly by stimulating patient's immune response. Advances in the field of molecular biology, genetics and chemistry continuously contribute to the expansion of anticancer armamentarium. Deeper understanding of carcinogenesis and tumour pathophysiology encourages development of many new drugs; still, it takes several years of clinical research and testing until they become approved for clinical practice.

Cytotoxic agents

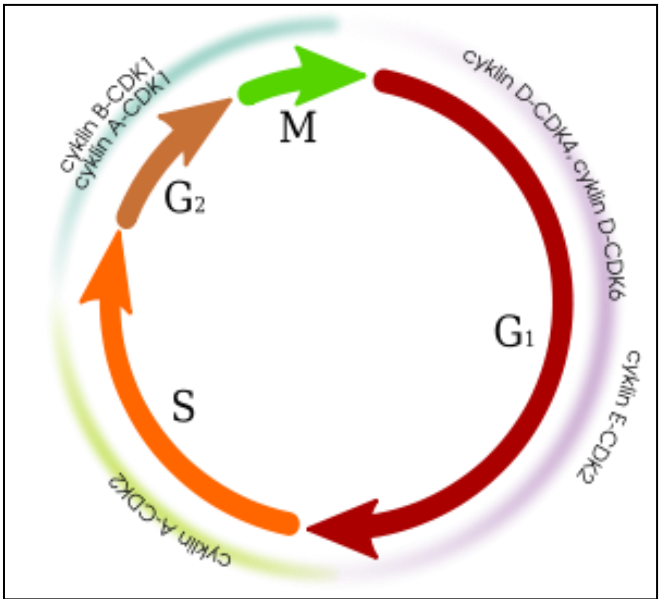
Chemotherapy encompasses a variety of drugs with cytotoxic effect, so-called *cytostatics*. They destroy tumour cells by interfering with DNA synthesis or cell division. Unlike surgery, the onset of action is gradual. Chemotherapy primarily affects rapidly proliferating cells (i.e. G1-M phase of the cell cycle), however, it lacks selectivity for cancer cells (Fig. 1).

According to the mechanism of action, cytostatics can be divided into several groups:

a) **alkylating agents** and **platinum derivatives:** they bind covalently to the DNA structure and prevent both transcription and replication.
b) **cytostatic antibiotics** (intercalating cytostatics): inserted between the chains of the DNA helix and prevent its interaction with DNA polymerase
c) **antimetabolites:** interfere with nucleic acid metabolism during the S-phase of the cell cycle. Depending on the substrate they inhibit, they are classified as **antifolates, pyrimidine analogues, guanine- and adenosine-derived purine analogues, ribonucleotide reductase inhibitors, etc.**
d) **vinca alkaloids and taxanes** are so-called spindle poisons, because they bind to tubulin and impair the microtubule formation and cell division.
e) **topoisomerase inhibitors**: include camptothecin derivatives that inhibit topoisomerase I and podophyllotoxin cytostatics that inhibit topoisomerase II (both enzymes essential for DNA transcription and replication)

f) **other** cytostatics not included in these groups are procarbazine, differentiation inductors and others.

Fig. 1. Phase-dependent effect of some cytostatics:



Cell-cycle phase	Cytostatic agents
Gap 1 (G_1)	Asparaginase, Prednison
G_1 / S junction	Kladribin
DNA synthesis	Cytarabine, Fluorouracil Gemcitabine, Fludarabine Hydroxyurea, Thioguanine Methotrexate, Topotecan
Gap2 (G_2)	Bleomycin, Etoposide Paclitaxel
Mitosis (M)	Vinblastin, Vinkristin Vinorelbin, Taxanes

Pharmacokinetics of cytostatics

A tumour population contains a number of non-proliferating cells (in G0-phase) that are relatively resistant to cytostatics. Cytostatics are most effective against cells undergoing nucleotide synthesis and chromosome replication prior to mitosis. Since a tumour mass comprises a myriad of asynchronously dividing cells, the rationale behind *repeated administration of cytostatic agents* is to increase the proportion of cells susceptible to DNA damage and inhibit cancer growth between chemotherapy cycles. However, a *clinical remission* usually does not mean a complete elimination of the tumour population, but only a reduction of cancer-cell count below 10^9, that is, below the detection limit of conventional imaging methods such as CT. Another drawback of chemotherapy is that it does not only affect malignant cells but also normal tissues, leading to a variety of haematological and non-haematological side effects.

Cytostatic dosage is individual and most often based on *the body-surface area* of a patient (calculated according to his height and weight) or, in some cytostatics, only on the basis of patient's *weight*. It is also necessary to modify the doses by liver and kidney function, depending on the way of drug clearance. In order to achieve the highest possible tumour response, it is important not to compromise on the dose rate, i.e. to respect scheduled doses and administration intervals. Sometimes, however, dose reduction is necessary with respect to each patient's individual tolerance and the severity of adverse effects. Concomitant early **supportive care** is crucial for maintaining

patients' adherence to the therapy, among other things, by mitigating possible side effects of cytostatic drugs.

Administration routes – most commonly, chemotherapy is given to the patient intravenously and orally. Regional chemotherapy can be administered intraarterially, intravesically (into urinary bladder), intrapleurally or intraperitoneally, intrathecally (via lumbar puncture, or Ommaya reservoir implanted under the scalp) or topically in non-melanoma skin cancers and precanceroses.

The choice of a cytostatic agent depends on the type and stage of each cancer. In addition, patient's overall health status and co-morbidities are taken into consideration. The treatment strategy usually follows evidence-based guidelines and specific indication criteria (such as the so-called Blue Book of the Czech Cancer Society, NCCN guidelines, ESMO guidelines). An alternative to a conventional chemotherapy regimen is the experimental treatment within **clinical trials** that are available in oncology centres.

Basic anticancer agents

Cytostatic agents can be classified by their mechanism of action into several categories:

1. Alkylating agents

They belong to the first cytostatic drugs used in oncology treatment. These substances interfere with DNA structures (as well as RNA and proteins) by alkylation and cause an arrest in the G1-S transition. They are used to treat a variety of solid and haematological malignancies. Typical alkylating agents are melphalan, chlorambucil, ifosfamide, cyclophosphamide, busulfan, temozolomide.

Platinum derivatives are also included in this group, although they induce damage to nucleic acids in a slightly different manner. **Cisplatin** causes DNA strand cross-linking and thus prevents its replication. It is widely used in the treatment of gynaecological, pulmonary, testicular and other malignant tumours. The major limitation of cisplatin is its unfavourable toxicity profile, including mainly nephrotoxicity, neurotoxicity (peripheral neuropathy and ototoxicity), emesis, etc. Therefore, several other platinum analogues have been developed in order to achieve lower toxicity. **Carboplatin** works by a mechanism similar to cisplatin but it has less side effects, the most common being myelosuppression. **Oxaliplatin** is derived from cisplatin by replacing chloride ligands with an oxalate. It is used to treat colorectal cancer and other malignant gastrointestinal tract tumours, mostly in combination with 5-fluorouracil. A typical dose-limiting side effect of oxaliplatin is peripheral sensory neuropathy.

2. Cytostatic antibiotics

They are structurally heterogeneous substances that exhibit cell damage through various mechanisms. Their common feature is DNA intercalation by different non-alkylating mechanisms. Typical representatives of these cytostatics are anthracyclines doxorubicin and epirubicin or a glycopeptide bleomycine.

3. Antimetabolites

They act by inhibition of enzymes involved in nucleic acid synthesis. **Methotrexate** (belongs to a subgroup of antifolates) inhibits the enzyme dihydrofolate reductase, which is responsible for the reduction of folic acid to tetrahydrofolate. The antidote is *leucovorin* - terahydrofolic acid. **5-Fluorouracil** (5-FU) is a pyrimidine analogue, which indirectly inhibits thymidylate synthase, a key enzyme for thymidine synthesis. **Capecitabine** is a prodrug that is metabolized to 5-FU in the liver and tumour tissue. **Gemcitabine** is a typical purine analogue. **Fludarabine** (an adenosine analogue) inhibits DNA polymerase-α and ribonucleotide reductase and predominantly affects lymphatic tissues.

4. Plant alkaloids

Vinca alkaloids (vincristine, vinorelbine), and **taxanes** (paclitaxel, docetaxel) impair formation or destruction of the mitotic spindle. **Camptothecins** (irinotecan, topotecan) inhibit topoisomerase I enzyme, whereas p**odophyllotoxin** (etoposide) inhibits topoisomerase II enzyme. This disables DNA cleavage and relegation of DNA strands, which is essential for DNA replication or transcription.

Cytostatic groups including examples are summarized in Table 1.

Table 1. Basic anticancer agents

Group of cytostatics		**Examples of cytostatics**	**Indications**	**Notes and selected side effects**
Alkylating agents	Nitrogene mustards	Melphalan	Myeloma, before bone marrow transplantation in myeloablative regimens	Myelosuppression, emesis, alopecia, allergic reactions, diarrhea, skin toxicity, local irritation
	Oxazophosphorins	Ifosfamide	Sarcomas, testicular cancer	Myelosuppression, emesis, alopecia, hemorrhagic cystitis, neurological toxicity (encephalopathy)
		Cyclophosphamide	Breast cancer, haematological malignancies	Myelosuppression, emesis, alopecia, haemorrhagic cystitis, stomatitis, SIADH

	Nitrosourea derivatives	Carmustine (BCNU) Lomustine (CCNU)	Brain tumours, lymphomas	Are lipophilic, have better blood-brain barrier penetration. Myelosuppression, nephrotoxicity, emesis, local irritans, cumulative pulmonary toxicity, alopecia, hepatotoxicity (veno -occlusive disease)
		Streptozocin	Insulinoma and other tumours from pancreatic islet ells	Nephrotoxicity, impaired glucose metabolism, nausea
	Platinum derivatives	Cisplatin	Pulmonary, testicular, gynaecological cancer, spinocellular, head and neck carcinomas	Nephrotoxicity, emesis, neurotoxicity, ototoxicity, local irritans causing tissue necrosis
		Carboplatin	Ovarian, head and neck, breast cancer	Myelosuppression, emesis, alopecia, mucositis, neurotoxicity
		Oxaliplatin	Colorectal carcinoma	Peripheral sensory neuropathy
	Tetrazines	Dakarbazine	Malignant melanoma, HL, sarcomas	Myelosuppression, emesis, mucositis, local irritans
		Temozolomide	Glioblastoma multiforme	p.o. administration, penetrates into the CNS. emesis, myelosuppression,
Anti-tumour antibiotics	Anthracyclines	Doxorubicin	Breast cancer, sarcomas, haematological malignancies; liposomal doxorubicin for Kaposhi sarkoma	Myelosuppression, mucositis, cardiotoxicity, emesis, alopecia, local irritans

		Daunorubicin	Acute leukaemia	Myelosuppression, cardiotoxicity, stomatitis, dermatitis,
		Epirubicin	Breast cancer	Myelosuppression, cardiotoxicity, stomatitis
	Anthracenediones	Mitoxantrone	Leukaemia, lymphoma, prostate cancer	Myelosuppression, nausea, stomatitis, cardiotoxicity, local irritans
	Polypeptide antibiotics that cause DNA cleavage	Bleomycin	Testicular tumours, NHL, HL, local therapy in pleural effusions	Pulmonary fibrosis, myelotoxicity, mucocutaneous toxicity, fever, hyprrpigmentation, alopecia
	Anti-tumour antibiotic with alkylating effect	Mitomycin C	Gastrointestinal tumours, non-small cell lung cancer, intravesical administration in bladder cancer	Myelotoxicity, nephrotoxicity (haemolytic-uremic syndrome), local irritans
Topoisomerase inhibitors	Topoisomerase I inhibitors	Irinotecan	Colorectal carcinoma, gastric cancer	Myelotoxicity, vomiting, acute and late onset diarrhea, cholinergic syndrome, alopecia
		Topotecan	Ovarian cancer, small cell lung carcinoma	Myelosuppression, nausea, alopecia, flu-like symptoms
	Topoisomerase II inhibitors	Etoposide	Testicular cancer, small cell lung cancer, HL, NHL, AML	Myelosuppression, emesis, alopecia, necrosis in case of extravasation
Antifolates (folic acid analogues)		Methotrexate	Osteogenic sarcoma, trophoblastic carcinoma, leptomeningeal cancer involvement, immunosuppressant	Myelosuppression, nausea, alopecia, mucositis, anorexia, hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity
	Multitarget antifolate: inhibition of	Pemetrexed	Pleural mesothelioma, bronchogenic	Myelosuppression, stomatitis, diarrhea, skin

	DHFR, TS, GARFT		carcinoma	toxicity
Purine analogues	Guanine analogues	6-Mercapto-purine Thioguanine	ALL, malignant lymphoproliferative diseases	Myelosuppression, nausea, mucositis, diarrhea, anorexia
	Adenosine analogues	Fludarabine	B-CLL, indolent B-NHL, AML, part of non-myeloablative preparative regimen for transplantation	Immunosuppression, myelotoxicity, CNS toxicity, nausea, liver test elevations
		Cladribine	Hairy cell leukaemia , Langerhans cell histiocytosis X	Immunosuppression, opportunistic infections, myelosuppression, nephrotoxicity
Pyrimidine analogues	Cytosine analogues	Cytarabine	Acute leukaemia	Myelosuppression, emesis, alopecia, mucositis, allergic reactions
		Gemcitabine	Pancreatic carcinoma, bronchogenic carcinoma, breast cancer, bladder cancer	Myelosuppression, flu-like symptoms, oedema, nausea, hepatotoxicity
	Uracil anagolues	5-Fluorouracil	Tumours of the gastrointestinal tract, breast cancer	Mucositis, diarrhea, skin toxicity, hand-foot syndrome
	5-FU prodrugs	Capecitabine	Tumours of the gastrointestinal tract, breast cancer	p.o. administration, nausea, hand-foot syndrome, mucositis, diarrhoea
Microtubule polymerization inhibitors	Vinca alkaloids	Vincristine	Hematologic malignancies, small cell lung cancer	Neurotoxicity, alopecia, local irritans, myelotoxicity constipation
		Vinblastine	Lymphomas, testicular cancer	
		Vinorelbine	Breast, lung, ovarian cancer	
Microtubule depolymerization	Taxanes	Paclitaxel	Breast, ovarian, stomach, lung, pancreatic carcinoma	Neutropenia, hypersensitivity reactions, neurotoxicity, local irritans

Inhibitors		Docetaxel	Breast, stomach, prostate, lung cancer	Fluid retention
		Cabazitaxel	Prostate cancer	Myelosuppression, anorexia, nausea
	Derivatives of epothilone	Ixabepilon	Breast cancer	Peripheral neuropathy, alopecia, myalgia, nausea
Enzymes		L-asparaginase	Acute leukaemia	Allergic reactions, coagulopathy, hyperglycaemia

Abbreviations: HL-Hodgkin's lymphoma, NHL- Non-Hodgkin lymphoma, CML- chronic myeloid leukaemia, CLL- chronic lymphocytic leukaemia, AML- acute myeloblastic leukaemia, DHFR- dihydrofolate reductase, TS-thymidylate synthase, GARFT- glycinamide ribonucleotide formyl-transferase, SIADH-syndrome of inappropriate antidiuretic hormone secretion

Resistance to cytostatics

In the course of oncological treatment, it is a matter of time until drug resistance occurs and the tumour fails to respond and begins to progress. **Primary resistance** means that the tumour cell is naturally irresponsive to a particular type of chemotherapy, however, more often we encounter **secondary resistance** that is acquired during cytostatic treatment. The mechanisms of resistance are related to *changes in pharmacokinetics* of a drug (e.g. by decreased resorption of a drug, or enhanced clearance of a cytostatic in the tumour cell), *changes in the tumour cell population* (when the majority of tumour cells enter resting phase in which the sensitivity to chemotherapy is limited) or *multi-drug resistance*, which results from overexpression of an ATP-dependent transport protein (most commonly P-glycoprotein) that actively pumps the drug out of a tumour cell.

Hormone anticancer therapy

Hormone therapy belongs to the oldest types of anti-cancer agents, used especially in the treatment of breast and prostate cancer.

Endocrine manipulation can affect the growth of malignant cells equipped with hormone receptors. Hormone therapy acts either by inhibition of hormone synthesis or by preventing hormone receptors on tumour cells from being activated. Depending on the mechanism of action, several groups of hormone treatment are recognized:

- **Antiestrogens** are competitive inhibitors of oestrogen and progesterone receptors, i.e. they prevent hormones, which act as growth factors for certain tumour cells, from binding to their receptor. The most common drug is **tamoxifen**, with both agonist and anti-oestrogen effect. **SERM,** *selective estrogen receptor modifiers***,** such as **fulvestrant** are pure anti-oestrogens used

in the treatment of metastatic breast cancer in postmenopausal women after tamoxifen or aromatase inhibitor failure.

- **Aromatase inhibitors (anastrozole, letrozole, exemestane):** aromatase is an enzyme involved in the transformation of adrenal androstendione and testosterone to estrone and estradiol, especially in postmenopausal women. It is found in peripheral tissues including fat, liver, or muscles.
- **Antiandrogens (bicalutamide, flutamide):** are substances that bind to androgen receptors in the target tissues (prostate, hypothalamus, etc.) and thereby block the effect of androgens. They are used to treat prostate cancer.
- **Gonadoliberin agonists (GnRH and LHRH analogues):** Gonadoliberin analogues have clinical efficacy in the treatment of breast cancer in premenopausal women, or in the treatment of prostate cancer as an alternative to castration.
- **Corticosteroids** are used to treat malignant lymphoproliferative diseases, in which they have the potential to induce apoptosis. In solid tumours, dexamethasone is often used in management of vasogenic oedema in patients with primary and metastatic brain tumours. Glucocorticoids also potentiate the effect of analgesic treatment of tumour pain. Their immunosuppressive effect is used in the treatment of autoimmune diseases.

Hormonal manipulation also includes surgical castration (orchiectomy, oophorectomy), and less commonly destruction of endocrine glands by irradiation.

Types and clinical indications of hormonal therapy are summarized in Table 2.

Tab. 2. Types of hormonal therapy by the mechanism of action

Mechanism of action	**Types of hormone therapy**	**Examples**	**Indication**
Ablative	Castration: pharmacological, surgical or by radiation	LHRH analogues: buserelin, goserelin, leuprolin	
Competitive	Antiestrogens	Pure anti-oestrogens: fulvestrant SERM (selective oestrogen receptor modulators) with dual estrogenic and anti-oestrogen activity: tamoxifen, raloxifene, toremifene	Breast cancer
	Antiandrogens	Cyproterone acetate, flutamide, nilutamide, bicalutamide	Prostate cancer

Inhibitory	Aromatase inhibitors (inhibit the formation of oestrogens)	Anastrozole, letrozole Irreversible aromatase inhibitor: exemestane	Breast cancer
	Androgen Synthesis Inhibitors	Ketoconazole Abiraterone acetate (selectively inhibits cytochrome P450, CYP17A1, thereby suppressing testosterone synthesis even in patients after castration).	Prostate cancer
Additive	Gestagens (progestins)	Medroxyprogesterone acetate megestrol acetate	Currently, it is mainly used in the treatment of tumour-related anorexia

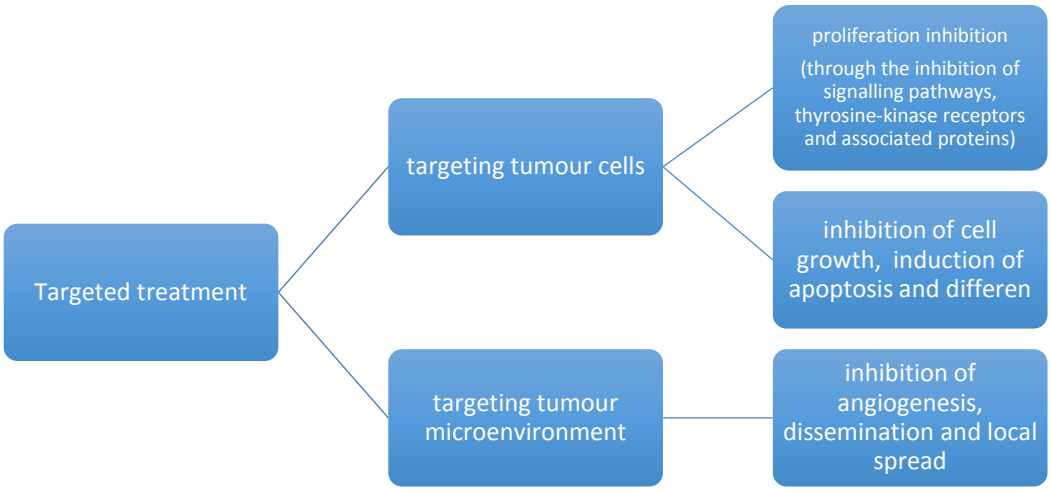
Somatostatin and its analogues (octreotide, lanreotide, and their depot forms) are used in the treatment of well-differentiated neuroendocrine tumours. Besides anti-proliferative effect, they also reduce hormone-mediated paraneoplastic symptoms (carcinoid syndrome).

Targeted anti-tumour therapy of solid tumours

Targeted therapy is a relatively novel modality among anticancer agents. These drugs target a specific molecular structure on tumour cells that plays an important role in carcinogenesis (Fig. 2).

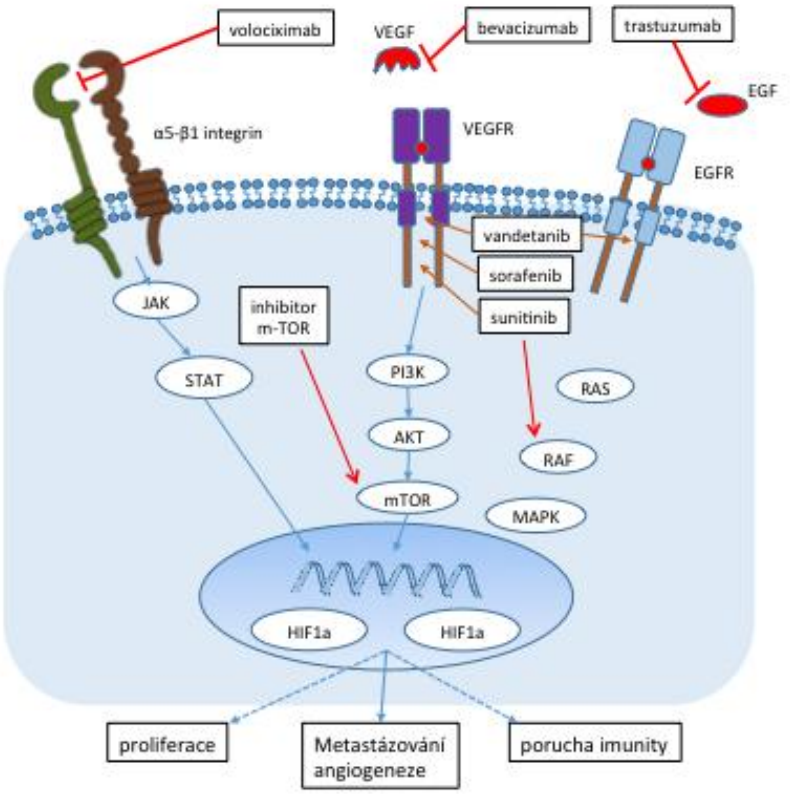
Their mechanism of action is different from that of chemotherapy, and the spectrum of side effects is very specific. Conventional chemotherapy interferes with cellular structures that are present in all somatic cells, such as DNA or various transcriptional enzymes. Targeted treatments act preferentially on tumour-specific cells structures. To some extent, they may also interfere with the metabolism of normal cells, corresponding to the character of associated side effects (Fig. 3). Because many targeted agents are partially synthetized from biologic materials they are sometimes falsely referred to as “biological” therapy, however, these two distinct treatment modalities should not be mistaken.

Fig. 2 Principles of targeted treatment



This chapter presents an overview of basic targeted agents, classified by their target molecule and associated signalling pathway. Examples of various mechanisms of action are shown in Fig. 3.

Fig.3. Examples of target structures and signalling pathways of selected targeted antitumour



treatment

Monoclonal antibodies

Monoclonal antibodies bind to epitopes of particular tumour surface antigens and soluble proteins. The most common target antigens include **growth factors** (e.g., VEGF, IL6), **receptors** (EGFR / ERBB /

HER, VEGFR), **membrane proteins** (e.g., CD20, CD52, CD33) and **adhesion molecules** (EpCAM, integrins). Their outline is provided in Table 3.

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against HER2 receptor that has been heralded as a major breakthrough in the treatment of HER2-positive breast cancer. Trastuzumab binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2 or c-erbB-2) and prevents further intracellular signal transduction. Amplification or overexpression of the HER2 gene is observed in approximately 25-30 % of breast cancers and 19 % of gastric cancers and leads to extensive proliferation signalling. Trastuzumab not only inhibits this process but it is also believed to induce antibody-dependent cell-mediated cytotoxicity.

Pertuzumab is a humanized monoclonal antibody against the extracellular domain of HER2. It prevents dimerization of the HER2 receptor and thus blocks its activity. In combination with trastuzumab and taxane, it is used in the first line treatment of HER2-positive metastatic breast carcinoma.

Bevacizumab (anti-VEGF) and **cetuximab** or **panitumumab** (anti-EGRF) are commonly used in the treatment of metastatic colorectal cancer in combination with chemotherapy. Cetuximab and panitumumab are ineffective in tumours harbouring activation mutations of RAS oncogenes, since these mutations lead to constitutive activation of RAS pathway independent of EGFR signalling. EGFR promotes cell growth of tumour cells as well as normal epithelial tissues such as skin and hair follicles.

Cetuximab is a chimeric IgG1 monoclonal antibody that blocks ligand-induced EGFR signalling, and thus inhibits tumour cell proliferation, angiogenesis and dedifferentiation and stimulates apoptosis. Other effects of cetuximab include inhibition of angiogenic factor production, mediation of antibody-dependent cellular cytotoxicity and potentiation of chemotherapy and irradiation.

Panitumumab is a recombinant, fully human monoclonal antibody IgG2 that binds to the epidermal growth factor receptor (EGFR). This leads to receptor internalization, inhibition of cell growth and induction of apoptosis.

Bevacizumab is a recombinant humanized monoclonal antibody against VEGF that prevents its interaction with tyrosine kinase receptors VEGFR1 and VEGFR2 expressed on the surface of endothelial cells. Bevacizumab is the first **anti-angiogenic agent,** which has been introduced into clinical practice. It is used in combination with chemotherapy to treat a wide range of metastatic malignant tumours (colorectal, non-small cell lung cancer, renal, cervical, ovarian and primary peritoneal carcinoma).

Ramucirumab is a recombinant humanized IgG1 monoclonal antibody against vascular endothelial growth factor receptor VEGFR-2. It is used in combination with chemotherapy in the treatment of gastric, colorectal and non-small cell lung carcinoma.

Denosumab is a fully human monoclonal antibody that is used in the supportive treatment of bone metastases. It belongs to the group of so-called BMA (bone modifying agents), because it reduces bone resorption.

Tab. no. 3. Summary of the monoclonal antibodies

Monoclonal antibody	**Target structure**	**Indication**	**Trade name**
Antibodies against EGFR/ErbB/HER family of receptors			
Trastuzumab	ErbB2 / HER2 / neu	Breast cancer, stomach cancer	Herceptin
Cetuximab	EGFR / ErbB1 / HER1	Colorectal, head and neck carcinoma	Erbitux
Panitumumab	EGFR1, EGFR2	Colorectal carcinoma	Vectibix
Pertuzumab	ErbB2 / HER2 / neu	Breast cancer	Scrubber
Monoclonal antibodies blocking growth factors			
Bevacizumab	VEGF	Colorectal, kidney,breast, cervical, ovarian, lung carcinoma	Avastin
Ramucirumab	VEGFR-2	Gastric, colorectal, non-small cell lung carcinoma	Cyramza
Ziv-aflibercept	VEGF	Colorectal carcinoma	Zaltrap
Antibodies against leukocyte surface proteins			
Rituximab	CD20	NHL, CLL	MabThera
Alemtuzumab	CD52	CLL	MabCampath
Other antibodies			
Denosumab	RANKL	Bone metastases	Xgeva
Catumaxomab	CD3, EpCAM	Treatment of malignant ascites	Removab

Abbreviations: NHL - Non Hodgkin's lymphomas, CLL-chronic lymphocytic leukaemia, HL-Hodgkin's lymphoma, RANKL- Receptor activator of nuclear factor kappa-B ligand, VEGF-vascular endothelial growth factor, EGFR-epidermal growth factor receptor

Tyrosine kinase inhibitors (TKI)

Tyrosine kinase inhibitors encompass a wide range of molecules used in anti-cancer treatment throughout oncology. They act competitively on the ATP binding site on the intracellular tyrosine kinase domain of a particular receptor, and prevent its phosphorylation and further signal transduction.

Tyrosine kinases (TK) are enzymes that catalyse transfer of a phosphate from ATP to an intracellular protein. They exist either in the form of a *membrane receptor with tyrosine kinase activity* **(RTK)** that activates particular signalling pathway (e.g. growth factor receptors EGFR, VEGFR), or as *cytoplasmic tyrosine kinases* (e.g. Ras, Raf) transmitting signals within the cell. This means that, unlike monoclonal antibodies, which bind only to extracellular domains of RTK, tyrosine kinase inhibitors are also able to influence intracellular signalling pathways.

The first TKI was introduced in 2001 as a treatment for chronic myelogenous leukaemia under name **imatinib**. It is an orally administered drug, which blocks BCR-ABL fusion protein with tyrosine kinase activity (encoded on Philadelphia chromosome that results from a reciprocal translocation between chromosomes 9 and 22). Imatinib was a groundbreaking drug that radically improved the prognosis of CML patients and pioneered a completely new strategy in anti-cancer therapy. Currently, it is also used in the treatment of c-KIT positive gastrointestinal stromal tumours and dermatofibrosarcoma protuberans.

Lapatinib is an oral reversible dual inhibitor of EGFR and HER2 associated TK, used in the treatment of HER2-positive metastatic breast cancer refractory to trastuzumab. Unlike trastuzumab, it is a small molecule that penetrates the blood-brain barrier, which is an advantage in patients with metastatic brain involvement.

Sunitinib is another oral multikinase inhibitor, indicated in the treatment of patients with metastatic renal cell carcinoma, gastrointestinal stromal tumour and well-differentiated pancreatic neuroendocrine tumour. Due to its inhibitory effect on VEGFR and PDGFR (platelet-derived growth factor receptor), it also blocks angiogenesis and tumour cell proliferation.

A more detailed overview and classification of tyrosine kinase inhibitors is shown in Table 4.

Tab. 4. Overview of tyrosine kinase inhibitors

TKI	**Target structure**	**Indications**
Multikinase inhibitors of tyrosine kinase proteins		
Imatinib	BCR-ABL, KIT, PDGFR	CML, GIST
Sunitinib	VEGFR1-3, PDGFR, KIT, RET, CSF1R	Kidney cancer, imatinib resistant GIST, well-differentiated pancreatic neuroendocrine tumour
Sorafenib	VEGFR1-3, PDGFR, RAF (including mutated BRAF), KIT, RET, FLT3	Kidney cancer, hepatocellular carcinoma, differentiated (papillary / follicular / Hurthle cell) thyroid cancer refractory to radioactive iodine therapy

Nilotinib	BCR-ABL, KIT, PDGFR	CML
Dasatinib	BCR-ABL, KIT, PDGFR	CML refractory to imatinib
Receptor tyrosine kinase (RTK) inhibitors		
Erlotinib	EGFR / ERBB1 / HER1	Non-small cell lung carcinoma, pancreatic carcinoma
Gefitinib	EGFR / ERBB1 / HER1	Non-small cell lung cancer
Lapatinib	EGFR / ERBB1 / HER1, ERBB2 / HER2 / NEU, ERK1, ERK2, ACP	Breast cancer with ERBB2 / HER2 / NEU overexpression
Afatinib	EGFR, HER2, HER4	lung carcinoma with EGFR exons 19 and 21 mutations
Vandetanib	EGFR / ERBB1 / HER1, VEGFR	Medullary thyroid carcinoma
Lenvatinib	VEGFR, FGFR, PDGFR, RET, KIT	Differentiated thyroid carcinoma
Cabozantinib	VEGF, MET, RET, KIT, TIE-2	Medullary thyroid carcinoma
Axitinib	VEGFR-1-3, PDGFR, c-Kit	Kidney cancer
Pazopanib	VEGFR1-3, PDGFR, c-Kit	Kidney cancer, soft tissue sarcomas, ovarian cancer
Nintedanib	VEGFR, PDGFR, FGFR	Pulmonary carcinoma

Notes: ErbB (erythroblastic leukaemia viral oncogene homologue) family of RTKs consists of four receptors: HER1 (EGFR/ErbB1), HER2 (Neu/ErbB2), HER3 (ErbB3), and HER4. Molecular antibodies cetuximab, panitumumab target EGFR/HER1 receptor, whereas trastuzumab targets ErbB2/HER2. Abbreviations: GIST - gastrointestinal stromal tumour, RET - Rearranged during transfection (a protooncogene encoding a RTK that activates MAPK and PI3K signalling pathway)

mTOR inhibitors

Rapamycin receptor (mTOR - *the mammalian target of rapamycin)* is a kinase involved in regulation of cell metabolism, proliferation and other vital processes.

Everolimus is an oral mTOR inhibitor that inhibits tumour cell growth and proliferation mediated by PI3K/Akt signalling pathway. It also indirectly inhibits angiogenesis by reducing VEGF levels. It is indicated for the treatment of renal carcinoma, well-differentiated pancreatic neuroendocrine tumours or in combination with exemestane in breast cancer therapy. In transplantation medicine, it is used as an immunosuppressant preventing graft rejections.

Temsirolimus is indicated in the treatment of poor-prognosis renal clear cell carcinoma or other types of kidney cancer.

MAPK/ERK pathway inhibitors

Sorafenib is an oral kinase inhibitor of RAF kinase, one of key components of the MAPK signalling pathway (also known as RAS/RAF/MEK/ERK cascade). It is used in the treatment of renal, hepatocellular or thyroid carcinoma.

Regorafenib is a multi-kinase inhibitor that targets VEGFR1-3, KIT, PDGFR, RAF and BRAF proteins. It is approved for treatment of metastatic colorectal carcinoma after chemotherapy failure.

Trametinib is a MEK inhibitor. **Dabrafenib** and **vemurafenib** inhibit BRAF kinase. These molecules both demonstrated efficacy in the treatment of malignant melanoma with BRAF V600 mutation. Combination of BRAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib) showed even better results compared to monotherapy.

Hedgehog signalling pathway inhibitors

Vismodegib is a novel treatment for metastatic basalioma.

PolyADP- ribose polymerase (PARP) inhibitor

PARP is an enzyme involved in DNA repair; therefore, the inhibition of PARP enzyme is particularly effective in tumours with preexisting defect in DNA repair mechanisms, such as BRCA1 or BRCA2 positive ovarian cancer. Currently, **Olaparib** is approved for advanced ovarian cancer in BRCA mutated patients who progressed on prior chemotherapy.

Cyclin-dependent kinase (CDKs) inhibitors

CDKs are proteins that regulate transitions through the cell-division cycle. **Palbociclib** is an inhibitor of CDK4 and CDK6 that showed a significant prolongation of progression free survival in patients with metastatic breast carcinoma treated with hormone therapy.

Immunotherapy

To date, immunotherapy represents the most progressive modality in anti-cancer treatment. Its specific mechanism of action is based on the concept of immune surveillance theory of cancer and aims at the activation of host‘s immune system against tumour cells.

The first immunotherapy agents applied in the therapy of malignant melanoma and renal carcinoma were **interferon alpha** and **interleukin 2**. Their immuno-modulatory effect is non-specific, and besides recruiting immune effector cells, they also have anti-proliferative and anti-angiogenic effect and promote cellular differentiation.

Novel agents are monoclonal antibodies that activate immunity by interfering with so-called immune checkpoints. Among these checkpoints, a protein receptor **CTLA-4** (Cytotoxic T- lymphocyte antigen

4) plays an important inhibitory role in early T lymphocyte activation. Its blockade leads to stimulation of T lymphocytes and promotes anti-tumour cytotoxic immune response.

PD-1 (programmed cell death) receptor is another negative regulator of T- cell activity that was proved to participate in the control of T- cell mediated anti-cancer immune response. Blockade of PD-1 receptor downregulates apoptosis of T-cells and increases their cytotoxic activity.

Overall, i**mmunotherapy with anti-CTLA-4 and anti-PD-1 antibodies** targets various functions of immune system, such as its adaptability (immune system recognizes changes in microenvironment including various cancer antigens) or memory (T-cells may survive for many years and remain capable of immediate response when encountering their target antigen).

The first checkpoint inhibitor approved in 2011 was **Ipilimumab**. It is monoclonal antibody against CTLA-4 used in the treatment of metastatic melanoma. It triggers a non-specific T-cell mediated immune response, which may also lead to serious autoimmune adverse effects.

Nivolumab is human monoclonal IgG4 antibody, which binds to PD-1 receptor on the surface of T lymphocytes and blocks PD-1 ligands from binding to it. It thereby stimulates T- cell anti-tumour response. Nivolumab is approved for the treatment of metastatic melanoma, non-small cell lung carcinoma, kidney, head and neck, and bladder cancer.

Another promising approach to activating immune response to cancer includes the use of locally active immunomodulatory substances like **T-VEC** (sold under trade name **Imlygic**). It is a genetically modified oncolytic herpetic virus indicated for intralesional application (injection into skin, subcutaneous or nodal lesions) in adults patients with unresectable melanoma. Besides responses in injected lesions, T-VEC is also believed to stimulate systemic anti-cancer immune response.

A more personalized approach to immunotherapy is represented by the development of **anti-tumour vaccines** that are designated to stimulate host's immune system by autologous infusion of dendritic cells activated against a tumour-specific antigen. In 2010, the FDA (Food and Drug Amdministration – an American authority for drugs and food control) approved the first cancer vaccine for the treatment of advanced prostate cancer - **Sipuleucel-T,** known under trade name Provenge.

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Adverse effects of anticancer drugs

J. Šedo

Introduction

Every anticancer drug has a specific profile of side effects depending on its mechanism of action. This is typical not only for conventional cytostatics, but also for modern targeted agents, which only differ in the character of toxicity.

Anticancer therapy often includes combination regimens and high-dose cytostatics that can lead to life-threatening conditions and complications (e.g. sepsis in a neutropenic patient or bleeding due to thrombocytopenia). Systematic assessment of the adverse events, their prevention and treatment are therefore an integral part of comprehensive oncology care.

Most adverse reactions are dose-dependent (but there are also particular exceptions). With a consistent prevention and treatment of side effects, we can achieve higher dose intensity and hence greater efficacy of anticancer therapy. Generally speaking, in curative or adjuvant therapies, we often prefer intensive treatment schedules with higher risk of serious reversible side effects, based on the rationale that intensity escalation leads to an increase in antitumour response and higher chances of cure. On the contrary, in palliative settings, the treatment strategy is focused on maintenance of quality of life and patients' comfort. In other words, in the case of unacceptable adverse reactions, we do not hesitate to modify the dose intensity (by reducing the dosage of a cytostatic or by extending the inter-treatment interval).

Typical side effects of most cytostatics

- Haematological toxicity (myelotoxicity).
- Gastrointestinal toxicity.
- Fatigue.

Toxicity specific to certain anticancer drugs

- Nephrotoxicity (cisplatin, methotrexate, ...).
- Urotoxicity (cyclophosphamide, ifosfamide).
- Cardiotoxicity (doxorubicin, epirubicin, duanorubicin, trastuzumab ...).
- Neurotoxicity (paclitaxel, docetaxel, oxaliplatin, vincristine ...).
- Pneumotoxicity (bleomycin, everolimus, ...).
- Hepatotoxicity (dacarbazine, irinotecan, pazopanib, vemurafenib, T-DM1, regorafenib, lapatinib, imatinib).
- Skin toxicity (5-fluorouracil, cetuximab, panitumumab, gefitinib, erlotinib ...).

- Acute infusion reactions (oxaliplatin, carboplatin, paclitaxel, docetaxel, cetuximab, rituximab).
- Immune-related adverse events (ipilimumab, nivolumab, pembrolizumab ...).

The severity of adverse events or so-called toxicity of anticancer treatment is usually graded based on internationally recognized criteria. Grade1 indicates the lowest degree of toxicity, whereas Grade 4 implies life-threatening complications. Examples are shown in Table 1.

Tab.1: Grading the toxicity of anticancer treatment

Grade	0	1	2	3	4
		mild	Moderate	severe	very serious / life-threatening
Neutropenia *Number of granulocytes (neutrophils)* *(x 10 * 9 / l)*	> 2.0	1.5-2	1.0- 1.49	0.5 - 0.99	<0.5
Thrombocytopenia *Thrombocyte count* *(x 10 * 9 / l)*	> 150	75 -150	50-74	25-49	<25
Anaemia *Concentration of haemoglobin (g / l)*	> 130	100-129	80-99	49-80	<49
Emesis *Number of episodes in 24 hours*	none	1-2	3-5	More than 6 episodes	life-threatening emesis
Diarrhoea *The number of episodes added to the usual number of stools in 24 hours*	none	≤3	4-6	≥7	life-threatening diarrhoea

Haematological toxicity

Haematological toxicity, sometimes referred to as myelotoxicity, is a common side effect of most conventional cytostatics. Rarely, it is also observed in patients treated with targeted therapy (***sunitinib*** , ***imatinib),*** although it usually does not reach the same degree as in the case of conventional cytostatics. Contrarily, with new drugs called PARP inhibitors (***olaparib, veliparib),*** it is often a dose-limiting side effect.

Myelotoxicity is strongly dose-dependent, therefore we can prevent it by reducing the intensity of cytostatic treatment. Specifically, we can prevent neutropenia and its associated risks by the application of so-called "growth factors" - granulocyte colony stimulating preparations (abbreviated as G-CSF, most often filgrastim). Myelotoxicity usually peaks in severity approximately 7-10 days after the administration of a cytostatic agent. That is because immature and vigorously proliferating stromal cells are most susceptible to cytotoxic effects of chemotherapy and their destruction causes a gap in haematopoiesis. The drop in blood count occurs when the circulating mature granulocyte pool is exhausted.

Leukopenia / neutropenia

This is the most common and often a limiting side effect of most conventional cytostatics. It is practically always dose-dependent. The patient is at high risk of acquiring an infection with rapid progression into a life-threatening sepsis.

Febrile neutropenia (FN)

is a serious complication of chemotherapy associated with a high risk of death. It is defined as a **fever above 38°C for at least one hour (or a single peak of temperature above 38.3°C)** with **a neutrophil count of less than 0.5 x 10*9/l** (or with a slightly higher level, if a rapid drop can be expected).

FN should be treated as a serious medical condition associated with high mortality rates, especially in institutions lacking adequate expertise. The mortality risk may be significantly reduced by an appropriate management with respect to specific guidelines.

Initial diagnostic investigations should include:

- physical examination,
- full blood count, basic blood chemistry including CRP, chest radiograph
- microbiology examination: blood culture, urine culture and throat swab test, culture from wounds

Clinical management algorithm:

- With a few exceptions, admission is necessary. Only low-risk patients can be managed on an outpatient basis. In case of hemodynamic instability or other complications, transfer to the ICU is indicated.
- Empiric antibiotic therapy should be initiated immediately after the admission (however, samples for microbiological examinations should be collected prior to antibiotic administration).
- Based on FN-specific recommendations a combination antibiotic therapy should be used:
    - low-risk patients should receive a combination of **amoxycillin-clavulanate + ciprofloxacin**

- In critically ill patients, the antibiotic regimen should include an antipseudomonadal agent (e.g. cefepim, piperacillin-tazobactam, meropenem). Depending on specific clinical circumstances and potential risks, therapy with aminoglycosides (amikacin or gentamicin) is often indicated. Antibiotic against Gram-positive bacteria (vancomycin or linezolid) might be considered.
- In the case of persisting signs of infection, high-risk patients or patients with positive fungal cultures should be treated with antifungal agents (e.g. amforeticin B, voriconazole, capsfungin).
- Empirical antibiotic therapy is adjusted according to clinical response and results of the microbiological examination.

- Protective isolation and specific hygiene measures are required.
- Providing an adequate hydration (usually parenteral) is crucial, especially in hypotensive patients.
- Monitoring of blood pressure, heart-rate and diuresis on a regular basis is advisable.
- We should consider administration of growth factors (G-CSF: filgrastim, etc.).

Recombinant growth factors

The recombinant human granulocyte colony stimulating factor (G-CSF) is designed to mobilize peripheral stem (progenitor) cells from bone marrow into the bloodstream.

G-CSF are indicated for:

- prophylaxis of febrile neutropenia (they are administered prior to the expected decrease in neutrophils to prevent their level from dropping below a critical level)
- shortening of neutropenia duration

Growth factors are also available in a pegylated form with prolonged half-life (pegfilgrastim). The most common side effects are flu-like symptoms, which include myalgia, arthralgia, back pain, fatigue or subfebrile temperatures.

Thrombocytopenia

Is another frequent adverse effect related to myelosuppression, which is associated with an increased risk of bleeding or other haemorrhagic complications.

The most common bleeding manifestations in oncology patients include:

- gastrointestinal bleeding
- urinary tract bleeding (especially in patients with bladder cancer)
- Intracranial haemorrhage (especially in the presence of brain metastases)
- cancer or metastatic bleeding by its location

Therapy

In the first place, it is necessary to identify the source of bleeding and control the haemorrhage by convenient means (local dressing, local or i.v. haemostyptic drugs).

In contrast to neutropenia, there are no available growth factors for platelet stimulation, therefore, in case of severe thrombocytopenia, a platelet transfusion can be used for an immediate increase of platelet count. It is of note, that platelet half-life is rather short compared to erythrocytes, ranging from 3-10 days. This means that transfusions may be needed repeatedly until patient's own haematopoiesis restores. Since the stocks of these preparations are often limited (because their manufacture is more demanding compared to other blood products), their administration should be reserved for serious bleeding only.

Indications for platelet transfusion include:

- serious bleeding in a patient with moderate thrombocytopenia (determined individually)
- prevention of bleeding in an asymptomatic patient with severe thrombocytopenia (platelet count below 10 x 10 * 9 / l).
- prevention of bleeding in a patient prior to an elective surgery

Anaemia

The incidence of anaemia is very high in oncology patients. There are several factors involved in the development of anaemia, with the influence of chemotherapy being rather negligible.

In cancer patients, we usually encounter anaemia of chronic disease (iron-deficient microcytic anaemia with increased ferritin levels) or anaemia due to cancer-associated blood loss.

Management of anaemia

The therapy of anaemia depends on the clinical context: haemoglobin level, underlying cause, severity of anaemia, associated diseases (particularly disorders with greater demands on blood supply e.g. IHD, COPD, cerebrovascular disease, etc.), in which we should maintain haemoglobin levels above 100 g / l.

Anaemia treatment options include:

- iron, folate or B12 supplementation in the case of proven deficiency (restitution of red blood cells and Hb increase occurs within a few weeks)
- transfusion of packed red blood cells (administration of 1 transfusion unit usually leads to an immediate increase in Hb levels by approximately 10 g / l)
- erythropoiesis stimulating agents (increase in Hb by 10 g / l usually occurs in the order of weeks)

Gastrointestinal toxicity

The most common adverse events related to digestive tract disturbances include:

- Nausea and vomiting
- Diarrhoea
- Mucositis

Nausea and vomiting

Nausea can be defined as a distressing feeling or urge to vomit. It is a serious complication of a number of cytostatic agents, which can aggravate weight loss and other cancer-associated symptoms. Nausea is often accompanied by anorexia, which is defined as loss of appetite and feeling of early satiety. It is important to discriminate between these two symptoms, since each of them requires a distinct therapeutic approach.

While there is a plethora of pharmacological agents to alleviate nausea (so-called antiemetics), cancer-related anorexia is very difficult to treat. It does not respond to antiemetics, and the use of progestins is associated with an increased risk of serious complications (thromboembolism).

Emesis is a complex neuromuscular reflex, which is usually preceded by nausea. However, there are also specific situations when emesis occurs without prior nausea (typically in intracranial hypertension caused by brain metastases). Chemotherapy-induced nausea or vomiting belongs to the most common adverse effects of many cytostatics, yet, there are significant differences in the emetogenic potential of cytostatic agents. By the degree of induced emesis, cytostatic agents are classified into several groups (see Table 3)

Table 3: Classification of cytostatic emetogenesis

Highly emetogenic	**Moderately emetogenic**	**Low emetogenic**	**Minimally emetogenic**
Cisplatin	Oxaliplatin	Etoposide	Vinkristin
Cyclophosphamide	Carboplatin	Gemcitabine	Vinblastine
Dakarbazin	Irinotecan	Fluorouracil, capecitabine	Bleomycin
Carmustine	Ifosfamide	Mitomycin	Vinorelbin
	Doxorubicin	Paclitaxel	
	Epirubicin	Docetaxel	

Chemotherapy-Induced Nausea and Vomiting (CINV)

In terms of the time relationship of nausea to the administration of anticancer treatment, CINV can be classified as:

- **Acute onset** - occurring within 24 hours of administration of anticancer treatment

- **Delayed onset** - occurring 24hours to several days (exceptionally longer) after chemotherapy initiation
- **Anticipatory** - before starting the next cycle of treatment (usually due to inadequate or insufficient prophylaxis in previous cycle of chemotherapy)
- **Breakthrough** - that develops in spite of an optimal antiemetic premedication
- **Refractory** - persists despite repeated or escalated antiemetic administration

While the acute form of CINV is known to be associated with the activation of serotonin receptors in the chemoreceptor trigger zone, the pathophysiological mechanism of delayed form of nausea is not completely understood (a role of the dopaminergic system is assumed) and its treatment is more complicated. For that reason, an adequate premedication before chemotherapy and the use of potent antiemetics to treat early nausea is the best way to prevent delayed or refractory forms of CINV.

Recommendations for antiemetic therapy with regard to the emetogenicity of a cytostatic agent are summarized in the following table:

Profylaxe zvracení po jednodenní vysoce emetogenní chemoterapii (HEC)

Medikace	Akutní fáze (den 1)	Opožděná fáze
NK_1 inhibitor	aprepitant 125 mg p.o. nebo netupitant 300 mg	aprepitant 80 mg p.o. dny 2–3
+5-HT_3 inhibitor (setron)	ondansetron 16–24 mg p.o. nebo 8–16 mg i.v. nebo granisetron 2 mg p.o. nebo 1 mg i.v. nebo palonosetron 0,25 mg i.v. nebo 0,5 mg p.o.	0
+ kortikosteroid	dexametazon 12 mg p.o. nebo i.v.[1]	8 mg p.o. nebo i.v. dny 2–4
± olanzapin	olanzapin 10 mg p.o.	10 mg p.o. dny 2–4
± benzodiazepin	alprazolam 0,25–0,5 mg p.o. po 6 hod.	0,25–0,5 mg p.o. po 6 hod.
± inhibitor H_2 receptorů nebo inhibitor protonové pumpy		

Profylaxe zvracení po chemoterapii s nízkou emetogenitou

Medikace	Profylaxe akutního zvracení (den 1)	Profylaxe opožděného zvracení
kortikosteroid	dexametazon 8 mg p.o. nebo i.v. 1× denně	0
nebo 5-HT_3 inhibitor	ondansetron 8 mg p.o. nebo 8 mg i.v. 1× denně nebo granisetron 2 mg p.o. nebo 1 mg i.v.	0
nebo D2 inhibitor	metoklopramid 10–20 mg p.o. nebo i.v. 4× denně	0
± benzodiazepin	alprazolam 0,25–0,5 mg p.o. 4× denně	0
± inhibitor H_2 receptorů nebo inhibitor protonové pumpy		

An overview of selected antiemetics available on our market is provided in Table 4. Some medications are only available to patients with CINV, others can be used also in other indications.

Table 4: Overview of selected antiemetics by the mechanism of action

Mechanism of action	Agent	Dosage and route of administration

D2 (Dopamine) receptor antagonist	metoclopramide	10 - 20mg tid, PO, IV
	triethylperazine	6.5mg tid, PO, IV, PR
	haloperidol	0.5mg-1mg every 6-12 hours, PO, IM
5-HT3 (serotonin) receptor antagonist	ondansetron	8mg tid, PO, PR, IV
	palonosetron	250-500ug once in 5 days, PO, IV
Antipsychotics	olanzapine	5-10mg qd, PO, IV
NK-1 (neurokinin) receptor antagonist	aprepitant	125mg the first day, 80mg day 2 and 3, PO
	netupitant	available in fixed combination with palnosetron, PO
Corticosteroids	dexamethasone	8mg qd, PO, IV
Anxiolytics	alprazolam	0.25mg-0.5mg tid, PO
	bromazepam	1.5mg q8h , PO

Diarrhoea

Diarrhoea is a common adverse effect of some conventional cytostatics (e.g. ***irinotecan, capecitabine***), as well as targeted agents (e.g. *sunitinib, sorafenib, kabazitaxel,* or *afatinib*). It is caused by damage to the intestinal epithelium, which leads to impairment of absorption and inappropriate fluid secretion. If unopposed, it can result in severe fluid depletion and electrolyte imbalance, whereas prolonged diarrhoea might also lead to malnutrition and fatigue.

Management of chemotherapy-induced diarrhoea (CID)

- dietary precautions,
- rehydration and ion substitution (mainly Na, K, Cl),
- opioid derivatives (loperamide, diphenoxylate) to decrease intestinal motility,
- somatostatin analogue (octreotrid) for refractory diarrhoea
- parenteral nutritional support in case of prolonged life-threatening diarrhoea and malnutrition

Disruption of the intestinal microflora is usually secondary to bowel wall inflammation, however, probiotics have shown efficacy in alleviating CID symptoms. Moreover, patients with CID are at higher risk of clostridial colitis (associated with overgrowth of an enterotoxin-producing bacteria clostridium difficile). If a stool culture is positive for Clostridium difficile antigen or toxin, a corresponding antibiotic therapy is necessary.

Mucositis

Oral mucositis is most often manifested by oral pain and burning sensation, erythema or ulcerations (aphtae) informally called canker sores. Extensive forms of mucositis may result in severe dysphagia and malnutrition. The most common etiologic factors include conventional cytostatics *(mainly 5-FU, methotrexate, melphalan and others),* but also certain targeted agents *(mTOR inhibitors).*

Management of oral mucositis:

- oral hygiene measures (mouth rinse, more frequent tooth brushing, flossing)
- dietary modification (avoidance of acidic, spicy, crusty foods)
- oral antiseptics (e.g., Tantum Verde, Corsodyl)
- systemic or topical analgesics (mesocain solution for mouthwash)
- oral antimycotics (intraconazole, fluconazole, clotrimazole) in case of candidiasis
- rehydration and parenteral nutrition in the most serious cases

Fatigue

Fatigue is a very common cancer-related condition that can be aggravated by the administration of anti-cancer treatment. It is a non-specific side effect of conventional cytostatics, as well as a dose-limiting factor of targeted therapy (*aflibercept, regorafenib, temsirolimus* and others).

Fatigue is a symptom that is difficult to cope with and it has to be perceived as a complex problem. Factors that contribute to fatigue are anaemia, malnutrition, pain, sleep deprivation etc. It is important to identify these conditions and provide the patient with an adequate treatment.

Nephrotoxicity

Cisplatin

Cisplatin, one of the most commonly used anti-cancer drugs, also belongs to the most nephrotoxic cytostatic agents. In contrast, kidney injury is rather rare in other platinum derivatives such as carboplatin or oxaliplatin. Nephrotoxicity of cisplatin is caused by tubular injury through a very complex mechanism. Its severity may vary from a mild reversible reduction of glomerular filtration to a complete renal failure.

A significant reduction in the risk of renal function impairment can be achieved by intensive concomitant i.v. hydration along with mannitol administration (so-called forced diuresis).

Methotrexate

High-dose methotrexate can cause kidney injury or even renal failure by precipitation of its metabolite crystals in renal tubules, particularly in acidic environment. The administration of high-

dose methotrexate must therefore be accompanied by intensive hydration and continuous urine alkalization with i.v. sodium bicarbonate.

Other potentially nephrotoxic drugs in oncology include anti-VEGF targeted agents or bisphosphonates.

Tumour lysis syndrome (TLS)

TLS is an oncology emergency that results from a rapid breakdown of a tumour mass following administration of an effective cytotoxic agent. It is not related to any particular chemotherapy, but rather correlates with the intensity of the tumour burden. As a result of tumour breakdown, a large amount of intracellular ions is released into the circulation leading to hyperkalaemia and hyperphosphatemia. Moreover, an excessive DNA catabolism induces hyperuricemia, which can lead to acute kidney injury due to tubular precipitation of the uric acid.

The development of TLS is more likely at the initial treatment of chemosensitive malignancies, mainly haematological diseases, testicular tumours, small cell lung cancer, and a few other solid tumours.

Renal impairment in TLS can be prevented by intensive hydration and initial dose-reduction of chemotherapy. A prophylactic administration of ***alopurinol*** or ***febuxostat*** also showed promising results in clinical trials (see the chapter Emergencies in Oncology). If hyperuricemia cannot be managed by standard therapeutic measures, ***rasburicase*** (a recombinant enzyme with rapid onset of action) is indicated.

Urotoxicity

Degradation of cyclophosphamide and ifosfamide yields a metabolite known as acrolein, a kidney-excreted substance that is responsible for haemorrhagic cystitis, which is manifested primarily by haematuria. For prevention, an infusion of **mesna** is given with or after the chemotherapy. Mesna is an antioxidant that reacts with acrolein to form a nontoxic metabolite.

Cardiotoxicity

Many cytostatics, including modern targeted drugs, may have cardiotoxic side effects mediated by various mechanisms.

In clinical practice, anthracyclines (***adriamycin, doxorubicin, epirubicin,*** *daunorubicin*) are the most prominent cardiotoxic agents. The toxicity displays a cumulative dose-dependent character. It is related to the formation of free oxygen radicals, which are a side-product of anthracycline metabolism. Cardiotoxicity is often irreversible and in rare cases, it can result in fatal heart failure. Cardiomyopathy has usually late onset, with symptoms occurring 10 or even 20 years after the

treatment. Therefore, patients with a history of anthracycline use should be under a long-term cardiologic dispensarization.

Women treated for breast cancer are in a particularly high risk of chronic heart failure, because they might be exposed to three different cardiotoxic factors during the course of treatment. Firstly, the abovementioned anthracyclines are a common part of most adjuvant and neoadjuvant (as well as palliative) regimens in breast cancer due to their notable efficacy. Moreover, in the case of HER2 positive breast cancer, targeted therapy with ***trastuzumab*** is a part of anticancer therapy**.** Although trastuzumab-related cardiac damage is mostly reversible, its use in combination with anthracyclines contributes to the increased cardiovascular risk. Another risk factor in breast cancer patients is the adjuvant ***radiotherapy,*** which may also increase the long-term risk of heart damage and ischemic heart failure, especially in left-sided tumours, depending on the radiation dose to which the heart is exposed. However, to date, modern radiotherapy techniques with respiratory gating or using a deep inspiration breath-holding manoeuvre significantly reduce the radiation exposure of heart as well as the risk of secondary lung tumours.

Besides the risk of coronary events, some cytostatics may act pro-arrhythmogenically. This is a non-specific side effect of conventional cytostatics like *anthracyclines* or *paclitaxel*. In addition, tyrosine kinase inhibitors *(crizotinib, vandetanib)* are reported to prolong the QT interval, which may also lead to fatal arrhythmia known as "torsades de pointes".

5-fluorouracil and its oral prodrug ***capecitabine*** may cause coronary artery spasm.

Neurotoxicity

Therapy with ***paclitaxel, oxaliplatin*** *and* ***vincristine*** is typically limited by their peripheral neurotoxicity. Comparatively lower neurotoxicity is also associated with the use of ***docetaxel or cisplatin.*** Central neurotoxicity is another rare neurologic complication that is mostly related to ifosfamide, methotrexate or cytarabine containing regimens, less commonly to other cytotoxic agents.

As noted above, neurotoxicity is predominantly manifested as **peripheral sensory neuropathy**. The symptoms include paraesthesia or sensory impairment (hypaesthesia), typically in fingertips and hands that may advance more proximally if the neuropathy progresses. Since it is dose-dependent and usually irreversible, the duration of therapy must be controlled in order to avoid severe damage to nervous system that may precipitate into severe motor impairment leading to immobilization of the patient.

Administration of ***oxaliplatin*** may be complicated by another distressing manifestation of peripheral neuropathy, which is an acute-onset laryngopharyngeal dysesthesia. It is characterized by numbness

or burning sensation in the area of larynx, tongue or chin. It usually subsides within a few minutes after treatment cessation. The neurotoxicity of oxaliplatin is cumulative and dose-dependent.

Paclitaxel-induced neuropathy includes diffuse myalgia and arthralgia, most often in the proximal parts of the lower limbs and back. These symptoms may emerge even with the first cytotoxic administration.

Pneumotoxicity

Pneumotoxicity belongs to relatively rare complication of anticancer therapy. A typical drug implicated in pulmonary toxicity is ***bleomycin,*** which is used in the treatment of Hodgkin's lymphomas and germ-line tumours. The risk of severe respiratory compromise is high especially in patients with pre-existing lung disease. It usually occurs in the form of interstitial pneumonitis and pulmonary fibrosis. With bleomycin treatment, it is necessary to avoid concomitant radiotherapy, which can also induce a similar type of lung injury.

An increasing use of modern targeted agents also raises the likelihood of adverse pulmonary effects. For example, *everolimus* and *temsirolimus* have been reported to cause interstitial pneumonitis. Moreover, pneumonitis and pleural effusions are a very common adverse effect of *dasatinib* or *imatinib.*

Hepatotoxicity

It belongs to less common side effects associated with particular cytotoxic agents. Conventional cytostatics known to cause liver injury are *dacarbazine, irinotecan* or high-dose *methotrexate.* Among targeted preparations, it is especially *pazopanib, vemurafenib, T-DM1, regorafenib, lapatinib* and *imatinib*.

The mechanism of drug-induced hepatic toxicity differs depending on its etiology and is beyond the scope of this textbook. As for the grade of hepatotoxicity, we can encounter liver injury ranging from subclinical liver test elevation to fulminant hepatic failure.

Skin toxicity

Skin toxicity may take a number of forms that are often specific to a particular anticancer drug. Especially dermatological side effects of targeted agents may be very diverse. The most common and clinically most important manifestations of skin toxicity are listed below.

Alopecia (hair loss)

It is a common chemotherapy-induced side effect; however, it is not primarily related to all cytostatics. It might be also caused by other drug classes such as CDK4 and CDK6 inhibitors, BRAF inhibitors, or hormone therapy.

Hand-Foot Syndrome (HF syndrome)

HF syndrome is a common complication of treatment with oral capecitabine or, less frequently, with 5-fluorouracil or doxorubicine. It is a skin reaction that involves mainly palms and soles. Affected skin is dry swollen and erythematous, with hyperkeratosis and desquamation. In most severe cases also blisters and bleeding may appear. These changes are accompanied by burning pain and a major deterioration of the patient's quality of life.

Skin toxicity related to the use of some targeted drugs (*regorafenib, sorafenib, vemurafenib*, etc.) may also include acral erythema, but in contrast to HF syndrome, it is localized at pressure points and is characterized by hyperkeratosis and painful blisters that may significantly impair patient's mobility.

Acneiform rash (papulo-pustulous exanthema)

This is a side effect typical for anti-EGFR targeted agents. Most commonly, it is related to monoclonal antibodies ***cetuximab*** and ***panitumumab*** that are used in palliative therapy of colorectal cancer, less often it is reported with ***erlotinib*** and ***gefitinib*** therapy of lung cancer.

The term "acneiform" suggests a similarity to acne vulgaris seen in adolescents and in youngsters. Although these lesions are caused by a completely different mechanism, localization and character of eruptions is identical – predominantly in the face and upper trunk. The most extensive forms can involve shoulders and scalp. Besides rash, nail changes, xerosis, or painful fissures may occur. Skin toxicity means a serious impairment of patient's quality of life and, particularly when manifested on the face, it can lead to emotional distress and withdrawal from social life.

Extravasation of cytostatics

Some cytostatics may cause extensive necrosis of the skin and deeper structures in case of accidental leakage from a vein to surrounding tissue. These agents are known as *vesicants* and include ***doxorubicin, mitomycin, vincristine*** or ***vinblastine***. Other cytotoxic agents can act as irritants and their extravasation is not that harmful.

Another complication of intravenous application of some cytostatic agents is superficial phlebitis caused mainly by ***5-fluorouracil (5-FU)***. This can be avoided by oral administration of its prodrug capecitabine, which, however, has a slightly different toxicity profile including higher incidence of the above-mentioned HF syndrome or diarrhoea.

Vascular access in oncology

For the reasons outlined above, it is often necessary to provide the patient with a reliable and long-term central venous access that can be used for safe chemotherapy administration.

The most commonly used central venous access device in oncology is an **intravenous port**, but there are also other alternative routes designed for repeated administration of intravenous drugs.

Table 7: An overview of venous access techniques

Type of device	Method of introduction	Use
Implantable intravenous port	A reservoir chamber is implanted into pectoral subcutaneous tissue, its catheter is inserted into subclavian vein. Drugs are administered with a special needle through the skin into the chamber and further to venous circulatory system.	Implantation in a local anaesthesia under X-ray or ultrasound control. Usually for long-term therapy longer than 6 months.
PICC (peripherally implanted central catheter)	The catheter is inserted via a peripheral vein (basilica or cephalic) into the systemic circulation (subclavian vein or superior vena cava). The end of the catheter is secured to the arm with a special tape or a suture.	Long-term therapy usually up to 1 year. Frequent changes of dressing are required to prevent infection.
Tunnelled central venous catheters	The catheter is inserted into a central vein and its distal part passes through subcutaneous tissue.	Longer-term therapy usually exceeding 6 weeks
Midline catheter	A 8-20cm long catheter is introduced under ultrasound control into basilica or brachial vein.	therapy in the order of weeks

Acute infusion reactions

Infusion-related reactions to cytostatic agents are often mistakenly referred to as "allergic", although their pathophysiological background is substantially different. Their severity may also range from light reactions that can be managed by slowing down of the infusion to fulminant anaphylactic reactions with fatal consequences.

Anaphylactic reactions

An anaphylactic reaction may occur both with monoclonal antibodies and with conventional chemotherapy. Cytostatics involved in anaphylaxis are mostly platinum derivatives (***oxaliplatin*** and ***carboplatin***), and also ***paclitaxel, docetaxel*** and ***etoposide***, although, in these cases, the hypersensitivity can rather be attributed to the vehicle, which ensures the stability of the cytostatic agent.

Of the monoclonal antibodies, an increased incidence of anaphylactic reactions is reported with ***cetuximab*** - a chimeric antibody widely used in the treatment of colorectal cancer and ***rituximab***, which is used in the treatment of B-cell proliferations.

Anaphylaxis is manifested by cough, dyspnoea, tachycardia, hypotension (sometimes hypertension), nausea, abdominal cramps, or blurred vision. In particular, skin symptoms such as urticaria, angioedema of face, lips and eyes, flushing, along with bronchospasm and hypotension, are often the

most specific indicators of anaphylactic reactions. Early recognition of anaphylaxis and immediate intervention is crucial for successful management of this life-threatening complication.

Medications used for treatment of anaphylactic reaction include:

- **antihistamines** (eg IV bisullepine / Dithiadene / 2mg in 10ml of 5% glucose)
- **corticosteroids** (eg IV Hydrocortisone - 200mg in 20ml saline)
- **epinephrine** (initial dose in severe reactions is 0.5mg IM or IV. One vial containing 1 mg of epinephrine is usually diluted to 10 ml of saline)

To some extent, anaphylactic reactions can be prevented by adequate premedication with corticosteroids and antihistamines. However, due to the high incidence of severe anaphylaxis with cetuximab, the first cycle should be administered at emergency department or similarly equipped unit (see the chapter Emergencies in oncology).

Adverse effects of immunotherapy

Stimulation of patient's immunity against cancer, which is the underlying mechanism of action of **check-point inhibitors** (***ipilimumab, nivolumab, pembrolizumab***) may also result in disruption of immune self-tolerance and side effects substantially distinct from the adverse reactions associated with cytostatics. They inherently correspond to autoimmune diseases that can involve any organ system in the body.

Despite an insidious onset of the symptoms, immune-related adverse events can escalate to life-threatening conditions that require an expert treatment, preferably in cooperation with an oncologist experienced in this type of toxicities.

The most common side effects of check-point inhibitors are:

- dermatitis (rash, pruritus, mild erythema)
- enterocolitis (diarrhoea, abdominal pain, intestinal bleeding, perforation in the most severe cases)
- endocrinopathy (symptoms specific for hypophysis, thyroiditis, or adrenal insufficiency)
- hepatopathy (elevation of liver tests, autoimmune hepatitis)
- pneumonitis

However, the immune system can attack virtually any organ in the body (heart, kidneys, nervous system, eyes, hematopoietic system and others). Side effects may occur several weeks or even months after the treatment. Their initial management involves immunosuppression by glucocorticoids. If symptoms do not improve after three days of corticosteroid therapy, additional immunosuppressants, such as infliximab or mycophenolate mofetil are recommended.

Case No. 1

A 50-year-old man who underwent a bladder tumour surgery is now being treated with adjuvant chemotherapy. He visits the clinic 10 days after the 2nd cycle of cisplatin + gemcitabine chemotherapy.

He complains of fatigue, weakness, night chills and fever above 39 ° C. Moreover, he had completely lost his appetite, was nauseous practically all the time after the chemotherapy, and had repeatedly vomited in spite of the use of antiemetics.

Laboratory Findings:

- neutrophils 0.3 x 10 * 9 / l,
- thrombocytes: 24,000 x 10 6 / l,
- haemoglobin 82g / l,
- CRP: 130 mg / l,
- creatinine: 145 µmol / l,
- Quick - INR: 1.35.

Clinical diagnoses:

1. Febrile neutropenia 10 days after chemotherapy
2. Grade 4 thrombocytopenia after chemotherapy
3. Renal failure – possibly due to nephrotoxicity of cisplatin or dehydration caused by prolonged emesis
4. Nausea and vomiting after chemotherapy
5. Fatigue due to anaemia / after chemotherapy.

Diagnostic and therapeutic measures:

- cultivation examinations: haemoculture, urine cultivation, throat and nose swab
- chest X-ray
- infusion of saline, parenteral nutrition, dietary restrictions
- admission to the intensive care unit, monitoring of vital signs and diuresis
- preventive isolation
- combination of antibiotics (in this case the combination of ampicillin potentiated with clavulanate and ciprofloxacin) after the collection of culture samples
- administration of growth factors (filgrastim)
- administration of antiemetics

Case No. 2

A 56-year-old woman with breast cancer and multiple bone involvement has received 6 months of first-line chemotherapy with paclitaxel. The last cycle of chemotherapy was administered a week

ago. A significant progression of the disease in the skeleton was diagnosed on a recent CT scan with a large number of new metastases.

- Waiting for the scheduled examination in the waiting room, she is nauseous and repeatedly vomits.
- The patient reports fatigue, headache and emesis in the last few days. She does not suffer appetite loss, she is able to eat small portions of meal, but she often feels a sudden strong urge to vomit.
- The patient has repeatedly used metoclopramide and ondansetron without any effect.

What strikes you as the most likely cause of emesis in this case?

What treatment do you suggest in order to alleviate the patient from nausea and vomiting, and what diagnostic imaging method would you recommend?

- With regard to the nature of symptoms described, we expect intracranial hypertension to be the most likely cause of emesis in this patient.
- The administration of corticosteroids (e.g. dexamethasone 8mg i.v.) possibly in combination with mannitol can reduce the tumour-associated oedema and relieve the symptoms.
- In differential diagnostics, we also need to exclude hypercalcemia.

Cancer pain management

O. Slama, L. Pochop

Pain belongs to one of the most devastating cancer-associated symptoms. Pain management is an integral part of oncology care. Pain relief usually does not mean complete painlessness, but rather a reduction of pain to a tolerable level. The aim of treatment is to prevent the pain from interfering with patient's daily activities and to minimize its negative impact on his quality of life.

Pain assessment

A rational treatment plan should be preceded by an adequate pain assessment. The basic evaluation criteria are:

- **cause of pain** : tumour-induced pain, a result of anticancer treatment, not related to cancer at all
- **type of pain** : somatic, visceral, neuropathic, mixed
- **duration of pain** : stable chronic pain, persistent with fluctuating intensity, intermittent
- **localization, intensity and quality of pain**
- **the influence of anxiety, depression or delirium** on perception and the manner of pain expression

The most important factor in cancer-related pain assessment is the intensity ("How much does it hurt?"). There are various tools used to help the patient to define his pain intensity, e.g. a *numerical rating scale* (a patient describes his pain on a scale of 0-10) or *verbal rating scale* (uses word categories to describe the pain intensity, e.g. none - moderate - strong - severe). It is always necessary to double-check whether the patient understands the particular way of pain assessment. Generally, patients prefer the verbal rating scale. The intensity of pain is significantly affected by patient's emotional state (anxiety and depression) and by his overall well-being and coping (the degree of frustration, anger, or the ability of positive adaptation).

Treatment of pain

The best method of cancer-related pain control is an effective anticancer treatment. Tumour mass reduction is usually associated with partial or complete pain relief. Where the prospects of causal treatment are limited, symptomatic therapy plays fundamental role in pain management. It encompasses both non-pharmacological and pharmacological measures.

Non-pharmacological therapy

- Analgesic radiotherapy for metastatic bone pain
- Neuroablative procedures (e.g. chemical neurololysis of ganglion celiacum used in the treatment of visceral pain caused by pancreatic cancer)
- Supportive psychotherapy and cognitive behavioural therapy
- Physiotherapy and rehabilitation (e.g. in musculoskeletal pain due to bone metastases)
- Prostheses and mobility aids (crutches, walkers, orthoses)
- Complementary procedures (for example acupuncture is reported to bring pain relief)

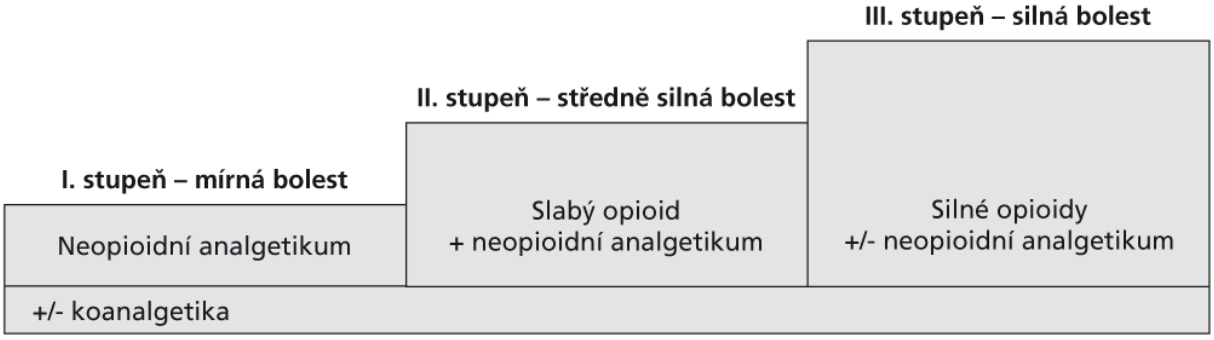
Pharmacological therapy

Pharmacotherapy is the mainstay of symptomatic cancer pain management.

General principles of pharmacotherapy:

- Treatment is primarily guided by patient's subjective perception of pain severity.
- The type of analgesic drug is selected according to pain intensity. A commonly used strategy proposed by WHO is represented by a three-step analgesic ladder (see Figure 1).
- Chronic pain should be managed by analgesics given on a regular basis, at intervals depending on the pharmacokinetics of a particular drug.
- The intensity of pain may vary throughout the day. In order to ensure adequate pain control, it is sometimes necessary to combine long-acting opioid drug with immediate-release opioid for breakthrough pain.
- The dose of an analgesic is always determined individually according to patient's responsiveness to therapy, as well as the profile of each drug's side effects.
- We should regularly monitor the tolerability of analgesic therapy and enquire about the presence of side effects. The emergence of adverse effects is not necessarily a reason to interrupt the administration of analgesics, since most of them are usually treatable.

Diagram 1: The WHO analgesic ladder



First-step analgesics according to the WHO

- Non-opioid analgesics are indicated as monotherapy for mild nociceptive somatic and visceral pain
- patients who fail to achieve pain relief at the maximum dose of a non-opioid drug within 1-2 days, are candidates for titration of “second-step” analgesics
- increasing doses of non-opioid analgesics above the ceiling level only increases the risk of serious side effects
- the combination of paracetamol or metamizole with non-steroidal anti-inflammatory drugs (NSAIDs) is feasible and increases the analgesic effect
- a combination of multiple non-steroid anti-inflammatory drugs is not recommended, while it increases only the risk of side effects

Table 1. Non-opioid analgesics:

Drug	**Route of administration**	**Onset of action**	**Usual dosage (mg)**	**Max. daily dose (mg)**	**Note**
Analgesics - antipyretics					
Paracetamol	po, pr, iv	30 min	4 × 500-1000	4 × 1000	With long-term use, the highest safe daily dose of paracetamol is 3000 mg / 24h. Caution should be taken in patients with liver dysfunction.
Metamizole	po, iv	30 min	4 × 500	6 × 1000	Not suitable for long-term treatment due to the increased risk of agranulocytosis
COX-2 non-selective NSAIDs					
Ibuprofen	po	15-20 min	4 × 400	4 × 600	In case of long-term use of NSAIDs, it is advisable to administer proton pump inhibitors at the same time to reduce the risk of a gastric ulcer (omeprazole 2x20mg)
Diclofenac	po, pr, im, iv	30 min	3 × 50	3 × 50	
Naproxen	po	2 h	2 × 250	2 × 500	
Indometacin	pr	60 min	2 × 50	2 × 100	

COX-2 selective NSAID					
Nimesulide	po	30-60 min	2 × 100	2 × 100	It is not suitable for long-term treatment. Severe hepatotoxicity is reported with long-term use

Second-step analgesics (weak opioids)

- weak opioids are indicated for the treatment of mild to moderate pain, preferably in combination with a non-opioid analgesic
- if pain relief is not achieved within a few days of maximum doses of a weak opioid combined with NSAID, escalation to strong opioids should be considered
- severe pain (e.g. in bone metastasis, soft tissue tumours and neuropathic pain) is indicated for an upfront use of strong opioids instead of taking a standard stepwise approach

Table 2: Overview of weak opioids

Substance	Application	Effect onset	The usual dose (mg)	Max. daily dose (mg)
Dihydrocodein	po	2-3 h	2 × 60	240 mg
Tramadol	po, pr, iv, im, sc	20-30 min	4 × 50	400 mg

Third-step analgesics ("strong" opioids)

- strong opioids are the mainstay of severe cancer pain treatment
- they are indicated whenever pain cannot be alleviated by weak opioids, regardless of patient's prognosis or the underlying disease
- doses are gradually increased ("titrated") until the desired analgesic effect is achieved, unless unacceptable adverse effects occur. The rate of dose escalation depends on pain intensity and pharmacological properties a specific drug. The most common initial doses for patients not previously treated with strong opioids are shown in Table 1. 3. If the pain control is not sufficient at a given dose, an increase by 30-50 % is recommended
- It is of advantage to start with immediate-release opioids when titrating an individual effective dose. Extended-release opioids will reach their peak effect in the order of days (3 days for retarded morphine, hydromorphone and oxycodone, 5-7 days for transdermal fentanyl and buprenorphine), therefore they not appropriate for acute pain management
- it is recommended to combine strong opioids with non-opioid analgesics and co-analgesics
- it is not appropriate to combine strong and weak opioids in long-term therapy

- there is considerable interpersonal variability in response to opioids and their adverse effects. Patients with inadequate pain control or serious opioid toxicity may benefit from switching to another opioid (so-called "opioid rotation")

Tab. 3: Overview of strong opioids

Substance	**Application**	**Effect onset**	**Duration of effect**	**Usual dose (mg)**	**Max. daily dose (mg)**	**Note**
Immediate-release morphine	po, pr, sc, im, iv	20-30 min	4-6 h	10 mg à 4 h	not established	equianalgesic doses depending on route of administration: po: pr = 1: 1 po: sc = 2 - 3: 1 po: iv = 3: 1
Extended-release morphine	po, pr	3-5 h	12 h	30 mg à 12 h	not established	
Fentanyl TTS	patch	8-12 h	72 h	25 µg / h	not established	
Fentanyl citrate for transmucosal application	Tablets for buccal and sublingual administration, nasal spray, buccal soluble film	5-15 min	3-4 h	Individual: 50-800 µg (see note)	See note	The highest single dose per an episode of breakthrough pain is 400ug for nasal spray and 800ug for buccal film and tablets
slow-release Oxycodone	po	1-3 h	8-12 h	10 mg à 12 h	not established	A fixed combination with naloxone (TARGIN) is available for patients with a significant opioid-induced constipation.
Buprenorphine TDS	patch	10-12 h	72-84 h	35 µg / h	140 µg / h	It is more convenient to change a patch every 84 hours, i.e. regularly two times a week
slow-release Hydromorphone	after	3-5 h	12 h	4-6 mg à 12 h	It is not established	

Slow-release Tapentadol	po	3-6 h	12h	50 mg and 12 hours	400 mg / d	
Strong opioids that are not suitable for the treatment of chronic cancer pain or there is a lack of experience with their use in this indication						
Pethidine, Piritramid , Sufentanil , Remifentanil						

Treatment of breakthrough (episodic) pain

Breakthrough pain (PB) refers to a short-term episode of severe pain in patients who have already been treated for chronic pain that is well-controlled by analgesic medication most of the day. Breakthrough pain is reported in 40-60% of patients with chronic cancer pain. Several treatment strategies are available depending on the character and intensity of pain:

1. to increase the dose of regular analgesic medication
2. to administer a "rescue dose" of a non-opioid analgesic (e.g. paracetamol 1 g, diclofenac 50 mg, ibuprofen 400 mg, metamizole 500-1000 mg).
3. to give the patient a "rescue dose" of an opioid. Parenteral administration of an analgesic (e.g., iv or sc morphine) takes effect in 3-10 minutes. Oral opioids (e.g. tramadol drops, morphine tbl) are less suitable for the treatment of breakthrough pain due to their slow onset of action (after 20-40 minutes). On the contrary, transmucosal, buccal, intranasal and sublingual fentanyl preparations are often used in this indication thanks to their rapid onset of action.

Adjuvant analgesics (co-analgesics)

Adjuvant analgesics are administered concomitantly with analgesics in order to achieve a better pain control, though their primary indication might be other than pain control. They are categorized by the type of pain they may help to manage:

- bone pain
- neuropathic pain
- visceral pain (due to malignant bowel obstruction)
- central neuropathic pain and headache in intracranial hypertension

Tab. No. 4: Most commonly used co-analgesics

Type of pain	**Adjuvant analgesic**	**Usual daily dose in mg**
Neuropathic pain	Gabapentin	900-1800

	Pregabalin	150-600
	Carbamazepine	600-1600
	Duloxetine	30-60
	Amitriptyline	25-75
	Clomipramine	25-75
Central pain, intracranial hypertension, visceral pain	Dexamethasone	8-24
Bone metastasis-related pain	Clodronate	1600 mg after
	Pamidronate	60-90 mg / 3-4 weeks
	Zoledronate	4 mg / 3-4 weeks iv
	Ibandronate	6 mg / 3-4 weeks iv
	Denosumab	120mg / 4 weeks sc
Visceral pain	Butylscopolamine	60-120

Management of opioid-related adverse effects

The most common side effects associated with long-term opioid treatment are nausea and vomiting, constipation and overall sedation.

Nausea and vomiting is a frequent side effect that emerges during the first 3-7 days after treatment initiation. Prophylactic use of antiemetics might be considered at the start of treatment in high-risk patients (e.g. metoclopramide 10 mg tid). Gastrointestinal tolerance usually develops within the first week of opioid therapy. In case of persistent nausea, opioid rotation should be considered.

Sedation and cognitive impairment is usually reported with high initial doses of opioids, especially in opioid-naïve patients. There is no specific treatment available for this compliacation, however, sedation is likely to subside by itself, usually after the first week of treatment. The risk of prolonged sedation significantly increases with concomitant administration of benzodiazepines, antidepressants and particular antipsychotics. In the case of unacceptable persistent sedation, patients might benefit from opioid rotation.

Constipation. There are several factors that contribute to constipation in oncology patients (decreased mobility, low dietary fibre and fluid intake, anticholinergic medication, etc.). Opioid-induced bowel dysfunction might seriously augment the problems; therefore, prophylactic administration of oral or rectal laxatives is routinely indicated. Transdermal opioids are associated with less constipation than oral preparations. Alternatively, the use of oxycodone/naloxone combination drugs has been proven effective against opioid-induced bowel dysfunction. If this treatment fails to improve constipation, the use of methylnaltrexone (RELISTOR) - a peripheral opioid receptor antagonist given by s. c. injection may represent an additional choice.

Cannabinoids

Recent preclinical and clinical studies have brought an evidence of a significant role of cannabinoid system in pain perception regulation. There is a large body of scientific evidence addressing the endocannabinoid system, the structure and distribution of cannabinoid receptors and their involvement in pain regulation. Currently, remarkable research efforts are aimed at the use of phytocanabinoids (substances derived from Cannabis sativa) for therapeutic purposes. The preliminary results of multiple studies suggest that cannabis might contribute to the control of cancer-induced pain, anxiety, anorexia and nausea. It was also found that clinical effects of cannabis are partially mediated by cannabinoids (tetrahydrocannabinol-THC and cannabinol-CBD), but also by other components such as flavonoids and terpenoids. Since 2018, medical marijuana has been legally available in the Czech Republic, either in the form of a dried Cannabis sativa plant (with various THC and CBD content) for inhalation (most often using a vaporizer) or in the form of capsules for oral administration.

Prerequisites for successful cancer-pain management

- careful initial assessment of pain and associated conditions (the intensity, character, duration etc.)
- involvement of both pharmacological and non-pharmacological approaches in the treatment
- regular monitoring of the analgesic effect, side effects and their control
- patient’s involvement in the decision-making process, supportive communication and psychological counselling to encourage patient’s coping strategies
- early referral to a specialized pain management centre in case of inadequate response to analgesic treatment

Nutritional Care in Oncology

Š. Tuček

Important terms, self-study topics:

malnutrition, cachexia, precachexia, anorexia, sarcopenia, sarcopenic obesity, nutritional screening, anthropometry, energy intake calculation, refeeding syndrome, simple and marantic starvation, stress starvation and hypoproteinemic malnutrition, kwashiorkor, sipping, enteral tube nutrition, oligomer / polymer nutrition formulas, parenteral nutrition, home parenteral nutrition, nutritional gastrostomy / jejunostomy, PEG / PEJ and differences among them (in terms of sterility, rate of nutrition administration, possibility of bolus administration), Blue Book of Czech Society for Oncology

Introduction:

Nutritional care is an integral part of anticancer treatment. **Malnutrition is much easier to prevent than to cure and there are certain situations, when the poor nutritional status of a patient is irreversible**. An early screening of malnutrition risks prior to its clinical manifestation is crucial for effective and patient-tailored nutritional support.

The network of nutrition outpatient offices in major hospitals in the Czech Republic covers only about 5% of all cancer patients, which is utterly insufficient (1). To date, there are also several medical societies that deal with nutritional care - the Society of Clinical Nutrition and Intensive Metabolic Care (SCNIMC) (2), the Working Group on Nutritional Care in Oncology (WGNCO) (3) at the Czech Society for Oncology (CSO).

Specific guidelines on nutrition can be found on the website of the European Society for Parenteral and Enteral Nutrition (ESPEN) (4), or its American counterpart (ASPEN). This issue is also briefly addressed in the Blue Book of CSO.

Definitions of the most important terms used in nutritional care are provided below:

The state of muscle mass or **lean body mass** (**LBM**) represents a metabolically active part of total body weight and is important for anticancer therapy dosing, or in determining patient's reserves in case of stress starvation.

Refeeding (realimentative) syndrome is a metabolic disorder resulting from an intensive anabolic process induced by food intake recovery following a long period of starvation. As a result of vigorous nutrient uptake, **clinically significant or even life-threatening hypophosphatemia** and other electrolyte abnormalities may develop. The potential danger of this condition dwells in late diagnosis

and inadequate management. Typical symptoms, such as qualitative and quantitative impairment of consciousness can be falsely attributed to other underlying conditions, particularly in elderly patients, in whom it could have fatal consequences. If the syndrome is diagnosed, it is necessary to decrease the rate of feeding and start intensive supplementation of minerals and phosphates (the amount of phosphate should be ten times higher than normal daily intake!). (5)

Diagnosis of malnutrition

Being able to diagnose malnutrition means to be aware of it! Diagnostic procedures include anthropometry - especially height, weight measurements, various indices calculation, thickness of skin fold, muscle strength measurement etc. Estimation or calculation of patient's energy needs and routine blood tests are also helpful. For detailed description of diagnostic tests, see the relevant literature.

Prior to assessing nutritional status based on patient's weight, it is necessary to rule out **oedema and third-space fluid accumulations (peritoneal or pleural effusions, etc.)**, especially in cancer patients, who are prone to hypalbuminaemia, or other aetiology factors. It is not uncommon that oedema or ascites completely disguise substantial weight loss, which leads to frequent malnutrition underdiagnosing.

Nutritional screening is a particularly sensitive diagnostic tool used mostly by nursing professionals, which helps to identify patients at high risk of malnutrition. To establish the diagnosis of malnutrition, an expert consultation and further assessment is required. Nutritional screening is based on patient's medical history focused on appetite, food intake, unintended weight loss over a certain period of time and other risk factors associated with metabolic processes (comorbidities, infection, sepsis, liver failure, etc.) Sometimes it also takes account of the underlying disease (e.g. primary tumour localization) presence of effusions, etc.

If a significant risk of malnutrition is identified, a stepwise nutritional plan is proposed, beginning with dietary counselling, administration of sip feeds, up to enteral tube feeding (6).

Malnutrition treatment in oncology

Artificial enteral nutrition is indicated in patients who cannot maintain adequate nutritional status through normal food intake or by supportive treatment aimed at factors limiting normal dietary patterns.

There are several ways of providing an artificial nutritional support: parenterally-via temporary and permanent central venous catheters or intravenous ports, orally, or via enteral tubes. Their use, introduction and management are the same as in other indications. In **intravenous ports**, there is a

higher risk of infectious and thrombotic complications (especially if they are used only for parenteral nutrition) resulting from their specific structure and, in particular, due to aspirations following needle placement.

An effective nutritional support, however, requires a successful **causal treatment of the underlying disease**. An effective nutritional intervention should therefore aim to improve patient's tolerance of anticancer therapy and reduce the interruptions of treatment schedules.

The treatment of malnutrition also includes intensive **supportive treatment** of cancer-associated conditions underlying reduced energy intake, such as pain, nausea, cancer anorexia, xerostomia, constipation, diarrhoea or depression (6).

Methods of nutritional support:

Enteral nutrition includes oral nutritional supplements as well as enteral tube feeding with standardized formulations. There are many commercially available products, especially for oral consumption, that reflect specific needs of cancer patients, for example, their altered taste perception.

A special diet containing **omega-3 unsaturated acids** in the form of fish oil (EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid) contributes to reduction of systemic inflammation, which is associated with cancer cachexia. It also demonstrated an improvement in muscle anabolism, plasma protein levels, stimulation of appetite and weight gain, better quality of life and even increase in survival rates (7, 8). A limiting factor is a poor patient adherence to fish oil, capsules or omega-3 enriched sip feeds. A recent monitoring of patient compliance with enteral nutritional support, carried out by Czech Society for Cancer, revealed that most patients do not tolerate recommended amounts of sip feeds.

Nutrition supplements also include thickeners used in patients with impaired coordination of swallowing muscles and dysphagia who benefit from more viscous consistency of their diet.

The **pharmacological armamentarium** for the treatment of cancer-related anorexia is limited. In practice, we may use **corticosteroids** with only a transient effect and **progestins** (megesterol acetate). To date, there is no sufficient evidence for the use of cannabinoids or other substances like ghrelin, anamorelin etc. Megestrol acetate was proved to down-regulate proinflammatory cytokines, and it was associated with a significant increase in appetite and food intake. The recommended dose is 240 - 480 mg (up to 800mg) per day, for at least 3 weeks. However, its benefit might be compromised by serious side effects such as fluid retention, an increased risk of thromboembolism, and sometimes even a decrease in muscle mass due to downregulation of circulating androgen levels. Adverse effects are more pronounced with higher doses.

Parenteral nutrition in oncology has several specific aspects. It can be provided also in home environment (approved nutritional centres are responsible for indications and reimbursement issues) to patients with expected survival of more than 2-3 months, who are unable to receive food orally or via enteral tube and who are willing to be administered intravenous nutrition. The vast majority of patients requires only a temporary parenteral nutrition, a limited number of patients may benefit from long-term parenteral nutrition. As for the content of nutrients, cachectic patients should receive formulas with relatively higher lipid ratio representing up to 50% of non-protein energy. Even higher proportion of lipids may be considered in patients with pleural or peritoneal effusions (9). Currently, home parenteral nutrition has become increasingly important thanks to its better availability.

Economic aspects of malnutrition and its treatment:

- regular diet in a hospital costs about 60-100 CZK / day
- special enteral nutrition cost about 300 CZK / day
- full parenteral nutrition is 3000 CZK / day
- malnourished patients are reported to have longer hospital stays, more frequent re-admissions, increased risk of reoperations and ICU admissions
- the treatment of clinical complications related to malnutrition (infections, decubitus) is expensive
- malnutrition decreases the efficacy of anticancer treatment and thus aggravates the underlying disease and consequently increases the total cost of care

This was convincingly demonstrated by a study evaluating outcomes of protein-rich sip feeding before and after surgery in patients with colorectal carcinoma. (10) An adequate nutritional support was associated with decreased risk of complications and lower rate of re-admissions, shortened length of hospitalization and significant reduction of overall treatment costs 6 months after the surgery.

Interesting notes:

- Fasting prior to particular procedures or surgery is often unnecessary and even detrimental in some cases. A starving cancer patient catabolizes and wastes his low energy reserves. Malnutrition resulting from exhausted reserves is associated with impaired wound healing and higher risk of postoperative mortality.
- BMI may not adequately reflect nutritional status, especially in patients with oedema and effusions. Even individuals with higher BMI might be at risk of severe sarcopenia and life-threatening stress starvation.

- Common sip feeding preparations contain 300-400 kcal and 12-20 g of protein per pack, the usual daily dose (two packs) covers 20-80% of recommended daily intake of vitamins and minerals.
- Some hospital diets are nutritionally insufficient and inappropriate for a long-term feeding (e.g. full liquid diet, low-fat diet or diabetic diet, which is also slightly weight-reducing).
- Patients with well-compensated diabetes do not need special nutritional supplements.
- In the Czech Republic, an average malnourished patient falls into an overweight category with BMI levels above 26.

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Psychological aspects of oncological care

R. Alexandrová

Each disease is usually a source of anxiety, stress, and can induce specific changes in human behaviour. Very serious somatic diseases, which undoubtedly also include oncological diagnoses, might elicit existential concerns and a fear of "losing oneself". Personal self-regulation mechanisms are endangered, psychosocial integrity and normal life's order might be compromised. Human being suddenly becomes an "oncology patient".

> ***He enters an active relationship with a physician, "educated professional and the carrier of the hope of recovery", mostly burdened with great expectations. It is very important to build a confiding relationship that will support and encourage the patient to overcome distressing situations and complications. This can be achieved by an unbiased acceptance, empathic understanding and open communication.***

The process of coping with the illness usually takes place on several distinct levels:

1. Cognitive level

Every patient reflects a disease in the context of his personality structure and subjective interpretation framework. He adopts a specific attitude towards the disease, which determines further adjustment and reactions to this stressful situation.

Active approach

- the patient has realistic view of the disease, he is able to handle the information without exaggeration and he cooperates with the doctor
- the patient does not have a realistic view, he dissimulates or aggravates, he is preoccupied with difficulties and fears, he is impatient and restless
- the patient is inclining towards denial, uses work as a form of escapism, he avoids the thoughts and reminders of his disease
- the patient requires overprotection, he draws excessive attention and seeks reassurance from the environment and his treating physician, he has an inappropriate need to be taken care of, he "exploits" his illness
- the patient is prone to self-accusation, or blaming of the others, he perceives the disease as a kind of punishment, he is alert and sceptical
- the patient is angry and malicious, particularly towards healthy people

Passive approach

- the patient is depressed, pessimistic, feels hopeless and he is resigned to the fact he has an incurable disease
- the patient is submissive and disengaged, he has lost his interest in treatment, acts apathetically
- the patient withdraws from social life, because he fears “stigmatization", his disease represents a threat to his relationships.

The oncologist should be able to identify patient’s coping strategies, avoid judgemental behaviour or taking certain patient’s reactions personally. On the contrary, he should respond to patient’s specific way of coping, facilitate a positive adaptation process and motivate the patient to treatment. For example, a passive patient should be given detailed information and more options in order to stimulate his feeling of own competence and his interest in treatment. A doctor should encourage patient’s participation in decision-making, it is crucial to emphasize doctor-patient partnership. In maladaptive active patients, it is better to briefly outline the situation, define your boundaries, lead the patient to self-awareness and perception of his own needs, allow fear and frustration venting, etc.

2. Emotional level

Every disease elicits an emotional response. It is an important self-regulation process that may significantly vary from patient to patient. The intensity of an emotional response in each patient is unpredictable and it might often seem inadequate to a given situation. Emotional reactions can be both adaptive or maladaptive - i.e. reactions that compromise coping with psychological stress.

It is important for a physician to accept patient's emotions as an integral part of processing an oncological diagnosis. He should not be afraid of patient’s emotional reactions and he should not take them personally, but rather perceive them as a source of information about the patient and his adaptive or compensatory mechanisms. Emotional disclosure might also be an indicative of a trustful and supportive doctor-patient relationship.

The most common emotional reactions in confrontation with cancer diagnosis include:

Anxiety - occurs in most patients, it is a subjective feeling of fear in the anticipation of a loss. The intensity may vary throughout the disease trajectory and, sometimes, it may culminate in maladaptive anxiety disorder.

Regression - in the sense of return to childhood stages of emotionality. This response may lead to physical and emotional overdependence during the course of the disease.

Anger - is an adaptive response if it occurs in the context of an active coping strategy. Patients need to deal with their distressing situation and encounter feelings of hopelessness and anxiety that generate anger, often towards the situation itself, though sometimes it might aimed at "substitute" targets. Maladaptive reactions can occur if the anger is so destructive to patient's social environment that he loses essential support.

Sadness and depression is normal and justified reaction to perceived loss. An adaptive response is usually redirectable, maladaptive form results in a pervasive depression that is pathological and negatively influences all aspects of patient's life.

3. Somatic level

Patient's quality of life depends on the character and stage of cancer, on the intensity of treatment and related side effects. Generally, the patient often loses his vitality and energy. The perception of physical symptoms might range from denial ("I do not feel pain, I am all right") to gradual acceptance of cancer-related complications such as pain or loss of self-care abilities. Cancer and its treatment may result in considerable alterations of patient's body image, which is linked to self-esteem and self-consciousness. Negative changes of self-image might precipitate feelings of lowered self-respect and dignity.

> ***Doctors primarily address physical symptoms of a disease and focus on their management. The patient needs to have trust in physician's expertise and competence. However, it should not be perceived as an expression of disloyalty, if the patient consults his or her medical condition with another physician or alternative medicine practitioner. It is necessary to communicate these needs with the patient, be attuned to his opinions and encourage his role in the decision-making process. It is also important to respect patient's shyness and to show understanding for patient's emotional strain and hyperreactivity to certain physical symptoms.***

4. Social Level

Besides cancer-related somatic problems, patients also need to adapt to changes in their social environment (e.g. a loss of job). Behavioural changes, loss of self-efficacy and motivation and other consequences of cancer place a burden on patient's close relatives and his social life. Patients unwillingly acquire a different status in family or society. Identifying oneself as "cancer patient" might have various implications depending on person's premorbid concept of the world and relationships; it can be misused in order to achieve specific benefits, however, for most patients it is a stigma that complicates, distorts and threatens social relationships.

5. Spiritual level

Every person is endowed with a certain form of spiritual awareness, whether in an ethical, religious or existential sense. This aspect may also be a source of frustration in the process of adaptation to a serious disease, for example, a believer can be "angry with God for imposing an illness on him", or one may lose his meaning of life, etc. Nevertheless, spirituality can often be a crucial source for coping with cancer and distressing situations.

> ***The management of patient's psychosocial problems and spiritual needs is not necessarily the physician's responsibility, but it is necessary to acknowledge the impact of these aspects on the course of illness, its symptoms and treatment. It is essential to engage family members in the communication and decision making since they might represent an important social support system for the patient and facilitate his involvement in cancer care and cooperation. Spiritual awareness might also have positive impact on patient's motivation and well-being, it can provide a sense of meaning and purpose, shape his values, beliefs and hopes. Patients might experience life transformation, however, they can also be paralysed by frustration, hopelessness and loss of meaning.***

Specific individual attitudes towards the disease depend on:

- Patient's personality
- Particular coping skills or strategies
- Social background
- Premorbid quality of life
- Previous health care experiences (doctor-patient relationship, communication, etc.)
- Age, sex

The responsiveness and adaptability to a threatening event change throughout the disease trajectory:

1. Confrontation with the diagnosis is usually accompanied by a shock, often bordering on a traumatic reaction, leaving the patient without any capacity to activate defence mechanisms. Disintegration impends in such cases.

2. Initiation of treatment - patients usually begin to adapt to the situation by activating their defence mechanisms. It is an inevitable process of coping with a stressful event that is very individual and depends on patient's type of personality and his attitudes.

Most common responses include:

- denial
- avoidance

- rationalization
- projection
- projective identification
- trivialization
- resignation
- escapism (fantasy, work, activity, etc.)
- regression
- aggression

Dealing with patient's defence mechanisms might be complicated and exhausting. Instead of trying to breach the defence, we should focus on building relationship and rapport, in order to enhance patient's feelings of security and acceptance and to provide an effective support for overcoming maladaptive defences.

3. Medical procedures, hospitalization, and the course of treatment - the patient is confronted with reality and adapts to a new life situation depending on his personal limits and abilities. It is an active phase in which the patient cultivates his sense of hope and believes in the curability of his disease.

4. Cancer remission brings relief, but also fears of cancer recurrence. Anxiety disorder may exacerbate unless patient's fear is "legalized". Some patients accuse themselves of failing to "be healthy," they are under pressure of their exhausted families. At this stage, patients lose support systems without having established sufficient self-efficacy.

5. Relapse (or progression of cancer) - mostly precipitates depressive reactions, strong negative emotions or denial.

6. Further treatment - patients tend to be more alert, they are rather distrustful, they find it difficult to find new hope. Doctor must rebuild the relationship.

7. Transition to palliative treatment (progression to an incurable stage of cancer) - treatment goals have substantially changed, care is focused on the quality of life. As death approaches, topics of end and loss emerge more often and affect the behaviour, expectations and communication of patients, their family members, as well as doctors.

"A doctor is just a human"

Being an oncologist is a psychologically demanding but also very enriching profession. A doctor enters into a relationship with a patient, mainly in a professional manner, but also as an individual who has his own ideas, experience, emotions, social background, coping abilities, actual moods, etc. In order to create a supportive environment, it is necessary to build mutual trust and cultivate one's

own sense of humility, empathy, sensitivity and compassion. A doctor should not hesitate to acknowledge and respond to the emotional nature of certain situations. He should dismiss the idea of his own omnipotence, flawlessness, and accept his level of work-related performance. Otherwise, he will lose control over his own capabilities when confronted with a difficult situation and he will suffer from feelings of incompetence, decreased self-worth, and eventually, he will start to question his motivation to work. He might experience a burnout syndrome.

What Helps:

- effective time management, to define clear boundaries, accept personal and external limitations (a day is only 24 hours!)
- to define your own motivation to work and personal support systems
- to be aware of your own weaknesses – personal emotions, attitude to illness, death and dying, etc., if possible, to build self-acceptance through self-experience and personal development
- to realize what might potentially corrupt your relationship with patients – personal fears, sympathies or antipathy, insufficient communication skills; if possible, get a communication skills training
- to take advantage of team support – build supportive relationships, take opportunity of supervisions and other colleagues' assistance, etc.
- to use spare-time resources of support - relationships, social background, hobbies, etc.
- to recognize your abilities and weaknesses and to grow within these boundaries, to cultivate your self-confidence by appraisal of personal achievements at work. Instead of being discouraged by your mistakes, take them as a challenge and motivation for personal development.
- do not hesitate to contact a psychologist or other specialist to assist you, etc.

If a physician cares for his mental health, well-being and integrity, he will also be able to provide better care and support to his patients. He will have enough energy and mental and physical strength for his difficult work, he will be open and responsive to feedback, and he will have inner capacity to cope with stressful situations. By defining his own borders and by the acceptance of personal limitations, he can overcome a stressful event more easily and cultivate his professional self-confidence. This can be achieved by good communication with the patient, his family and between health-care team members.

How can a doctor assist a patient in coping with a stressful situation?

Five stages of coping with a terminal illness by Elizabeth Kübler Ross:

Ways of expressing patient's feelings and the most common questions he asks	**How to react in order to encourage patient's**

	coping
SHOCK AND DENIAL Shock is a common response to the disclosure of a cancer diagnosis that might result in patient's temporary inability to listen and concentrate. Denial might include a long-term rejection of the information, or tendency to address it with numbness and emotional detachment, as if it concerned someone else. "That is impossible, it has nothing to do with me, it must be a mistake." "But I still do not believe what the doctors have found ..." "There must be some hope for cure." "It's almost nothing. I just can not walk and I feel a little weaker, but that's going to be all right."	It is important to build relationship and trust that could facilitate further communication. Patients should be given time to process the information. Reiterating and checking patient's understanding is crucial at this stage. It is necessary to be prepared for various reactions, e.g. burst of inadequate emotions (laughter, raising of voice...), loss of orientation, speech impairments, etc. The doctor should remain calm, supportive, and he should not steer the conversation away or arouse false hopes.
ANGER AND AGGRESSION The patient acknowledges his diagnosis, but the information is in great conflict with his self-concept. This tension usually precipitates a vigorous emotional response, and the patient is angry at all possible causes of his or her illness, whether real or unreal. The intensity and character of response may range from affective reaction to an aggression against the others or oneself. The patient accuses doctors, God, proximate persons, he is angry with his family, complains, blames. "Why me? Who is to blame? Nothing was wrong with me until I've seen a doctor!" "What actually happened? How is it possible?" "Nurses do not care about me at all, they neglect their duties"	For a doctor, this stage might be very challenging - it is necessary to remain calm and balanced, stay within the limits of one's own competencies, maintain authority and, at the same time, keep patient's trust. A doctor should treat the patient professionally, he should not take his reactions personally, show disrespect or disapproval. Instead, he should comfort and reassure the patient that his emotions are natural in such a situation. The patient needs time and space to handle his emotions, express them, and if the environment and relationship with a physician is safe, then even release them and allow for a healing process. (The emotions often pass from one to another, crying to laughing, etc.).
BARGAINING, NEGOTIATION The patient is trying to invent other possibilities how to deal with the disease. He would give anything in exchange for escaping his fate. He is extremely vulnerable at this point, prone to believe in anything - superstitions, alternative healers, special diets, and miraculous drugs that supposedly helped someone. He collects all the available information, enquires about	This is the time when most patients discontinue or refuse the treatment, change doctors or healthcare services. The treating physician should not get offended or act offensively, but on the contrary, he should show understanding and be extremely patient and supportive, consolidate the relationship so that the patient could possibly resume the treatment. At the

alternatives, he bargains, changes doctors, medications, he offers money, etc. "Doctor, I think I should have my blood count checked once more." "Would you refer me for another CT scan?" "If I made a generous donation to the hospital, would you find some better drugs for me?"	same time, it is necessary for a doctor to withhold his attitudes and professional authority, because his self-confidence might also provide support and reassurance to the patient.
4. DEPRESSION, DESPAIR, SADNESS This period, which usually follows after a full recognition of an inevitable death, is associated with profound emotions that are adequate to this situation - despair, sadness, the awareness of loss, fear of future and the unknown, concerns about family members, their security, etc. The emotions are evoked by a real cause. Patients look back, they give up their expectations, succumb to apathy, give up fighting. Sometimes, they might ask for euthanasia. "I am going to die, why bother with anything." "I will never be able to walk again, it is not going to improve." "If they gave me some pill, there is no point to go on anyway."	At this point, relationships and social support play a crucial role. The patient becomes more depressive and apathetic, if he is left on his own. This is a chance to express our sympathies to the patient, attuned understanding and support. If possible, the doctor can help to resolve disturbed family bonds, or encourage the patient to build new relationships and assure him that when he will be dying, he will not be alone.
5.ACCEPTANCE,INTEGRATION, RECONCILIATION This is the stage of embracing the fact of death, acceptance of the inevitable change, reconciliation and integration. The patient stops to fight the situation, instead of refusing the death, he accepts it and starts to prepare for it. He feels the need to say goodbye, resolve and complete important unfinished arrangements. This stage might occur only shortly before the actual death or may cover a relatively long period, but there are also many patients who will never reach this level of coping. It is the ultimate issue of every person's life. "It is finished." "I'd like to get home for the last time." "It's a beautiful day out there." "I'd like to celebrate my last birthday, invite my relatives and order some sandwiches ..."	It should be an important goal of healthcare providers to help the patient to reach this level of understanding. Interpersonal proximity and compassionate support are important at this stage. Non-verbal contact and empathic approach are more influential than verbal communication. Doctor should encourage family involvement, offer help and support and reassure the patient that will can handle the situation.

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Communication with a cancer patient

J. Halámková

During the course of his work, basically every doctor happens to encounter a cancer patient and therefore he should not lack appropriate communication skills. Inadequate communication style may seriously harm the patient and cause a major breach of confidence in the doctor-patient relationship.

Malignant tumour is a life-threatening disease. In spite of the emergence of new drugs that increase the chances of cure and life prolongation, a cancer diagnosis still evokes fear, anxiety and uncertainty. Patients' hunger for information concerning their illness is increasing, and they approach their oncologists with a need for advice, as well as psychological support.

An effective communication:

- improves satisfaction and quality of life of the patient and his family
- facilitates patient’s coping with his disease and treatment
- strengthens patient’s motivation for treatment and his willingness to cooperate
- reduces the level of stress and decreases the risk of burnout syndrome in caregivers

Patients’ preferences for information are very individual, actually, a number of patients avoids being informed about their medical condition. Patient attitudes towards information may also change throughout the course of their illness. The extent to which an individual patient wants to be informed is difficult to estimate, therefore it is important for a clinician to communicate about patient’s preferences and ask how much information is acceptable for him.

Physician-patient communication is multidimensional and includes the actual message of a dialogue, emotional component, and non-verbal aspect. In oncology, communication skills are the key to a good rapport with a patient.

The doctor-patient relationship is based on mutual trust. The patient believes that the doctor will do his best to help him, and the doctor trusts that the patient will follow his recommendations. This relationship is extremely fragile and can be easily disturbed, even by an apparently insignificant communication error.

The patient expects his physician to have high professional competence, but also empathy. Only a combination of these two factors might result in patient’s trust and appreciation. A doctor who has the ability of empathy can acknowledge patient’s feelings and emotions and respond to his needs by adequate patient-tailored diagnostic and therapeutic procedures.

Communicating with the patient and the family is an essential medical skill. There is a rule of 5E that should be implemented in good communication:

- **E**ngaging the patient
- **E**liciting the patient's understanding
- **E**ducating the patient
- Addressing **E**motions
- **E**nlisting the collaboration of the patient and caregiver

At the **first consultation**, a doctor should ascertain how much the patient perceives his medical situation and create a picture of his information preferences (how much the patient wants to know about his illness). Accordingly, the physician should then tailor the information about the diagnosis and recommended treatment strategy to patient's individual needs. It is also necessary to address specific age-related differences among patients. **Elderly patients** have a poor ability of adaptation to a new situation, and unless there is a sufficient support from younger family members, this can have a major negative impact on further course of treatment. **Younger patients**, on the other hand, are often confronted with new socio-economic conditions. An economically active person loses his capacity to work or becomes fully disabled which might be associated with a substantial economic burden to his family. This is also a source of great uncertainty that the patient experiences both in relation to his illness and socio-economic status. The doctor should approach the patient with respect to all these circumstances.

The initial consultation plays an important role in building a trustful relationship between the doctor and the patient. The disclosure of cancer diagnosis should be sensitive and stepwise. Only an honest communication of the diagnosis will allow the patient to understand the situation and adapt to it. Overall, the question shifts from "whether to communicate the diagnosis" to "**how to communicate it"**.

The Convention on Human Rights and Biomedicine states that everyone has the right to information, as well as the right not to be informed against his will. Therefore, the patient should be asked at the beginning whether and how extensively he wants to be informed about his diagnosis.

In the Czech Republic, doctors have a **legal obligation to *adequately* inform the patient**, while the word "**adequately**" allows the doctor to tailor the information to a particular patient with regard to his specific needs. It is essential to inform the patient about the intent of treatment from the very beginning and if the disease is incurable, then honestly and emphatically discuss the prognosis and palliative treatment options. A patient who is not fully informed might have unrealistic expectations that can give rise to misunderstanding or conflicts with healthcare providers.

Ten principles of disclosing a cancer diagnosis

There are certain rules that might provide a useful **guidance for communicating cancer diagnosis:**

- Information about the character of the disease should be provided **to all patients** with cancer, however, the way of communication should be **differentiated** with regards to particular patient preferences.
- Important information is **always provided by a physician**. The patient should have an opportunity to choose persons who are present at the consultation (e.g. family members, friends, other physician, nurse, psychologist).
- **Reiterate** the diagnosis and important issues, it **is not enough to convey crucial information only once**. Always check whether the patient understands the message, encourage questions.
- Information should **be firstly given to the patient**, then to his or her family members or other designated persons. **The patient himself decides** who and to what extent to inform.
- The character of the disease and associated diagnostic and therapeutic procedures should be explained to the patient **prior to the start of treatment**. Offer treatment opportunities, but do not give false hopes.
- Answer patient's questions and respond to his concerns and feelings. **Take time,** take notice of patient's emotions and **discern his unspoken worries**.
- Information **about the prognosis** in terms of life-expectancy should be given with caution, **only upon patient's inquiry**. Avoid giving an exact date, rather, **set an approximate timeframe** based on your experience and general knowledge. Emphasize uncertainty and possible deviations from the usual course in both directions.
- Ensure **consistency of information** by efficient communication between involved healthcare providers (e.g. in medical and nursing documentation).
- Show your commitment **to guide the patient throughout his illness** and to deal with all the difficulties that the cancer and its treatment might bring.
- By your approach to the patient, help to maintain **realistic hopes** and expectations.

Breaking bad news is a frequent and important communication challenge for all physicians. Besides diagnosis disclosure and prognostication, the increasing number treatment options also raises the necessity to convey information about debilitating side effects of therapy, disease-associated complications and other unfavourable clinical information.

ABCDE of delivering bad news

- **Advance preparation** - prepare for patient's visit (go through his documentation).
- **Building therapeutic relationship** – establishing a rapport is crucial for an open dialogue
- **Communicating well** - assess what the patient already knows about his illness, to what level has he been informed so far, use non-technical language.

- **Dealing with reactions** – respond to patient's emotional reactions and provide realistic hope.
- **Encouraging** the patient (even supportive care is a treatment that will alleviate cancer-related symptoms, though it cannot cure the disease).

Internationally recognized guidelines for communicating unfavourable information include a six-step protocol known as **SPIKES** :

- **Settings** - ensure private atmosphere, manage time constraints, involve patient's family members in case he agrees with it.
- **Perception** – assess patient's perception, make sure he understands important issues concerning his illness, the purpose of examinations, etc.
- **Invitation** - ask the patient about the extent of information he patient wants to know, or whether he wants to know his prognosis.
- **Knowledge** - communicate the information in a simple language, check patient's understanding, give the patient time to process the information. It is advisable to prepare the patient that bad news is coming ("I'm sorry to tell you ...").
- **Emotions / Empathy** – respond to patient's emotions, provide compassionate support.
- **Summary / Strategy** – summarize the information provided, encourage and answer questions.

Besides the way of breaking bad news, it is necessary to take account of the atmosphere and the **context** of the **communication**. The doctor should have **enough time** to inform the patient and respect **patient's privacy**. It is also necessary to consider risks and benefits of disclosing a diagnosis individually in every patient. The doctor should be able to work with silence that can occur after the patient is confronted with bad news. *"Disclose the unfavourable information to the patient in a way you would like to be informed."*

Do not forget to involve **patient's family** in the discussion as well, however, provide all the information only with patient's consent. The doctor should also **involve family members in caregiving** and encourage their participation in home care. **Whenever** patient's expectations are not in accord with the current knowledge or are inadequate to his medical conditions, they need to be addressed and the discrepancies should be **properly explained**. Psychological processing and acceptance of an unfavourable information may take several weeks. Physician's professionality lies in his **patience and empathy**.

End-of-life communication

It is crucial to raise the issue of **palliative and hospice care** early in the course of patient's disease. It should be presented as an integral part of active and comprehensive oncological care, instead of a passive waiting for the end of life. Physicians are often reluctant to open the discussion about the

end-of-life care in patients with advanced disease. However, the avoidance of this issue is a fundamental mistake because it was proved to lead to reduced quality of life, mistrust and more anxiety among patients. If a doctor is able to motivate his patients to adopt an attitude: "The time left is short, but I can use it meaningfully," then he has done his job well.

For further information see the website of International Psycho-Oncology Society: https://docs.ipos-society.org/education/core_curriculum/en/Baile_comm/player.html)

or check online communication skill courses on http://vitaltalk.org/

Emergencies in oncology

M. Svoboda

Tumour lysis syndrome (TLS)

Introduction

Tumour lysis syndrome is a group of several metabolic disturbances caused by rapid release of intracellular substances from a tumour mass, usually as a result of its destruction by anticancer treatment. Less often, TLS might occur spontaneously due to high turnover of tumour cells. The syndrome is characterized by hyperphosphatemia, hyperuricemia, hyperkalaemia, hypocalcaemia (caused by its precipitation to calcium phosphate) and acute renal failure resulting from uric acid and/or calcium phosphate nephropathy.

Etiopathogenesis

In association with anticancer treatment, TLS is most commonly encountered in non-Hodgkin's lymphomas of high aggressivity (e.g. Burkitt lymphoma), acute lymphoblastic leukaemia and acute myeloid leukaemia, more rarely in medulloblastoma, small cell lung carcinoma and germ cell tumours. Spontaneous TLS is rare, mainly seen in patients with Burkitt lymphoma.

Besides tumour type, its extent, proliferation rate and chemosensitivity, other risk factors for TLS include: renal insufficiency, dehydration, renal infiltration by tumour cells, administration of nephrotoxic agents.

Clinical presentation

Clinically manifest TLS usually develops within the first two days, but most often within a few hours after the initiation of chemotherapy. Acute renal failure is manifested by decreased diuresis and hyperuricemia symptoms (nausea, vomiting, diarrhoea, weakness, altered mental status) and fluid overload (swelling, arterial hypertension). Acute hyperkalaemia and hypocalcaemia can lead to cardiac arrhythmias, which may even result in cardiac arrest. Hyperkalaemia might also cause paraesthesia, muscle weakness, paralysis and areflexia. Symptoms of hypocalcaemia include tetany manifested by paraesthesias, muscle cramps (Trousseau sign – hand pinched fingers), hyperreflexia (Chvostek's sign – facial muscles contract when tapping on n. facialis due to neural hyperexcitability).

Diagnostic procedures

Always consider TLS in differential diagnosis of oliguria following the administration of cytostatic treatment. Initial assessment should comprise blood chemistry tests including BUN, creatinine, Na,

Cl, K, Mg, total and ionized Ca, P, osmolality, uric acid, LFT and albumin. It is useful to rule out acid-base disorder by Astrup method from arterial blood. Complete blood count and coagulation should be check routinely, urine examination for pH and urate crystals is recommended as well. It is of note, that oncology patients are at risk of renal failure from other possible aetiologies such as postrenal urinary tract obstruction, pyelonephritis, hypercalcemia and nephrocalcinosis, drug-induced renal impairment. In the differential diagnosis it is particularly necessary to exclude urinary tract obstruction due to retroperitoneal tumour mass by ultrasonography examination, since the treatment of TLS is based on aggressive IV hydration (which could be harmful to a patient with postrenal obstruction).

Basic principles of prophylaxis and treatment of TLS

1. Sufficient hydration and diuresis monitoring: optimal fluid requirements are 3 l / m^2 / day (4-6 litres daily) in adults or 200 ml / kg daily in children weighting less than 10 kg.
2. Promotion of alkaline diuresis in order to prevent intra-tubular uric acid precipitation: this can be achieved by adding 50 to 100mmol of sodium bicarbonate to each litre of IV saline.
3. Control of hyperuricemia: administration of allopurinol (i.e. a xanthine oxidase inhibitor) or rasburicase (urate oxidase that metabolizes uric acid to allantoin). Haemodialysis might be an alternative.
4. Treatment of hyperphosphatemia: intestinal phosphate reabsorption can be decreased by administration of an aluminium-containing antacid (e.g., 15ml of Maalox every 3 hours). Continuous haemodialysis might be more effective, since it can reduce the levels of serum phosphate by 10g/day. In TLS, the increase of serum phosphate levels ranges from 2 to 7g per day.
5. Treatment of hyperkalaemia: severe or clinically manifested hyperkalaemia requires prompt correction due to ensuing risk of malignant arrhythmia. This is done by a) intracellular transfer of potassium (IV glucose with insulin, beta-agonists), b) membrane stabilisation (calcium gluconate), c) reduction of potassium load (ion resonium, furosemide, haemodialysis) and dietary restrictions
6. Frequent monitoring of clinical status and electrolytes.
7. Preventing (reducing) the administration of nephrotoxic drugs.

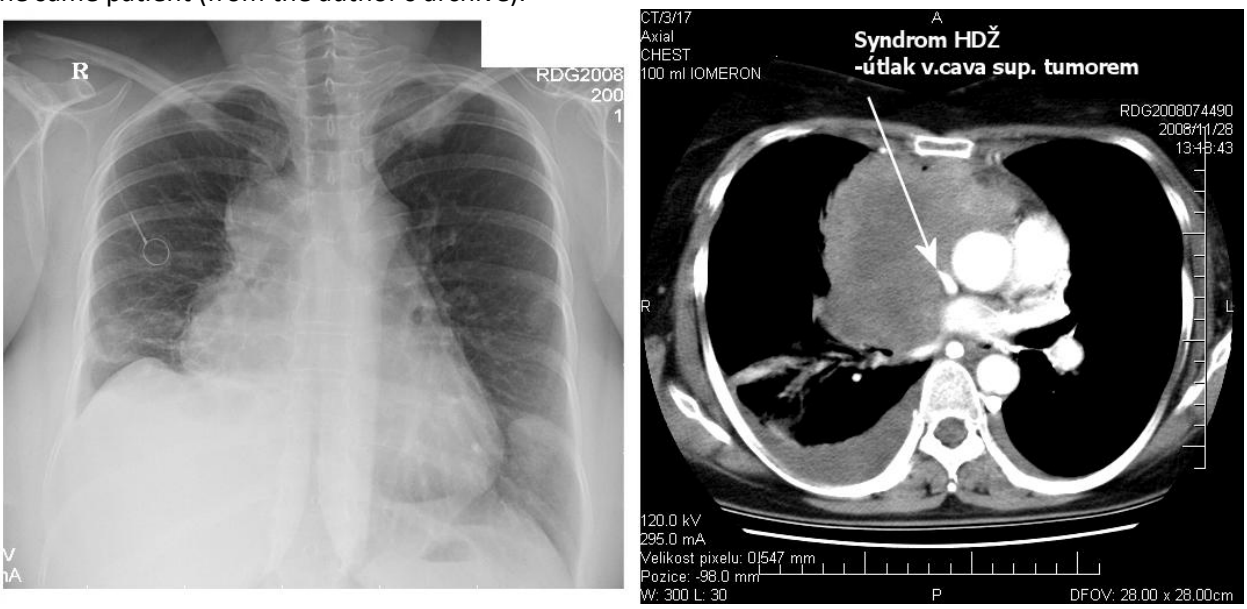
Superior vena cava syndrome

Introduction

Superior vena cava syndrome (SVCS) is a group of symptoms caused by partial or complete obstruction of blood flow through the superior vena cava into the right ventricle *(Figure 1)*. The obstruction may occur due to external compression, tumour mass, thrombosis, or fibrotic changes to

SVC. Bronchogenic carcinoma (especially small cell type) and non-Hodgkin lymphomas belong to the most common culprits of SVCS in adult patients.

Figure 1: Superior vena cava syndrome – The AP chest X-ray shows enlarged mediastinum, the CT image shows the underlying anatomy and the site of vein suppression site. The pictures come from the same patient (from the author's archive).



Clinical presentation

When SVC becomes obstructed, blood flows to the heart through the collateral veins, especially the azygos, intercostal veins and inferior vena cava. Sudden and complete SVC obstruction leads to a substantial elevation of upper body venous pressure, which might result in cerebral oedema, thrombosis or fatal intracranial bleeding. However, these life-threatening complications are rather rare, since the development of SVCS and the onset of associated symptoms is usually gradual and takes several weeks. Most commonly, it is manifested by facial oedema, headache, visual disturbances (due to optic nerve oedema), cough, hoarseness, shortness of breath, chest pain, dysphagia, lethargy, convulsions or impaired consciousness (e.g. syncope). Predominant symptoms of SVCS include oedema of head, eyelids, tongue, neck, upper torso and arms. There are markedly dilated veins on the neck and chest, and can be expressed unilaterally. Cyanosis and plethora may be present. Typically, symptoms are more pronounced when the upper torso is below the heart level.

Diagnostics

Due to relatively low sensitivity of conventional chest X-ray (false negative in 3-16 % of cases) it is recommended to perform a CT scan that might determine the underlying obstruction, including tumour size, its location and relationship to other mediastinal structures. CT scan might also be used to detect associated thrombosis, airway obstruction or pericardial effusion. In the case that the

underlying cancer has not been histologically verified yet, CT scan might also provide information on the possibilities of diagnostic biopsy.

Therapy

A patient with SVCS should be elevated to an upright position; supplemental oxygen might provide a relief from respiratory symptoms. In case of airway obstruction and/or signs of increased intracranial pressure, corticosteroids (e.g. dexamethasone, methylprednisolone) are indicated. Corticosteroids help to mitigate the inflammatory response that occurs in the tumour and adjacent tissues and have an antioedema effect. Diuretics might help to reduce congestion and laryngeal oedema, though their efficacy is often disputed.

Up to 50 % of patients with SVCS are diagnosed with concurrent partial venous thrombosis. The anticoagulation therapy should be used with caution due to an increased risk of intracranial haemorrhage. Prophylactic administration of low molecular weight heparin may be considered in patients without any evidence of thrombosis.

Causal treatment of SVCS strongly depends on the chemo- and radiosensitivity of the underlying malignancy. For chemosensitive tumours, which account for up to two thirds of cases of SCVS in adults (e.g. lymphomas, small cell lung carcinoma, germ cell tumours), chemotherapy is the treatment of choice. In particular patients, it can be combined with targeted treatment or radiotherapy as well. Emergency radiotherapy is indicated in patients: (a) already pretreated with chemotherapy, whether they are afflicted by an early relapse or a progressive disease; b) in chemoresistant disease; (c) supposing we are unable to provide a biopsy or histological verification of an otherwise undisputable malignancy; d) in case there is a need for urgent improvement of symptoms.

Radiotherapy and chemotherapy can improve symptoms associated with SVCS within 1-3 weeks after treatment initiation. In case of emergency, or if anticancer treatment cannot be initiated, endovascular stenting might be performed. In chemo- and radiosensitive malignancies, the prognosis of a patient with SVCS is rather poor.

Upper respiratory tract obstruction

Introduction

Upper respiratory tract is the most common site of airway obstruction. Besides tumour, the most common causes include foreign body inhalation, laryngeal oedema in allergic reaction, postoperative or radiation- induced stenosis, or an infection. The most common tumours in aetiology of airway obstruction are head and neck tumours, thyroid, lung, breast and oesophageal cancer, mediastinal

lymphomas, germ cell tumours and metastatic malignant melanoma. Specifically, airway obstruction might occur in carcinoid syndrome as a result of bronchospasm.

Clinical features

The first symptom that occurs due to reduced airway lumen is dyspnoea on exertion, which is usually progressive and accompanied by stridor if the lumen is ≤ 5mm in diameter. The other symptoms include tachycardia, orthopnoea and accessory respiratory muscle use. An acute obstruction is manifested by severe respiratory distress, cyanosis and bradycardia. It may result in death within several minutes. To detect the site of obstruction, we usually perform an endoscopic examination (either laryngoscopy or bronchoscopy) or a CT scan (especially for subglottic assessment).

Therapy

The symptomatic therapy includes intravenous administration of corticosteroids (eg dexamethasone 8 mg i. v.), and bronchodilator (e.g. syntophyllin 240 mg / 250 ml saline infused over 30 to 45 minutes, every 6 hours, max. daily dose is 1500 mg), and oxygen inhalation (4 or more litres / minute). Maintenance of airway patency depends on the site of obstruction. Supraglottic and laryngeal obstruction is managed by surgical tracheostomy; in acute setting, we attempt to intubate the patient to or to perform an awake tracheotomy or coniotomy. Tracheal obstruction can be managed by endoscopic balloon dilation, tracheobronchial stenting or by bronchoscopic laser therapy.

Massive haemoptysis

Introduction

Haemoptysis, or expectoration of blood from lower respiratory tract, might be of capillary, venous or arterial origin. The term massive haemoptysis is reserved for cases when blood volumes exceed 100ml per episode or 600ml over a 24 hour period. Massive haemoptysis is a life-threatening emergency due to potential airway obstruction and haemodynamic instability (manifested by hypotension and tachycardia). In one third of all cases, it results in immediate death. The main cause of death is suffocation and its risk increases with the volume of blood expectorated.

The most common cause of haemoptysis in the oncology setting is a tumour, bronchitis, pneumonia and bleeding disorders. Among malignancies, the highest risk of massive haemoptysis is associated with bronchogenic carcinoma, especially small cell lung cancer and accounts for 3% of deaths in these patients. However, bleeding is also a common complication of metastatic lung involvement, especially in malignant melanoma, breast and kidney cancer primaries. Bleeding might also occur due to contiguous spread of oesophageal carcinoma into trachea. Infections (especially mycotic) and

bleeding disorders are a common cause of haemorrhage mainly in hematooncology patients after marrow transplantation. In addition, lung damage caused by radiotherapy or cytostatic might be manifested by haemoptysis.

It is crucial to differentiate haemoptysis from expectoration of blood from sources other than lower respiratory tract (e.g. bleeding from upper airway, hematemesis aspirated to lungs, etc.)

Therapy

In patients with massive hematemesis that leads to hemodynamic instability, severe hypoxemia and respiratory distress, the priority is to maintain airway, stabilize hemodynamic status and avoid haemorrhagic shock. If possible, we perform bronchoscopy prior to intubation, in order to identify the cause of bleeding. In the case of moderate bleeding, bronchoscopy might not only localize the source of bleeding but also provide an immediate control of the airway by: a) topical haemostatic and vasoconstrictive agents (thrombin, fibrinogen-thrombin, adrenalin, dicynone, cooled saline rinse) b) coagulation by laser or diathermy c) or temporary endobronchial balloon tamponade. If endobronchial therapy fails to control the bleeding, angiography and embolization should be considered. Recurrent massive haemoptysis warrants emergent surgical intervention including partial or complete pulmonary lobectomy if necessary. Palliative radiotherapy of the bleeding site is an alternative in mild haemoptysis. The haemostyptic effect of radiotherapy lies in the induction of vascular thrombosis or necrosis in the irradiated field. Conservative treatment of haemoptysis consists of systemic administration of haemostyptics - etamsylate, terlipresin, antifibrinolytics (see chapter: "Acute gastrointestinal haemorrhage").

Acute gastrointestinal haemorrhage

Introduction

Gastrointestinal bleeding should always be considered a life-threatening condition in a cancer patient. The most common source of bleeding is a vessels disrupted by tumour or oesophageal and gastric varices that developed due to portal hypertension in massive metastatic liver involvement. In addition, liver metastases in combination with poor nutritional status of an oncology patient often leads to bleeding disorders due to coagulation factors depletion.

Clinical picture and diagnostics

Depending on the source of bleeding, we speak of **upper gastrointestinal haemorrhage** (from the oesophagus, stomach or duodenum) which is most commonly manifested by hematemesis and / or melena, if the volume of blood that passes further to digestive tract reaches at least 100ml. Melena occurs approximately 12 to 40 hours after the onset of bleeding. In case of massive upper

gastrointestinal bleeding, the transit of stool is very rapid and manifests as haematochezia. **Lower gastrointestinal bleeding** refers to bleeding from colon and small intestine. Most commonly, it presents with haematochezia, though melena may also occur in particular cases. In contrast to upper GI bleeding, in 80% of cases, it stops spontaneously and the mortality rate is low.

The initial diagnostic approach to a patient with GI bleeding should include a thorough medical history (especially pharmacological), physical examination and laboratory tests that help to assess the severity of bleeding and the level of blood loss (see the algorithm below). In differential diagnosis, it is necessary to exclude bleeding from respiratory tract (epistaxis, bleeding from lower airways), which may be manifested by haemoptysis, vomiting of swallowed blood or melena. Blueberries, blood sausages, and particular medications (e.g. activated charcoal, iron supplements) can make stool appear black and mimic melena. When evaluating laboratory findings, it is important to realize that the decrease in haematocrit occurs after a minimum of 24 hours after the onset of bleeding. The source of bleeding can be best identified by endoscopy. Angiography or scintigraphy using technetium-labelled erythrocytes might be helpful, especially in case of obscure bleeding at rate of at least 0.5 ml/min. An alternative diagnostic method in suspected occult bleeding or bleeding from small intestine is a capsule endoscopy.

Therapy

The principles of treatment of acute bleeding are the same for both upper and lower digestive tract. The algorithm includes general supportive measures to maintain patient's vital signs. Local endoscopic treatment can be attempted after the initial hemodynamic stabilization, in case of upper GI bleeding usually within 24 hours. Colonoscopy in lower GI bleeding is rarely performed urgently, since it requires preparative bowel cleansing prior to the procedure. Only rectoscopy and sigmoidoscopy can be performed in an urgent setting using enema preparation.

In patients with suspected GI bleeding, the therapeutic approach includes:

1. General management

1. The patient should be admitted to the intensive care unit in a health care facility providing emergent surgical procedures.
2. Perform urgent blood typing. Ensure at least 2 to 4 blood transfusions ready for immediate administration. If the blood group is unknown, the patient might receive 0 negative red blood cell concentrate. It is important to remember that even a small initial bleeding may get complicated at any time.
3. Laboratory tests should include full blood count, coagulation parameters (INR, aPTT, fibrinogen, antithrombin III), serum chemistry (urea, creatinine, ions, liver tests, total protein, albumin, glycaemia, CRP).

4. Obtain central venous access (e.g. by cannulation of subclavian, femoral or jugular vein) for possible fluid resuscitation or temporary support with vasopressors.
5. Patient should be restricted from eating or drinking.

2. Systemic therapy

a) vasoactive medication. The administration of vasoconstrictive agents such as terlipresin (Remestyp - an analogue of vasopressin), or agents reducing splanchnic perfusion (e.g. somatostatin analogue - Octreotide) are the most common drugs to improve haemostasis. Terlipresin is administered at a dose of 5 to 20μg/kg of body weight in an IV infusion over 20-40 minutes every 6 (4 to 8) hours. During the treatment, blood pressure, heart rate and fluid balance should be closely monitored. High-risk patients with hypertension, heart disease and elderly patients might require dosage reduction. In patients with suspected variceal bleeding, somatostatin can be administered by continuous IV infusion (6 mg / 24 hours at a rate of 250 μg / hour), following an initial bolus of 3.5 micrograms/kg (i.e. one 250μl vial for a patient weighting 75kg). During the treatment, regular monitoring of blood glucose is necessary.

Other haemostatic drugs include **anticoagulants**, **antiplatelet agents** such as etamylate (Dicynone) and **antifibrinolytic agents** such as aminomethylbenzoic acid (Pamba). Dicynone is given as an initial IV bolus of 500mg/20ml of saline or undiluted as an intramuscular injection, followed by an infusion of 250mg every 4-6 hours until the cessation of bleeding. Pamba is given in acute fibrinolytic bleeding at a dose 50-100mg IV (in 20 to 100ml of saline as a slow bolus or infusion) or 100mg IM. Pamba can also be given as a continuous IV infusion at a rate of 100 mg/hr. In case of massive bleeding and / or coagulopathy, transfusion of FFP or prothrombin complex concentrate is required.

b) Fluid resuscitation. If the blood loss accounts for more than 30% of the circulating volume (up to 1500 ml blood), an adequate IV fluid administration of colloidal volume expanders is necessary, e.g. hydroxyethyl starch (duration of action is approximately 3-4 hours), 6% dextran (Dextran, Rheodextran, 6-8 hours), or polygels (Haemaccel). Hydroxyethyl starch (e.g., HAES-Steril 10 % 500ml) is infused over 1-2 hours at a maximum daily dose of 20 ml/kg (i.e. 1500 ml/75 kg). The first 10-20 ml should be applied very slowly due to an increased risk of anaphylactic reaction. The patient might also be given crystalloids (e.g. Ringer, saline, Plasmalyte). If the blood loss exceeds 35 % of the circulating blood volume it is recommended to initiate blood transfusions. One unit of FFP and 10ml of 10% calcium gluconate should be administered with every 2-3 units of packed red blood cells (because blood transfusions contain calcium-binding citrate that might impair coagulation parameters).

(c) Proton pump inhibitors. For haemorrhages due to gastric ulcer, it is recommended to give drugs that inhibit gastric acid secretion, such as omeprazole (at an initial dose of 80 mg in 100-250 ml of saline over 20 minutes, followed by an infusion of 8mg / kg / h over 48hours).

3. Local treatment

a) In a hemodynamically stable patient, we perform an **urgent endoscopy** as a diagnostic and therapeutic method. Bleeding can be controlled by: (i) injections of vasoconstrictors (epinephrine) or sclerosants (polidocanol, 98% alcohol) or fibrin glues (N-butyl-2-cyanoacrylate, fibrin adhesives); ii) application of clips or ligation; iii) heat probe coagulation, argon plasma coagulation or bipolar electrocoagulation. Injections should be repeated in 4 - 6 days and then after 7 - 14 days, since only a limited amount of the substance can be applied at a time (due to the risk of tissue necrosis). Endoscopy is the method of choice in upper GI bleeding. If the endoscopic intervention is unavailable, we can place a **Sengstaken-Blackmore tube**. In lower GI bleeding, we perform colonoscopy after patient stabilization and proper bowel preparation. This does not apply to sigmoidoscopy and endoscopic rectal examination.

b) If medical therapy and endoscopic intervention is not successful (or unavailable) and surgery is contraindicated, **arterial embolization** may provide a safe control of upper GI bleeding. The efficacy of procedure is decreasing in lower digestive tract because of numerous collateral circulations in splanchnic vascular bed. Moreover, it might be associated with higher risk of impaired vascular supply to other intraabdominal organs.

c) Surgical treatment. If the conservative and local therapy fail to control the bleeding and the patient is at risk of developing a haemorrhagic shock (if the transfusion volume exceeds 2liters of blood / 24 hours), we should pursue with surgical intervention - most commonly a resection of the affected part of the digestive tract (e.g. partial or total gastrectomy, hemicolectomy). Variceal bleeding can also be managed by spleno-caval shunts for decompression of portal hypertension. This is achieved by an interventional radiology procedure known as **TIPS** (trans-jugular intrahepatic portosystemic shunt), which establishes a communication between portal and hepatic veins using an implantable metallic stent. Prior to both surgical and radiology interventions, the risk associated with continued bleeding should be weighed against patient's prognosis and quality of life.

4. Supportive treatment

Supportive treatment depends on the severity of the bleeding, associated complications and patient's comorbidities. Most commonly, it encompasses parenteral nutrition and the use of vasopressors (e.g. dopamine 10-30-60 mg / hr). Supportive treatment also includes supplemental oxygen (4-6l / min), pain and anxiety management. For pain relief, we can administer tramadol

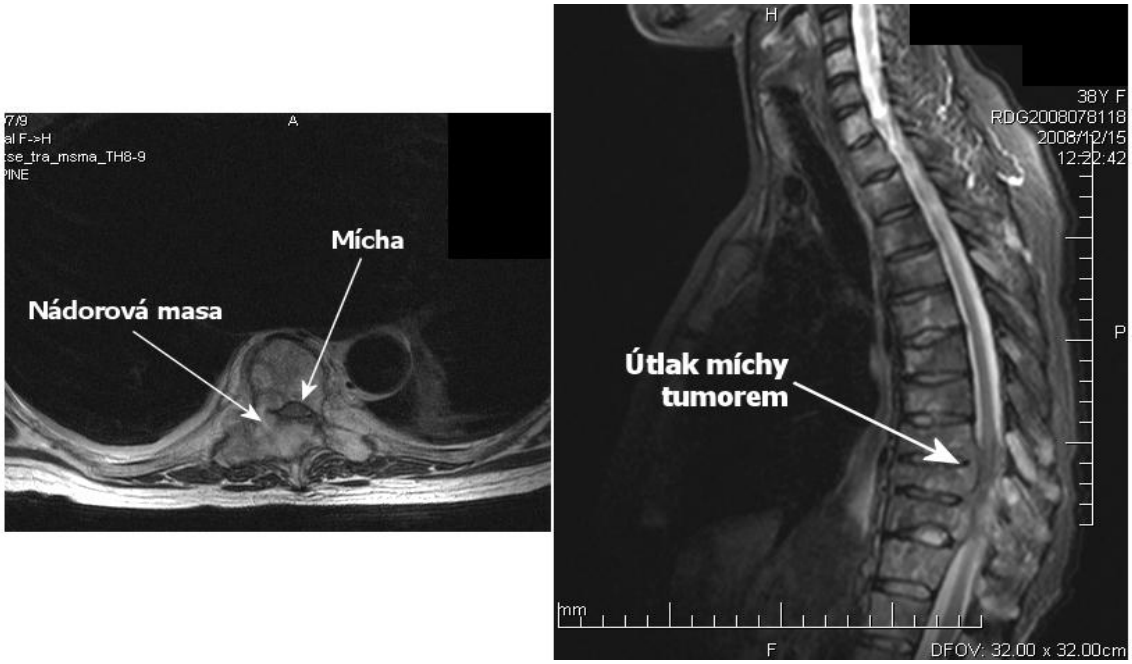
(Tramal) 100 mg / 20 ml IV bolus every 4 hours to a maximum dose of 600 mg per day, or pethidine (Dolsin) at a single dose of 25-50mg IM or SC tid. NSAIDs are contraindicated because they might increase the risk of ulcer haemorrhage. Recommended anxiolytic drugs include short-acting agents (e.g. midazolam / Dormicum 2-2.5mg IV at a rate of 1 mg/30 seconds) or long-acting drugs (e.g. diazepam / Apaurin 5-10mg IV over 10-20min). In patients with hepatic impairment, prokinetics and lactulose administration might help to increase bowel transit time and prevent the development of liver encephalopathy.

Malignant spinal cord compression

Introduction

Spinal cord compression (SCC) is a medical emergency that requires immediate intervention if irreversible neurologic damage is to be prevented. SCC occurs in approximately 5-10% of the oncology population and in 95 % of cases it is caused by a metastatic tumour or contiguous tumour spread. Only a small proportion of SCC is attributable to primary tumours of the spinal cord and spinal column. The most common site of SCC is the thoracic spine (70 %), since the spinal canal in this part is the narrowest. Back pain is often the first and the most common presentation of spinal cord compression. It can be localized or radicular and usually precedes other symptoms by several months. Motor weakness and sensory dysfunction in a corresponding dermatome are typical neurological symptoms in case of advancing SCC. Autonomic nervous system disorder might be manifested by constipation or urinary retention. Physical examination findings include decreased peristalsis, perianal numbness and poor anal sphincter tone, urinary bladder might be palpable through the abdominal wall. Sphincter disorders are often indicators of an advanced irreversible SCC. Neurological examination is a key part of the initial assessment of a patient with suspected SCC, since it may provide a clue to the location of spinal cord injury. Imaging studies include an X-ray examination of the spine in both projections, as most patients with spinal cord syndrome have apparent pathological fractures and osteolytic metastases of spinal column. However, the investigation of choice is an urgent MRI, which can also show paravertebral masses or intramedullary tumours. (Figure 2)

Fig. 2: Malignant spinal cord compression



Therapy

The main goals of SCC treatment are pain relief and restoration of neurologic function, in particular cases, we focus on local tumour control or spinal column stabilization. Antioedema treatment with corticosteroids should be started immediately. Dexamethasone is the most commonly used agent due to its long half-life (36 hours) and minimal mineralocorticoid effect. There is no agreement on the optimal dosage, usually, 8 to 16 mg of dexamethasone are administered every 8 hours and tapered gradually after the improvement of symptoms.

If a radiosensitive cancer is the cause of SCC, causal therapy by irradiation should be initiated in patients with stable spinal column. However, if the underlying tumour is of unknown origin or in patients with spinal column instability, spinal decompression surgery may be indicated as the primary treatment. Surgery is not performed in patients with poor prognosis or massive metastatic spinal column involvement. Irradiation with concurrent chemotherapy may be used in patients with chemosensitive cancer. Stand-alone administration of cytostatic agents is indicated when radiotherapy or surgical treatment is not feasible.

Intracranial hypertension syndrome

Introduction

In oncology setting, intracranial hypertension usually occurs as a result of elevated intracranial pressure due to primary CNS tumours or metastatic brain involvement. Other causes may include

benign expansions such as hematoma due to subarachnoid haemorrhage or cerebrospinal fluid circulatory disorders resulting in hydrocephalus.

Clinical presentation and diagnosis

Intracranial hypertension syndrome (IHS) is manifested by altered level of consciousness, headache, nausea and vomiting, nystagmus, diplopia and seizures. The most serious complication of IHS is uncial herniation in which temporal portion of brain tissue is pushed below the tentorium, causing compression of the brain stem. It is manifested by unconsciousness, systemic hypertension and bradycardia. If IHS is suspected, an emergent CT scan without contrast enhancement is indicated for diagnosing the underlying cause. If acute haemorrhage is ruled out, contrast-enhanced CT examination may be obtained. Brain MRI is used only in stable patients because of its time-consuming character.

Therapy

If IHS is diagnosed, antioedema therapy with mannitol and corticosteroids should be started immediately. Mannitol is given in an IV bolus or rapid infusion every 6-8 hours, during the first 3-5 days. The immediate effect of mannitol can be seen within minutes after the administration, however, the duration of action is usually short. Administration of corticosteroids may be long-term, dexamethasone being the drug of choice, given at a dose of 8mg every 8hours. If symptoms resolve, the dose of dexamethasone is reduced to 4 mg and then gradually tapered with respect to patient's neurological status. The effect of corticoids occurs within several hours after the initiation of treatment and the duration of action depends on the half-life of a particular corticosteroid drug (e.g. 36 hours in the case of dexamethasone).

Status epilepticus

Introduction

The International Classification of Epileptic Seizures defines status epilepticus (SE) as a single seizure lasting more than 30 minutes or series of seizures between which consciousness is not regained in a 30-minute period. Basically all types of epileptic seizures (convulsive and non-convulsive) may advance to SE. In oncology setting, the most common cause of epilepsy is a primary or a secondary brain tumour. Malignancies most likely to spread to brain are lung, breast, prostate, kidney cancer and melanoma. Other conditions that may precipitate SE are electrolyte disturbances, CNS infections or drug-induced seizures.

Therapy

The primary goal of treatment is to ensure sufficient cerebral perfusion, prevent hypoxia, terminate the seizure activity as soon as possible and to prevent systemic complications and metabolic acidosis. Detection and management of the underlying cause is crucial for management of SE. The initial workup should include laboratory tests to rule out hypoglycaemia and electrolyte abnormalities. It is important to find out, whether the patient has a medical history of epilepsy or metastatic brain involvement. In any case, prompt administration of anticonvulsants is indicated, usually a short-acting benzodiazepine (e.g. Diazepam 5-10mg diluted to 20ml 5% glucose in a slow IV injection) followed by general measures to maintain vital signs (airway, breathing and circulation). In patients with brain tumours, we pursue with the administration of antioedema therapy (mannitol and corticosteroids). In patients with a previous history of epilepsy, we check the levels of chronically administered anticonvulsants, empirically apply antioedema treatment and after stabilizing then patient we perform a CT or MRI brain examination. In epileptic seizures resistant to anticonvulsant therapy, general analgosedation and intubation of the patient is indicated.

Hypercalcaemia

Introduction

Calcium absorption takes place in the small intestine, whereas 98% of total body calcium is stored in bones. The excretion is provided by the kidneys. There are three hormones primarily involved in the regulation of calcium metabolism: parathormone (PTH), 1,25-dihydroxycholecalciferol (calcitriol) and calcitonin. Normal levels of plasma calcium range from 2.2 to 2.6 mmol/l. Hypercalcaemia refers to a situation when the total serum calcium concentration is higher than 2.63 mmol/l or ionized (free) calcium levels exceed 1.2 mmol/l.

Pathophysiology of hypercalcaemia

Malignancy associated hypercalcemia may be caused by two basic mechanisms: a) increased osteoclastic activity and bone resorption due to skeletal metastases, and b) humoral hypercalcaemia resulting from autocrine secretion of hormones and cytokines involved in the regulation of calcium homeostasis, most commonly PTHrP (parathyroid hormone-related peptide), PTH and calcitriol.

Clinical presentation

Hypercalcaemia is usually clinically manifested when plasma calcium levels exceed 3.0 mmol/l. Severity of symptoms depend on how rapidly the rise occurred. Patients may present with nausea, vomiting, altered mental status (such as lethargy, confusion, bradypsychism), muscle weakness, polyuria, headache, back pain (in the kidneys), abdominal cramps and constipation. Hypertension

may also occur. In severe cases, (calcium concentration ≥3.5 mmol/l) there is a risk of cardiac arrhythmia and coma.

Therapy

Treatment of hypercalcaemia depends on the patient's overall status and the severity of hypercalcemia. Patients with mild symptoms and serum calcium levels below 3.0mmol/l can be managed in an outpatient setting. Treatment of symptomatic hypercalcaemia is based on volume repletion, we usually give 4 to 6 litres of crystalloids within 24 hours. Due to the high volume of fluids administered, it is often necessary to monitor fluid balance. Simultaneous administration of loop diuretics (e.g. furosemide 20 - 40 mg) blocks renal calcium reabsorption and prevents hypervolemia. We do not give thiazide diuretics, which may increase calcium levels. Prevention of fluid overload is particularly important in the elderly and patients with cardiac dysfunction. Haemodialysis is indicated in patients with refractory hypercalcemia higher than 4.5 mmol/l or in patients with severe heart or renal disease. After correction of plasma calcium levels and volume repletion, we pursue with treatment focused on the underlying causes of hypercalcaemia. In the case of paraneoplastic hypercalcaemia, we administer drugs that inhibit osteoclastic activity (e.g. bisphosphonates, zolendronic acid, ibandronate or monoclonal antibody denosumab). Anticancer therapy might also provide an effective control of the underlying cause of hypercalcemia.

Myelosuppression and febrile neutropenia

Introduction

Neutropenia is a serious and often a dose-limiting side effect of systemic anticancer treatment. Complications resulting from neutropenia are associated with an increase in morbidity and mortality rates and may adversely affect the overall outcome of potentially curative anticancer treatment. In addition, their management also imposes a significant financial burden on healthcare resources. The most common myelosuppression-related complications include i) febrile neutropenia (FN) and ii) reduction of the relative dose intensity (RDI) of chemotherapy. Febrile neutropenia is an emergency requiring a prompt and adequate management. It may be prevented by the use of growth factors (G-CSF) and other primary and secondary preventative measures.

I. Definitions

Febrile neutropenia is defined as a fever above 38°C for at least one hour (or a single peak of temperature above 38.3°C) with a neutrophil count of less than (or expected to fall bellow 0.5 x 10*9/l). Due to widespread use of antipyretics among oncology patients and the inability to

accurately predict the course of neutrophil count, a clinically accepted definition of febrile neutropenia **is a fever of 38°C or higher with a neutrophil count <1.0 × 10*9/l.**

According to WHO, **four degrees of neutropenia** are distinguished**:**

G1 - neutrophils in the range of 1.5-1.9 × 109 / l
G2 - neutrophils in the range of 1.0-1.5 × 109 / l
G3 - neutrophils in the range of 0.5-1.0 × 109 / l
G4 - neutrophils in the range of <0.5 × 109 / l

Febrile neutropenia is an emergency requiring a prompt and adequate management because, although patients may not initially present with clinical signs of infection, they are at high risk of developing a life-threatening sepsis. Mortality rate of patients with febrile neutropenia ranges from 2 to 37%. The highest mortality is among haemato-oncology patients and high-risk patients with multiple comorbidities. In low-risk patients (see below) with solid tumours, mortality rate of febrile neutropenia does not exceed 4%.

II. Incidence and risk factors

The risk of FN is usually highest during **the first two cycles of chemotherapy** (up to 74% episodes). Since the nadir of neutropenia occurs **most frequently 7-14 days after the last dose of chemotherapy**, febrile neutropenia often develops in an outpatient setting. Patient education about the risk and symptoms of FN and possible preventative measures should be communicated prior to any anticancer treatment, with high risk of serious myelosuppression. Besides the character and intensity of chemotherapy itself, there are several other factors that might increase the risk of FN.

Risk factors for febrile neutropenia:

(a) related to anticancer treatment:

- myelotoxic chemotherapy regimens that are known to be associated with FN incidence ≥ 20%
- myelotoxic chemotherapy regimens associated with neutropenia nadir <0.5 × 10*9/l or duration of G4 neutropenia > 5 days (probability of fever increases by 10% each day when the neutrophil count is <0.5×10*9/l)
- concomitant radiotherapy
- chemotherapy associated with significant mucosal and skin toxicity

b) patient-related conditions:

- presence of two or more serious comorbidities such as COPD, diabetes mellitus, cardiovascular disease, poor nutritional status, poor renal function (GFR <30 ml / s), primary immunodeficiency

- presence of indwelling catheters, mucositis
- bone marrow infiltration or previous radiotherapy of a large portion of the axial skeleton
- age ≥65 years or poor performance status
- advanced disease
- sepsis or serious infection in the last 4 weeks
- history of prior FN
- poor compliance

III. Initial assessment

The initial assessment of a patient with febrile neutropenia should include the following investigations:

a) **Physical examination** including careful assessment of potential infectious foci (oropharynx, lower respiratory tract), state of hydration, skin examination for abrasions, open wounds or bleeding manifestations, evaluation of haemodynamic status, mental status assessment, etc.
b) **Assessment of vital signs:** pulse, blood pressure, temperature, oxygen saturation and respiratory rate
c) **Laboratory investigations**: CBC, blood chemistry (urea, creatinine, electrolytes, LFT, CRP, glomerular filtration rate, albumin, total protein, coagulation parameters (INR, aPTT, fibrinogen), urinalysis.
d) **Imaging methods**: always perform plain chest radiograph and abdominal ultrasound. Further investigations depend on specific clinical and laboratory signs of infection (e.g. echocardiography, BAL, CT scan, etc.).
e) **Microbiological examinations**: an essential part of the initial diagnostic workup includes **blood cultures** from peripheral vein or indwelling catheters. It is recommended to take extra blood cultures during an episode of fever or chills. Besides blood cultures, routine investigations include throat swab test, urine and wound cultures (including surface swabs from catheters and drains). Other tests should be performed based on specific clinical symptoms (sputum or stool cultures, CSF examination, etc.).

IV. Treatment of patients with febrile neutropenia

The management of FN is determined by patient's risk of serious medical complications. Based on specific criteria, patients can be stratified into "low-risk" and "high-risk" categories. High-risk patients are further divided into hemodynamically stable patients and patients with symptoms of sepsis or SIRS. They should be admitted to a standard ward (stabilized patient) or ICU for close monitoring of vital signs. Compliant low-risk patients can be managed in outpatient setting, supposing that immediate transfer to hospital is available in case of complications.

Factors associated with high-risk of complications:

a) related to anticancer treatment:

- prolonged (> 10 days) neutropenia <0.5 × 10*9/l
- neutropenia <0.1 × 10*9/l
- decrease in CD4 + lymphocytes <0.2 × 10*9/l (risk of pneumocystic pneumonia)

b) Patient- related risk factors:

- two or more serious medical comorbidities (COPD, diabetes mellitus, poor nutritional status, anaemia, poor performance status, primary immune deficiency)
- age > 65 years
- history of prior FN
- presence of open wound, indwelling catheters and / or signs of acute infection
- severe damage to mucosal barriers
- poor patient compliance
- renal or hepatic insufficiency
- haemodynamic instability
- bleeding, DIC

Empirical antibiotic therapy

Initial empirical therapy should encompass a broad-spectrum antibiotic with antipseudomonal activity covering both Gram-positive and Gram-negative pathogens. Approximately 60-70% of infections in FN patients are caused by Gram-positive bacteria, 15% are polymicrobial and 5% are mycotic. The most common bacteria associated with infections in FN are *Staphylococcus aureus* and *Streptococcus viridans and pneumoniae*. From Gram-negative pathogens, it is mostly *Pseudomonas aeruginosa* and *Klebsiella* spp. However, the prevalence of infectious agents may vary between populations and geography areas. Therefore, every hospital should have regularly updated local epidemiological microbial isolate and resistance patterns of bacterial pathogens prevalent at given healthcare facility and patient population. Local epidemiological information may be valuable especially in determining empirical antibiotic therapy in high-risk patients or in patients unresponsive to initial antimicrobial treatment. Treatment with carbapenems should be reserved for ESBL positive microbial strains.

During the antibiotic therapy, fever trends, signs of infection and renal functions should be monitored, especially in the case of aminoglycoside or glycopeptide therapy. Prophylaxis of pneumococcal infections might be considered in high-risk patients.

Low-risk patients

Outpatient treatment of FN in low-risk patients includes combination oral antibiotic therapy, usually amoxicillin-clavulanate with ciprofloxacin or levofloxacin. Patients allergic to penicillins may be given a macrolide or, in very exceptional cases, ciprofloxacin monotherapy may be considered.

In an inpatient setting, antibiotics can be administered intravenously, especially at the beginning of treatment. Intravenous route of administration broadens the spectrum of available antimicrobial agents (e.g. piperacillin / tazobactam or cefoperazone / sulbactam).

High-risk patients

Stable patients without any specific signs of infection or other chemotherapy-associated side effects should be commenced on a broad-spectrum IV antibiotic such as piperacillin/tazobactam, cefoperazone/sulbactam, cefepime or imipenem/cilastine. Patients with signs of serious infection or at risk of other chemotherapy- associated toxicity or nosocomial infection should be given combination therapy with an aminoglycoside (amikacin, isepamicin, gentamicin) or ciprofloxacin (preferable in suspicion for atypical pathogens). Combination therapy with vancomycin is reserved for patients with suspected catheter-related infection, severe mucositis, Gram-positive bacteraemia, or penicillin / methicillin-resistant pathogen (e.g. MRSA). Alternatively, teicoplanin may be used in allergic patients. We always consult an infectious disease physician prior to the initiation of empirical antibacterial therapy in severely compromised patients.

The next course of treatment

Daily clinical follow-up and assessment of therapeutic response is required until the patient is apyrexial and neutrophil count starts to rise. If the patient is still febrile after 48 hours of empirical therapy and he is clinically stable, the initial antibacterial therapy should be continued. However, if the patient is clinically unstable, or his symptoms worsen, the therapy should be rotated or broadened. As soon as the patient is afebrile, neutrophil count is above 0.5x10*9/l and microbial cultures are negative, we can change to oral antibiotics and consider discharge. The average duration of FN is 2-7 days, median 5 days, in low-risk patients it takes usually 2 days.

In patients with complicated or persistent symptoms of infection, we can repeat microbiology examinations and broaden the antimicrobial therapy. If the patient presents with fever after 5 days of treatment, antifungal therapy is indicated.

Protective measures

Protective isolation and specific hygiene measures are required in patients with FN.

V. Primary and secondary prophylaxis of febrile neutropenia

Prophylactic administration of granulocyte colony-stimulating factors (G-CSF) can reduce the risk of severe G4 neutropenia and shorten its duration. The relative risk of FN in patients with primary G-CSF prophylaxis was lower compared to control group and ranged from 0.43 to 0.67. G-CSF prophylaxis was also associated with a significant decrease in hospital admission rates, use of antibiotic therapy and supportive care, and reduction of life-threatening complications. Routine administration of G-CSF is not recommended if the risk of FN is < 20%. In patients with intermediate risk (10-20%), G-CSF prophylaxis can be considered depending on the presence of other risk factors (mentioned above).

Every other FN episode increases the risk of serious complications and delays the administration of chemotherapy. Secondary prophylaxis of FN (G-CSF given for the course of chemotherapy following the episode of FN) is indicated in patients undergoing curative treatment or if a possible delay in chemotherapy might significantly impair patient's quality of life. With regard to the intention of treatment, an alternative to prophylaxis with G-CSF is a reduction of chemotherapy dosage, prolongation of intervals between chemotherapy cycles or the use of another cytostatic agent with lower risk of myelosuppression.

Principles of palliative care and care in oncology

O. Slama, L. Pochop

Despite considerable advances in modern oncology, the mortality of cancer remains high and more than a third of oncology patients succumb to their disease. An advanced tumour is associated with a number of unpleasant physical symptoms (such as pain, dyspnoea, anorexia, fatigue, weakness, nausea, diarrhoea, constipation), psychological distress (maladaptation to a serious illness, frustration, anxiety, depression, confusion), social difficulties (e.g. loss of social role, isolation, loneliness, loss of regular income, financial burden) and spiritual crisis (e.g. loss of meaning, feelings of guilt, fear of death). These complications have a detrimental impact on patients' quality of life. The primary goal of palliative care is to maintain an acceptable quality of life through comprehensive treatment of cancer-related symptoms and psychosocial support to the patient and his family throughout the whole disease trajectory.

Palliative treatment and palliative care

The terms "palliative treatment" and "palliative care" might have a number of connotations depending on the type of discourse employed. The term *"palliative treatment"* usually refers to anticancer therapy without curative intent. In oncology, we speak of palliative surgery, palliative chemotherapy, radiotherapy, targeted treatment, etc. However, the impact of these procedures on patients' survival and quality of life may greatly differ. In some patients, palliative therapy may control the disease for several years; in others, it can improve the overall survival only by a few months. The term *"palliative care"* has mistakenly been used as a synonym for end-of-life care (i.e. care provided in the order of weeks or days prior to patient's death), which is aimed at maintaining comfort in patients approaching death. However, in the last decade, palliative care has been recognised as a comprehensive care aimed at alleviating cancer-associated symptoms and providing support to the patient and his family early after the diagnosis of an incurable disease. Palliative care should not be delayed until the last weeks or days of patient's life or when all treatment possibilities have been exhausted. This shift in the understanding of palliative care is reflected in its latest definition by the World Health Organization (WHO 2007).

World Health Organization Definition of Palliative Care (WHO 2007)

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing physical symptoms
- systematically integrates the psychological, social and spiritual aspects of patient care
- offers a support system that allows the patient to live as actively as possible until death
- offers a support system to help the family cope during the patients illness and in their own bereavement
- stems from a profound respect for life, but considers dying to be a natural process
- neither hastens nor delays death
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Indications of palliative (non-curative) anticancer treatment

Palliative anticancer treatment should be indicated with respect to its possible benefits in terms of:

- ***Overall survival*** (what is the survival benefit of anticancer treatment over palliative care alone?)
- ***Quality of life*** (Will the treatment lead to alleviating the symptoms of cancer? What are the treatment-associated risks?)

A treatment strategy is not entirely a physician's decision made with respect to a particular histological type of tumour, its clinical stage and predictive factors. Medical decisions should be a result of sensitive but honest discussion with a patient, who is well informed about treatment intents, benefits (Is the survival gain worth undergoing chemotherapy?) and its possible risks. Palliative care is based on a belief that the basic prerequisite of shared decision-making is patient's full understanding of his medical situation. Patients with incurable disease should therefore receive **clear information that:**

- their illness is not curable by any means of contemporary medicine,
- systemic treatment is likely to provide a survival gain in the order of months (rarely years) compared to supportive care,
- systemic therapy may temporarily alleviate some of the cancer-associated symptoms (e.g. pain, ascites, dyspnoea),
- Systemic treatment may have serious side effects, that can usually be managed with adequate supportive care

Only well-informed patient can make autonomous decisions and give informed consent to palliative chemotherapy or targeted treatment.

In case the doctor considers a treatment futile (it neither prolongs patient's survival, nor improves his quality of life), he should clearly communicate this belief to the patient and stop the anti-cancer

treatment. It is important to offer the patient symptomatic palliative care and arrange necessary supportive services at this phase.

Pain and other symptom management

An important role of comprehensive palliative care is attributed to the management of pain and other cancer-associated symptoms. The assessment and treatment of pain is described in detail elsewhere (see chapter no. 12). This chapter outlines the management of other most common symptoms of advanced malignant tumours.

Dyspnoea

Dyspnoea is a subjective perception of shortness of breath and effortful breathing. The presence of symptom only partially correlates with objective ventilation parameters such respiratory rate, oxygen saturation, respiratory volumes or laboratory parameters such as pO_2 and pCO_2. Dyspnoea can be influenced by patient's emotional state and is often aggravated by anxiety.

Underlying conditions:

- airway obstruction (tumour, COPD, acute infection, bronchospasm)
- restriction of functional lung parenchyma (tumour, fibrosis, infection, pleural effusion, bleeding, pulmonary embolism, postoperative changes)
- restriction of breath movements (muscle weakness, pain, elevation of the diaphragm due to ascites, hepatomegaly, paresis of phrenic nerve)
- other: cardiovascular disease (left heart failure, cardiomyopathy, pericardial effusion, shock, sepsis, massive blood loss), anaemia, anxiety

Therapy

Causal treatment of the underlying condition is a preferred approach whenever it is possible and appropriate to the clinical situation (e.g. cardiologic compensation, bronchodilator therapy in COPD, drainage of a pleural effusion, transfusion, antibiotic treatment, etc.).

Symptomatic treatment

- fresh air - opening of the window, breathing and relaxation exercises, relieving position
- Supplemental oxygen is indicated if the patient is hypoxic. Only a minority of patients in the terminal phase of their disease need oxygen therapy. Similar relief may be provided by opening the window or by ensuring sufficient air circulation. Home oxygen therapy with oxygen concentrator (maximum capacity is 6 l O_2 / min) might be arranged for particular patients.

Pharmacotherapy

- Bronchodilator therapy: patients with COPD should be given salbutamol inhalations at a dose of 100-200ug (1-2 breaths) every 4-6h, ipratropium bromide 20-60microg (1-3 breaths) every 4

hours and aminophylline 5-7mg / kg slowly IV followed by continuous infusion of 0.4-0.6 mg / kg / h.

- Opioids: 5-10mg of morphine subcutaneously or orally every 4 hours, titrated until the symptoms resolve. For patients with chronic use of morphine preparations due to cancer pain, the dose should be increased by 30-50 %.
- Anxiolytics: Diazepam 2 mg orally every 8 hours or 5-10 mg before bedtime, bromazepam 1.5-3mg orally every 8 hours, alprazolam 0.25-0.5mg 2-4 times a day .
- Corticosteroids have anti-inflammatory and thus bronchodilator effects in specific medical conditions. They may be effective in case of dyspnoea in multiple lung metastases, carcinomatous lymphangitis or pneumonitis. Prednisone 20-40mg/day, methylprednisolone 16-32mg/day, or dexamethasone 4-8 mg/day are the most commonly used preparations. Tapering should be initiated several days after dyspnoea resolves. If no clinically significant reduction in dyspnoea is achieved within 3-5 days, corticoids can be discontinued without tapering.
- facilitate expectoration by mucolytics, saline nebulisation, acytylcysteine 10% orally or 6-10ml via nebulizer every 6-8hours.

In patients with severe dyspnoea and signs of respiratory failure, who are not indicted for invasive ventilatory support with respect to their poor prognosis or advance directives, *non-invasive artificial pulmonary ventilation* may be considered. However, it is necessary to decide individually, whether it might contribute to good quality of life in a terminal phase of cancer disease.

In patients with severe refractory dyspnoea irresponsive to the interventions described above, it might be necessary to consider *palliative pharmacological sedation*. The initial dose includes 5-10mg of IV morphine followed by a continuous infusion at a rate of 1-5mg/h. In case of marked distress and anxiety, midazolam 2-5mg as an IV bolus followed by continuous infusion at a rate of 1-4mg/h might be added. We titrate the doses individually according to the severity of symptoms in order to relieve suffering and provide comfort to the patient.

Malignant pleural effusion

If anticancer treatment is effective, effusion will usually reduce or resolve spontaneously. Refractory malignant effusion is one of the most common indicators of anticancer treatment failure.

Possibilities of symptomatic management of pleural effusion include:

- thoracentesis (do not evacuate more that 1.5 l of pleural fluid at a time, in a repeated thoracentesis maximum of 2.5 litres is recommended).
- catheter drainage (suitable for gradual evacuation of voluminous effusions and for drainage in home environment.)

- pleurodesis - indicated in patients without lung entrapment who report relief of dyspnoea after thoracentesis**.** Before attempting pleurodesis, pleural effusion must be fully drained and lung expanded in the chest cavity. Most commonly used agents are talc and bleomycin.
- Surgical treatment (pleurectomy) should be reserved for patients with persistent debilitating effusion who have otherwise good performance status and whose life expectancy exceeds 6 months.

Ascites

Fluid in the abdominal cavity is a frequent manifestation of advanced gynaecological and GIT tumours. It causes abdominal discomfort, nausea, vomiting and shortness of breath. In the case of metastatic peritoneal involvement, the effusion is usually exudative, whereas in patients with hepatic dysfunction and portal hypertension it has a character of transudate.

Therapy

Effective anti-cancer therapy may lead to complete abatement of ascites. Under certain circumstances, symptomatic treatment is necessary. It includes:

- Diuretics: Spironolactone 50-200mg/day, Furosemide 20-40mg/day. It is effective especially in case of portal hypertension. Salt or fluid restriction is not recommended in oncology patients.
- Paracentesis: a single paracentesis or peritoneal drain may provide an immediate relief of symptomatic ascites. Removal of 5l of ascites at a time is recommended.
- Peritoneo-venous shunting: This method is used in treatment of refractory ascites in a number of institutions abroad, however, it is not available in the Czech Republic so far.

Cough

Causes:

- airway irritation (tumour, aspiration, tracheo-oesophageal fistula, gastroesophageal reflux, infections, asthma, sputum retention),
- pulmonary parenchyma impairment (infection, tumour infiltration, fibrosis, COPD, pulmonary oedema, pulmonary embolism),
- irritation of the pleura, pericardium or diaphragm.

Therapy:

Causal treatment is indicated whenever the clinical situation allows it. Symptomatic therapy includes:

- removal of irritating odours, relieving position, fresh air, chest physiotherapy: breathing exercises and massages
- facilitating expectoration in case of productive cough (room humidifiers, mucolytics)
- inhalation therapy and nebulisations of saline or acetycysteine in case of productive cough

- for dry or irritative cough: opioids (oral codeine 15-30mg every 4-8 hours, ethylmorphine 15-30mg every 6-8 hours or morphine 5-20mg every 4-6 h), non-opioid antitussives (butamirat 10-20mg every 6-8 hours), inhalation of local anaesthetics (lidocaine 1% 5 ml through nebulizer over 15-50 minutes, every 4-6 hours).

Patients with a persistent cough that is physically exhausting might be given benzodiazepines or neuroleptics in addition to opioids in order to induce sedation.

Anorexia / cachexia

Anorexia in oncology patients may take various forms ranging from loss of appetite to an unpleasant feeling of fullness. Persistent anorexia inevitably leads to weight loss and cachexia. Management of anorexia is difficult and should involve nutritional and pharmacological intervention, as well as rehabilitation stimulating patient's physical activity.

- *Nutritional approach* involves measures aimed to increase patient's energy and nutrient intake through various forms of nutritional support, such as enteral nutrition supplements, nutritional counselling and diet adjustments in order to satisfy patient preferences, sip feeds, enteral tube feeding, occasionally also parenteral nutrition.
- The aim of the *pharmacological approach* is to reduce anorexia by mitigating metabolic inflammatory reaction that contributes to energy and protein loss. The most commonly used drug is megestrol acetate in a dose of 480-800mg / day, preferably in the morning. Corticosteroids may be used in very compromised patients: prednisolone 20-40mg / day or dexamethasone 4-8mg / day.

Depression

Anxiety and depression often accompany distressing physical symptoms of incurable disease and often converge into one clinical presentation with different intensity, depending on the course of the disease. There is a strong relationship between the physical, psychosocial and spiritual aspect of patient's experience of the disease, therefore, only a comprehensive multidisciplinary approach might provide an adequate support.

Generally, we combine *psychotherapeutic* and *pharmacological* approaches:

- Supportive counselling and psychotherapy
- Anxiolytics: benzodiazepines: alprazolam 1.5-3mg /day, gabapentin 900-1800mg / day
- Antidepressants: SSRI (citalopram 20mg / day, escitalopram 10mg / day) or SNRI (venlafaxine 75-150mg / day). In case of sleep disorders, trazodone 75-300 mg / d or mirtazapine 15-45 mg / d are highly preferred.

Psychological and social care

Advanced cancer disease represents a substantial psychological burden for patients. The process of coping with an incurable illnesses can be facilitated by several factors:

- supporting and caregiving family of the patient
- open and empathic approach of health care professionals, honest communication of the diagnosis, treatment and prognosis
- personal treating physician ("a guide through the disease")
- good arrangement and coordination of care
- high-quality inpatient health-care services, short waiting times for outpatient checks, etc.

Even a short-term psychology counselling provided by a qualified psychotherapist may be very beneficial to patients and their families.

In addition, an incurable illness has serious impacts on patient's social roles (loss of income, limited mobility, social isolation, decreased ability to manage day-to-day activities, higher degree of dependency, etc.) and those close to him (higher direct and indirect expenditures, fear from the loss of a close person, burden of caregiving, etc.). In such a situation, the patient and his family need qualified social support and counselling concerning the possibilities of state welfare benefits, home care and heath assistance, mobility aid rental, hospice care services, etc. It is important to actively offer and inform patients about this kind of services.

Spiritual aspects of palliative care

Spiritual domain encompasses individual’s search for his true identity, meaning and purpose of life, connections with others, or with God. Spirituality can provide patients with a sense of meaning, hope and inner self. Some people experience transcendence with regard to a traditional religion (e.g. Christianity or Islam) while others might approach it in a completely "non-religious" manner. It would be a gross simplification to reduce spiritual care to a phrase "meeting patient’s spiritual needs". In palliative care, spirituality is an important source of inspiration, motivation, and power to cope with illness. In the context of a life-threatening disease, spiritual issues become more pervasive. Health-care professionals should be responsive to this fundamental aspect of patient’s experience and provide him with an attentive support. At the same time, physicians should be aware of their occupational and personal limits and, if necessary, refer the patient to a pastoral carer or hospital chaplain.

End-of-life care

A major tenet of the end-of-life care is to relieve suffering and alleviate physical, emotional or spiritual distress associated with an incurable illness and maintain comfort of a patient approaching death.

- All diagnostic and treatment procedures that do not contribute to patient's comfort should be abandoned. Treatments that do not influence patient's quality of life and lead to delaying of imminent death (e.g. the use of antibiotics, parenteral hydration and nutrition, haemodialysis, mechanical ventilation) may often unnecessarily prolong the process of dying and increase the suffering of both the patient and his family. Their deployment needs to be considered individually with respect to patient's preferences.
- With respect to the anticipated course of disease, an early communication of possible cancer-associated complications and specific life-extending treatment procedures is a crucial prerequisite for good end-of-life care. Patients' preferences and advance directives concerning the extent of medical care should be respected.
- If it is a patient's wish, end-of-life care may take place in home environment. If a patient in the terminal phase stays in a hospital, it is necessary to allow for the relatives to sit at his bedside.
- In every dying patient, pain, dyspnoea, anxiety and delirium must be regularly assessed and managed.

Management of the most common symptoms in a terminal patient:

Symptom	**Therapy**	**Note**
Pain	Metamizole 1-2.5 g iv TID Diclofenac 50 - 100 mg iv, im, TID Morphine 5-10 mg every 4-6hours iv, sc, or by continuous iv or sc infusion at a dose of 30 mg / 24 hours	Non-opioid analgesics are sometimes preferred due to their antipyretic effect. For pain management in a terminal phase of cancer they are usually replaced by opioids. The initial dose of morphine should be increased by 30-50 % a day until achieving desired pain relief. Patients who have not been previously treated with strong opioids do not require doses higher than 60mg/24h sc. Patients with chronic use of opioids might require doses higher than 500-1000 mg / 24h.
Dyspnoea	morphine 2.5 - 10 mg every 4-8 h sc, iv	In patients with long-term use of

	10 - 20 mg orally every 4-6 hours Supplemental oxygen therapy, usually at a rate of 3-5 l/min with a nasal cannula	morphine, a 30-50% increase of the chronic dose is recommended. Oxygen therapy is rather of symbolic or psychological significance for the patient and his family. Patients often report relief from dyspnoea, although the objective ventilation parameters and including oxygen saturation remain unchanged. Portable oxygen concentrators can be used in home environment.
Anxiety	midazolam 2.5 mg iv, or sc every 2 hours, or 20 mg over 24 hours in a continuous iv or sc infusion diazepam 5-10 mg every 12 hours im, iv, pr alprazolam 0.5-1 mg 2-3 daily	The level of anxiety is very individual. Doses of benzodiazepine necessary to maintain adequate comfort are very variable among patients, ranging from anxiolytic to strongly sedative. The initial doses may be substantially increased in some patients. Sometimes only non-pharmacological intervention might suffice: proximity to relatives, empathic approach of health-care professionals or religious rituals.
Delirium	haloperidol 1-5 mg po, iv, every 30 min. until the desired effect is achieved levomepromazine (TISERCIN) 25 - 50 mg every 6h iv, im	Haloperidol can be combined with benzodiazepines - see Anxiety and Delirium Antipsychotics are indicated primarily in case of agitated delirium. Patients might also benefit from their antiemetic effect.

Palliative sedation (PS) in the terminal phase

PS refers to the administration of sedative drugs to a terminally ill patient with the intent to relieve refractory symptoms and maintain his comfort. The level of sedation is always individual and depends on the intensity of symptoms as well as the overall clinical context. Some patients might prefer a mild sedation in order to retain the ability to communicate, others require deep sedation leading to complete unconsciousness.

- The most common indication for PS is refractory dyspnoea, anxiety, agitated delirium. Pain can usually be effectively managed without significantly affecting the state of consciousness.
- For palliative sedation we commonly use continuous administration of midazolam (10-200 mg / 24 h i. v.), sometimes combined with morphine (10-200 mg, according to intensity of pain). Propofol can also be used.

Hospice care

Hospice service is a form of palliative care designed for patients with a terminal disease (usually in their last weeks and days of life). Hospice integrates modern palliative and nursing practices with social and psychological counselling. Care is provided by an interdisciplinary team, either in the form of inpatient hospital or in home setting. In 2018, there were 17 inpatient hospices with a total capacity of 450 beds. Hospice care is partially reimbursed by public health insurance, still, less than 10% of cancer patients die in a hospice. Most (65%) of them die at intensive care units in a hospital. More information about hospice care in the Czech Republic including contacts to particular hospice facilities is available on the webpage www.umirani.cz.

Head and neck tumours

R. Obermannová, R. Němeček

Epidemiology and risk factors

Head and neck tumours are the sixth most common cancer disease in the Czech Republic, with approximately 2000-2200 cases diagnosed annually. **Incidence is 2-8 times higher in males** than in females and the typical age at diagnosis ranges from 50-70 years.

Anatomically, this group comprises tumours of **the mouth, oral cavity, paranasal cavities, pharynx, larynx, salivary gland tumours, unknown primary** and **mucosal melanoma**.

Risk factors include tobacco smoking, alcohol abuse, chronic infections, viral diseases (HPV, EBV, HIV rarely), and physical factors such as mechanical irritation, sun exposure and occupational risks. Mostly, however, these are tumours associated with **smoking**.

Head and neck tumours is a heterogeneous group of malignancies affecting a number of organs and tissues - skin, muscles, cartilage, nerves, vessels, lymph nodes and salivary glands. In the last two decades, there is an increase in the incidence of carcinomas associated with HPV **infection**, which occur typically in oropharynx, in patients with no history of smoking or alcohol abuse and at younger age. From the perspective of etiopathogenesis, tumours are similar to HPV-associated cervical carcinoma in women. The data on the impact of vaccination on the incidence of HPV-positive tumours are still lacking.

According to histopathological findings, we distinguish **squamous cell carcinoma,** which is the most common type of head and neck tumours. **Nasopharyngeal carcinoma** is a specific subtype characterized by endemic occurrence and association with EBV infection. Salivary glands may be affected by adenoid cystic carcinoma and mucoepidermoid carcinoma.

Screening and prevention

There is no screening for this disease. The main preventive measure is to refrain from smoking and excessive alcohol consumption. As mentioned above, the role of HPV vaccination has not been elucidated yet.

Clinical presentation

At the early stage, the tumour usually presents as painless ulceration. Leucoplakia (white patchy lesions in the oral cavity) is considered a precancerosis. An advanced tumour is manifested by a painful resistance that occurs most frequently in the neck (as a result of nodal spread). A common

symptom is a secondary paresis due to nerve involvement. Typically, laryngeal tumour presents with hoarseness caused by the recurrent nerve paresis. Late symptoms include odynophagia or dysphagia, cough, airway obstruction, trismus, mucus hypersecretion, haemorrhagic complications, or ***foetor ex ore***.

Diagnosis and staging

Diagnostic procedures are aimed at determining a precise TNM stage. The classification is very similar across all tumour subtypes, with only a few subtle differences. Basic work-up includes **ENT examination with panendoscopy** and biopsy, CT-scan or possibly an MRI of the head and neck and chest X-ray. Chest CT-scan should be performed only in locally advanced disease (up to 3% probability of lung metastases). Abdominal ultrasound is indicated in order to exclude dissemination prior to radical treatment. An alternative is a PET / CT examination.

Basic principles of treatment by clinical stages

Treatment of head and neck cancers is multimodal. The choice of treatment strategy depends on the location and extent of the primary tumour, patient's overall medical condition (including the nutritional status), comorbidities, age and patient preferences. The treatment strategy is usually decided on a **multidisciplinary team board** that involves an ENT physician, maxillofacial surgeon, radiation and clinical oncologists, radiologist and other experts. Depending on the clinical stage, it might include the following modalities:

1) **Surgery** (radical surgery) or **radiotherapy**, both as a standalone treatment modalities in case of early stage tumours (approximately 30-40 % of carcinomas).
2) In locally advanced cancer, we use a combination of both modalities, i.e. **resection** including **cervical lymph node dissection** followed by **adjuvant radiotherapy.** In case of high-risk disease, **concomitant chemotherapy** (with cisplatin or carboplatin) is indicated.
3) **Curative chemoradiotherapy with cisplatin** or alternatively **with cetuximab** (without primary surgery) is preferred in patients with an advanced tumour in order to avoid a mutilating surgery. This approach may also include a so-called "salvage surgery" in case of persisting tumour. Curative chemoradiotherapy (CHT/RT) is the treatment of choice in locally advanced laryngeal tumours as a larynx-preserving approach. Otherwise, surgery is a debilitating procedure that leads to the loss of vocal cords.
4) In the case of nasopharyngeal carcinoma, curative CHT/RT followed by adjuvant chemotherapy with 5-FU / cisplatin is indicated.
5) Palliative chemotherapy or targeted treatment is given to patients with disseminated tumour (stage IV disease). It might comprise a combination of cytostatics or it may be given as monotherapy (commonly used cytostatics include **5-fluorouracil (5-FU), cisplatin** or carboplatin. Methotrexate, taxanes, or cetuximab are used as single agents).

6) Recent data show that treatment with an anti-PD-1 antibody nivolumab in a second-line setting was associated with survival prolongation in patients with metastatic disease, however, it is not reimbursed in the Czech Republic yet.
7) A crucial role in curative and palliative therapy is attributed to adequate **supportive treatment**, which includes dental care (stomatology treatment prior to radiotherapy), maintenance of airways (preventive tracheostomy in patients with high risk of airway obstruction due to oedema associated with CHT / RT), nutritional support (**PEG**, or enteral tube feeding), management of mucosal and skin toxicity, supportive treatment of myelosuppression (transfusions, hematopoietic growth factors), analgesic therapy (including short-term use of opioids in patients with severe mucosal and skin toxicity), psychological supportive counselling or pharmacotherapy with anxiolytics and antidepressants, if necessary.

Comprehensive supportive care is a sine qua non of a successful curative treatment.

Prognosis

The main prognostic factors are the extent of illness, gender (better survival in women), age, performance status and comorbidities, tumour localization and HPV infection (HPV-associated oropharyngeal tumour has a better prognosis compared to other subtypes).

Dispensarization

In the first year after accomplishing the treatment, ENT examination is indicated every 3 months, second year at 3-6 month intervals, and then once in 6-8months up to five years. Beyond 5 years, an annual check-up is required. Following radiotherapy, monitoring of TSH and regular dental examinations are necessary. CT-scan of the neck is recommended within 6 months after the therapy and subsequently based on individual clinical conditions.

Case Reports:

Case No. 1

A 70-year old patient, smoker, with coronary artery disease and angina pectoris syndrome, with left ventricular ejection fraction of 60 % and normal renal functions was diagnosed with a T3N2M0 laryngeal tumour, histologically an HPV-negative squamous cell carcinoma. *Which treatment method would you indicate?*

The patient was treated with concomitant chemoradiotherapy resulting in a complete remission of the disease.

Case No. 2

A 30-year old patient reported muffled hearing, a feeling of fullness in the ears, recurrent upper airway infections. *What investigations would you recommend?*

He underwent ENT examination including panendoscopy, which revealed nasopharyngeal carcinoma.

What is the treatment of choice in this patient?

He was given concomitant chemoradiotherapy (with cisplatin), followed by adjuvant chemotherapy with the effect of complete remission.

References:

NCCN guidlines, version 2.2018
Blue Book, COS, version 2018

Tumours of the oesophagus and gastroesophageal junction

R. Obermannová, R. Němeček

Epidemiology

Oesophageal tumour is the nineteenth most common cancer in Europe and the sixth most common cause of cancer-related death. According to the Czech National Cancer Registry data from 2015, the incidence of oesophageal cancer displays stagnating trend, with an annual rate of 6.34/100,000. Oesophageal cancer is a male dominant disease (**75%** of cases occur in **males**), its incidence increases with age, reaching the peak in the seventh decade of life. The most common histological type is **squamous cell carcinoma** (SCC) and **adenocarcinoma** (AC). Adenocarcinoma has recently become more prevalent than SCC in some countries, which may be attributed to increasing prevalence of gastro-oesophageal reflux and obesity.

Risk factors

Smoking and excessive **alcohol consumption** are known to increase the risk of SCC, whereas AC is mainly associated with conditions underlying the development of **Barett's oesophagus**; i.e., gastro-oesophageal reflux disease and obesity. Secondary malignancies in patients with oesophageal cancer include head and neck tumours and lung cancer.

Screening and prevention

Routine screening for oesophageal tumours is not performed.

Clinical presentation

The disease is usually manifested by dysphagia or odynophagia, vomiting, anorexia, weight loss and malnutrition. Locally advanced disease may result in tracheo-oesophageal fistula and aspirations. Advanced disease is manifested by local as well as systemic symptoms (fever, abdominal pain, bone pain in the case of metastatic spread, jaundice in massive liver involvement). The cancer is often associated with other chronic diseases such as ischemic heart disease, hypertension, diabetes or hepatopathy, which considerably impinge on the radical intent of treatment.

Diagnosis and staging

The mainstay of diagnostic procedures is a **gastro-esophagoscopy** including a biopsy for further histological examination. **Endoscopic sonography** is used to specify staging, especially the depth of invasion and regional node involvement. **Chest CT scan and abdominal CT** or **PET / CT** are indicated to exclude distant metastatic spread supposing a radical surgery is to be considered.

Staging according to TNM classification:

Stage I: carcinoma limited to the mucosa.

Stage II: carcinoma invades the muscularis propria and spreads to up to 2 regional lymph nodes.

Stage III: tumour invades surrounding tissues and/or there is multiple nodal involvement.

Stage IV: metastatic disease.

Basic principles of treatment by stages

Stage I

Early carcinoma can be managed by endoscopic methods - endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) or by open surgery. Tumours invading deeper into the mucosa or high-grade tumours should be treated as stage II tumours.

Stage II-III

The five-year survival of patients in these clinical stages is less than 20% if only one treatment modality is used. Therefore, a comprehensive multimodal therapy should be the routine approach to locally advanced oesophageal cancer. Proximal oesophageal tumours (cervical portion) are usually treated with **definitive concomitant chemoradiotherapy**, because surgery in these tumours is associated with substantial morbidity and mortality rates. The management of **resectable** middle and distal oesophageal cancer includes **preoperative concomitant chemoradiotherapy**, most commonly based on 5-fluorouracil and platinum derivative, or alternatively taxane and platinum derivative followed by radical surgery. Patients with poor performance status or serious comorbidities are candidates to definitive chemoradiotherapy (without subsequent surgery) or a so-called "salvage" surgery in case of locoregional tumour progression after primary chemoradiotherapy. An alternative treatment method for adenocarcinoma of gastro-oesophageal junction is **perioperative chemotherapy** (see gastric cancer).

Stage IV

Patients with metastatic disease are, with regard to their clinical status, treated with **palliative chemotherapy**, or best supportive care. Palliative chemotherapy is based on 5-fluorouracil and a **platinum derivative**. In patients with **HER2-positive** adenocarcinoma, chemotherapy might be potentiated by a monoclonal antibody against HER2 - **trastuzumab**, which was proved to prolong survival in these patients. Other drugs used in the treatment of oesophageal carcinoma are taxanes and irinotecan, or anti-VEGFR2 antibody **ramucirumab** used in the second line setting.

Supportive and palliative treatment consisting mainly of nutritional support and analgesic therapy, is an inherent part of care across all clinical stages. Percutaneous endoscopic gastrostomy (PEG), operative feeding jejunostomy or endoscopic oesophageal stenting are common procedures used to provide artificial feeding routes in order to prevent malnutrition. However, supposing a radical

oesophageal resection is planned, the introduction of PEG is contraindicated as it might interfere with construction of gastric conduit that represents a substitute for resected part of oesophagus.

Prognosis

Only patients with early oesophageal cancer have a chance of long-term survival after radical surgery. The 5-year survival of locoregionally advanced carcinoma is rather low - ranging from 5 to 30%. The reason for such an unfavourable prognosis is the anatomical location of oesophagus, which often impedes radical surgery, as well as higher age at the time of diagnosis and the presence of numerous comorbidities that increase the risk of postoperative complications.

Follow up

Physical examination is indicated every 3-6 months in the first 2 years after accomplishing curative treatment, every 6 months during subsequent 5-year period and then once a year. Laboratory tests, imaging methods, and gastroscopic examinations are performed only when clinically indicated.

Case Reports:

Case No. 1

A 74-year-old patient with a history of smoking 20 cigarettes per day for 24 years and alcohol intake of 1-2 beers a day presents with swallowing difficulties in the past 3 months and a sensation of food stuck in the middle third of the oesophagus and occasional urge to vomit. He is 170 cm tall and weights 85 kg. He reported weight loss of 6 kg / 3 months. **Past medical history** includes ischemic heart disease without angina pectoris syndrome and hypertension. *What investigations wold you suggest?*

Diagnostics: Gastroscopy revealed a tumour in the middle third of the oesophagus, histologically, it was a G3 squamous cell carcinoma, T3N1 according to TNM classification. PET / CT did not show any distant metastases. *What would be the therapeutic strategy?*

Treatment: Neoadjuvant concomitant chemoradiotherapy was followed by radical surgery (transthoracic oesophagectomy). However, the patient suffered serious postoperative complications. He developed an intra-abdominal abscess that required percutaneous drainage and prolonged the duration of hospital stay up to 35 days. Moreover, postprandial syndrome and reflux disease occurred in the patient.

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Gastric cancer

R. Obermannová, R. Němeček

Epidemiology and histopathology

Gastric cancer is the fourth most common tumour worldwide. According to the Czech National Cancer Registry, about 1300 new gastric cancers are diagnosed annually (i.e. an incidence rate of 13 per 100 000), predominantly in men. Typically, gastric cancer patients are 70-80 years old. In contrast to Asian countries, where the incidence continues to be very high, a steady decline has been noticed in Western world. However, prognostically less favourable tumours of the gastro-oesophageal junction has become more prevalent in these countries.

The most common histological type of gastric cancer is an adenocarcinoma. In the differential diagnosis, it is important to rule out lymphoma (MALT), neuroendocrine carcinoma, adenoacanthoma, GIST (gastrointestinal stromal tumour) or squamous cell carcinoma. According to **Laurene pathology classification**, adenocarcinomas are divided into **intestinal** cancers (with better prognosis) and **diffuse** carcinomas (also known as poorly cohesive cancer according to WHO classification from 2010), which are associated with significantly worse survival rates.

Risk factors

The incidence of gastric cancer is higher among individuals with high salt intake (esp. when using salt as a food preservative or in smoked meat), smoking, excessive alcohol intake (non-cardia tumours), low fruit and vegetable consumption, high levels of nitrates in the diet and male gender. Of genetic factors, the most common underlying disorder is an autosomal dominant mutation of the E-Cadherin gene (CDH1) causing hereditary diffuse carcinoma in patients younger than 50 years of age. Other associated etiologic conditions include chronic atrophic gastritis, Helicobacter pylori infection and EBV.

Screening and prevention

Routine screening is not performed in Western countries. Smoking cessation and eradication of Helicobacter pylori (HP) infection are the most effective preventive measures.

Clinical picture

Symptomatology of gastric cancer resembles symptoms of gastroduodenal ulcer disease. Early in the course of the disease, patients report sensations of postprandial fullness and bloating, dyspepsia, epigastric pain, persistent pyrosis, nausea, vomiting, weight loss and fatigue. Tumour might also be

manifested by hematemesis or melena. Anaemia is a common accompanying symptom. In the case of dissemination in the abdominal cavity, acute abdomen may be the initial presenting symptom.

Diagnosis and staging

The diagnostic method of choice is gastroscopy and endoscopic biopsy of the tumour for further histological and molecular investigations. Endosonography might assist in determination of the depth of invasion and assessment of nodal status. Routinely, chest and abdominal CT scan, or PET/CT is performed to exclude dissemination. In the case of diffuse carcinoma, PET scan may often be inconclusive and thus, it is not recommended for staging. Staging laparoscopy is used to rule out miliary dissemination in the abdominal cavity, but is not a routine diagnostic procedure in many institutions. Tumours are staged according to TNM classification (see oesophageal tumours).

Basic principles of treatment by clinical stages

Tis and T1 stage tumours can be treated with endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD), or by surgical resection.

In the case of **locally advanced disease (T2-4, N1-3),** three therapeutic approaches are possible:

- perioperative chemotherapy (chemotherapy - surgery - chemotherapy) – is a preferred option in most of European countries (most commonly used cytostatics are: fluorouracil, leucovorin, oxaliplatin and docetaxel - so-called FLOT regimen)
- Radical gastrectomy and lymphadenectomy, followed by adjuvant chemotherapy – is a method of choice in Asia
- radical surgery, followed by adjuvant chemoradiotherapy – is a preferable approach in the USA

Metastatic disease (M1) is treated with **palliative chemotherapy** or **targeted agents**. Several regimens are used in this setting, most of which include cytostatics like **5-fluorouracil, platinum derivatives** (cisplatin and oxaliplatin), **taxanes** or **irinotecan**. Correspondingly to oesophageal cancer, gastric tumour with HER2 amplification can be treated by **trastuzumab**, or with second-line **ramucirumab**, irrespective of HER2 status. Palliative and supportive therapy aimed primarily at maintaining adequate nutritional status (stent implantation, nutritional jejunostomy, or nasojejunal tube feeding) is a standard part of the treatment at any clinical stage. Patients after total gastrectomy should be supplemented with B12 vitamin.

Prognosis

Patients with stage one disease have a high probability of cure, with a five-year survival rate being up to 50 %. In the case of metastatic disease, the mean overall survival ranges from 8 to 16 months.

Follow up

Guidelines for dispensarization are similar to those in oesophageal cancer.

Case report:

A 59-year-old male, a non-smoker without any serious co-morbidities (except for gastroduodenal ulcer disease) reported upper dyspepsia in the past 4 months and a weight loss of 4kg / 6 months.

What is the investigation of choice?

Gastroscopy was performed and revealed a carcinoma of cardiac region. Staging was completed using endosonography and CT scan. The tumour was moderately differentiated (G2), stage III (T3N1M0) adenocarcinoma.

What is the recommended treatment procedure?

The patient received perioperative chemotherapy based on 5-fluorouracil and cisplatin. Intraoperatively, peritoneal metastatic spread was diagnosed and the treatment intention changed to palliative.

What molecular testing should be performed?

HER2 overexpression of 3+ was diagnosed and the patient initiated palliative chemotherapy in combination trastuzumab. The progression free survival was 12 months.

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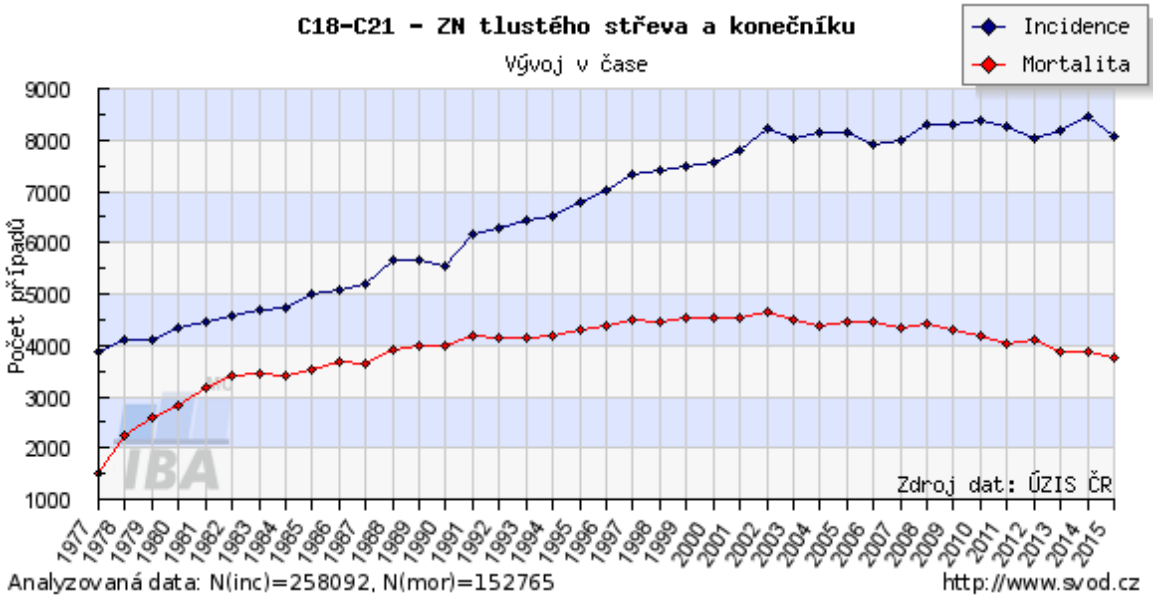
Colorectal carcinoma

I. Kiss, I. Kocáková, P. Šlampa

Epidemiology

Colorectal carcinoma (CRC) is the most common cancer of the digestive tract and one of the most common malignancies worldwide. Every year, there are more than 8000 new cases diagnosed in the Czech Republic and around 4,000 colorectal cancer-related deaths are reported annually. While the incidence is gradually rising, mortality stagnates.



Aetiology

Colorectal cancer might be either sporadic or hereditary.

Sporadic carcinoma

Sporadic carcinoma accounts for 80 to 90 % of the total CRC cases. It is not related to a specific genetic predisposition, but it develops as a result of gradual accumulation of mutations. Incidence increases with age. It is associated with environmental factors like high dietary fat, obesity, excessive consumption of red and processed meat, low fibre diet and alcohol intake. Chronic inflammatory bowel diseases (ulcerative colitis and Crohn's disease) are also reported to increase the risk of CRC.

Protective factors include physical activity, vegetable and fruit intake, diet rich in calcium, D and C vitamin, folic acid, vitamin C, beta-carotene and selenium.

Hereditary forms of colorectal carcinoma

Tumours related to **familial adenomatous polyposis syndrome (FAP)** comprise 1-2 % of all CRC. FAP is an autosomal dominant hereditary disease caused by a mutation of the APC gene, which belongs

to tumour suppressor genes. A specific form of FAP, **Gardner's syndrome,** is characterized by the presence of multiple bowel polyps as well as a number of extracolonic manifestations (osteomas, subcutaneous fibromas). A specific type of hamartomatous polyps increasing the risk of CRC is associated with **Peutz-Jeghers syndrome**, which is also characterized by hyperpigmentation of mucocutanseous transition zones (eyelids, lips, nostrils).

Hereditary non-polyposis colorectal carcinoma (HNPCC), or Lynch syndrome, is an autosomal dominant disease caused by a congenital mutation of genes involved in DNA repair (*mismatch repair genes, MMR*). As a result, genetic stability is compromised and mutations begin to cumulate. This is referred to as ***microsatellite instability (MSI*)**. Approximately 90 % of HNPCC develop due to mutations in MLH1 and MSH2 MMR genes.

Clinical presentation

Clinical manifestations of colorectal carcinoma depend on the location and extent of the disease. Right-sided tumours rarely present with obstructive symptoms. More commonly, they are associated with occult iron-deficiency anaemia and abdominal pain. Left-sided tumours are more frequently manifested by change in bowel habits or acute abdomen due to bowel obstruction (faecal content becomes denser in terminal parts of digestive tract and ileus is more likely to occur). Rectal tumours often present with bleeding, tenesmus (frequent and painful urge on the stool caused by infiltration of rectal nerves), or the presence of mucus in the stool. Haematochezia or enterorhagia is seen in tumours of all colonic sites. Advanced tumours of all localizations often result in significant weight loss and malnutrition.

Rectal cancer (C20) is a distinct group of tumours. In contrast to colon and recto-sigmoidal cancer (C18, C19) it is more prone to local spread and requires a different treatment approach (e.g. involvement of radiotherapy). Colon cancers tend to metastasize more often and frequently present with symptoms of metastatic disease.

Screening of Colorectal Carcinoma in the Czech Republic (www.kolorektum.cz)

Screening of colorectal cancer was introduced in the Czech Republic at the beginning of 2009, and since 2014, a direct invitations to investigations have been launched under this program. All the people at average risk of CRC aged 50 and above are included in the program. Individuals who meet the criteria for increased or high-risk of colorectal cancer (have a positive personal or family history of CRC) follow specific screening programs, which vary according to the particular level of risk. Patients are referred for CRC screening by their GPs, alternatively, women can be referred by their treating gynaecologists (for details see chapter no. 2 Prevention and screening).

Diagnostic methods and staging

Every physical examination should include digital rectal examination. In rectal tumours, it provides the information on tumour localization and relationship to surrounding tissues. The mainstay of diagnostic procedures is colonoscopy, which localizes and visualizes the lesion and provides biopsy for further histological investigation. A proper preparation for the procedure is crucial, so that the whole colon up to caecum may be examined. Colonoscopy might detect synchronous tumours or include removal of high-risk polyps. CT colonography (so-called virtual colonoscopy) represents an alternative to colonoscopy, especially in patients who are not able to tolerate endoscopic procedure. his method uses computer tomography to create a computer-reconstructed images resembling an endoscopic image and also requires mechanical bowel preparation.

The extent of rectal tumours is determined by rectoscopy combined with trans-rectal endosonography or MRI of the pelvis. Abdominal CT scan is performed to rule out distant metastasis and for the assessment of nodal status. Chest X-ray is indicated to rule out pulmonary metastases. Laboratory investigations include CEA and CA19-9 tumour markers. In case of any ambivalence, findings PET / CT screening might be appropriate.

TNM staging

The TNM staging classification provides a basic framework for treatment decision-making as well as prognosis estimation. According to the local and distant extent of the disease, the patient may be assigned to one of the following clinical stages:

Stage I: Tumour is limited only to the mucosa (T1) or the muscularis propria (T2).
Stage II: Tumour invades through the intestinal wall (T3-4), there are no lymph node metastases.
Stage III: metastatic involvement of lymph nodes (N1 and above)
Stage IV: Distant metastases are detected (M1).

Treatment

Radical resection is the only curative method in patients with CRC. Chemotherapy or targeted treatment is a treatment modality used either in neoadjuvant setting in order to achieve operability and avoid an extensive mutilating procedure, as an adjuvant therapy aimed at reducing the risk of postoperative recurrence or in palliative indication intended to maintain quality of life and prolong survival.

Localized early-stage disease (Stage I) – primary surgical resection is the treatment of choice. The character of procedure depends on the site of tumour. Hemicolectomy is indicated in both right- and left-sided tumours; rectal tumours are managed either by low anterior resection or abdomino-perineal amputation by Miles (with terminal sigmoideostomy) in the case of sphincter infiltration.

Curative surgical management should also include adequate lymphadenectomy (with removal of at least 12 regional lymph nodes).

Locally advanced disease (Stage II and III) - Surgical resection followed by six-month adjuvant chemotherapy based on 5-fluorouracil (5-FU) or its oral analogue capecitabine is indicated. Patients with stage III disease should receive a combination therapy with oxaliplatin. In rectal tumours, neoadjuvant chemoradiotherapy (with 5-FU) is followed by surgical resection and post-operative chemotherapy.

Metastatic disease (Stage IV) – patients are usually treated by palliative combination chemotherapy based on 5-FU and oxaliplatin (FOLFOX regiment) or irinotecan (FOLFIRI regimen). The effect of chemotherapy might be potentiated by the addition of targeted agents, such as anti-VEGF or anti-EGFR monoclonal antibodies (cetuximab or panitumumab). Analysis of RAS status (KRAS and NRAS) must be conducted prior to considering anti-EGFR therapy.

Basically, patients with metastatic CRC may be approached in three different ways:

- **Initially resectable disease** - these patients might undergo resection of metastases and subsequently receive systemic adjuvant chemotherapy. An alternative approach consists of perioperative administration of chemotherapy (e.g. 2-3 months of systemic treatment, then surgery and another 3 months of postoperative chemotherapy). In these cases, targeted agents are not indicated. Long-term results speak in favour of the perioperative chemotherapy strategy.
- **Potentially resectable disease** - if patient general health and comorbidities allow for it, an intensive preoperative chemotherapy with or without biological treatment might be indicated. The aim is to achieve a tumour reduction and enable subsequent curative resection. Usually, a combination of cytostatics such as irinotecan or oxaliplatin with 5-FU and bevacizumab or EGFR inhibitors (in patients with wild-type RAS proto-oncogenes) is used.
- **Unresectable disease or poor general state of health -** if metastases are inoperable or the patient is unable to undergo intensive chemotherapy, the treatment strategy should be directed towards survival prolongation and maintenance of good quality of life. Palliative systemic chemotherapy is based on 5-FU and oxaliplatin or 5-FU and irinotecan, possibly with the addition of targeted treatment.

An optimal treatment approach and the assessment of operability in patients with locally advanced or metastatic CRC should be discussed within the framework of interdisciplinary tumour board (so-called **multidisciplinary team board**). Besides surgical treatment of metastases (which is always preferred), local ablative techniques can be considered (for example radiofrequency or microwave ablation, cryoablation, stereotactic ablative radiotherapy), trans-arterial chemoembolization (TACE) or local intra-arterial chemotherapy.

Prognosis

Prognosis strongly correlates with the clinical stage of the disease. Five-year survival reported with stage I and II disease is 90%, in stage III it decreases to 70%. 5-year overall survival for patients with oligometastatic resectable stage IV CRC ranges from 40 to 50%, patients with unresectable metastatic disease treated by combination therapy have a median survival of 20-30 months. Estimated survival in patients who receive best supportive care is 5-6 months.

Follow-up in CRC survivors

- Colonoscopy in the first year, and then every 3-5 years aimed at detection of adenomas or recurrence of the disease
- Liver ultrasound every 6 months in the first 3 years, chest and abdominal CT scan in high-risk patients biannually in the first 3 years
- Chest X-ray once a year for 5 years
- Tumour marker examination (CEA) every 3-6 months for the first 3 years, then every 6-12 months up to 5 years (supposing the levels were increased prior to treatment)

Case Reports:

Case No. 1

A 55-year-old man complains about abdominal pain in the past three months, located mainly in the upper right quadrant accompanied by a feeling of fullness, irregular bowel movements and occasional presence of blood in the stool. At physical examination, hepatomegaly is evident and subsequent abdominal ultrasound examination reveals multiple liver metastases. The patient is referred to colonoscopy, which shows a semi-circular non-stenotizing tumour infiltration of the descendent colon. Histopathology confirms the diagnosis of G2 tubular adenocarcinoma with wild-type RAS. With these findings, the patient is referred to an oncologist.

What additional investigations should be performed?

The patient undergoes an abdominal CT scan which demonstrated multiple metastatic involvement in the left liver lobe and two metastases in the right lobe. Chest X-ray is negative, CEA is significantly elevated. Patient's general state of health is good despite a number of comorbidities. His abdominal pain is managed by weak opioids and the patient is otherwise asymptomatic, there is no risk of intestinal obstruction.

What treatment approach would you indicate?

The patient was started on palliative chemotherapy (5-fluorouracil + oxaliplatin) in combination with panitumumab (monoclonal anti-EGFR antibody). In the course of treatment, his bowel movements

improved and regression of hepatomegaly and decrease in CEA levels were observed. After 3 months of treatment, there was a marked disease regression (Figure 1.2) seen on the abdominal CT scan. Side effects of the treatment included peripheral neuropathy due to oxaliplatin and panitumumab-associated skin toxicity (Fig. 3).

Fig. 1: Metastatic liver involvement before therapy and regression after treatment

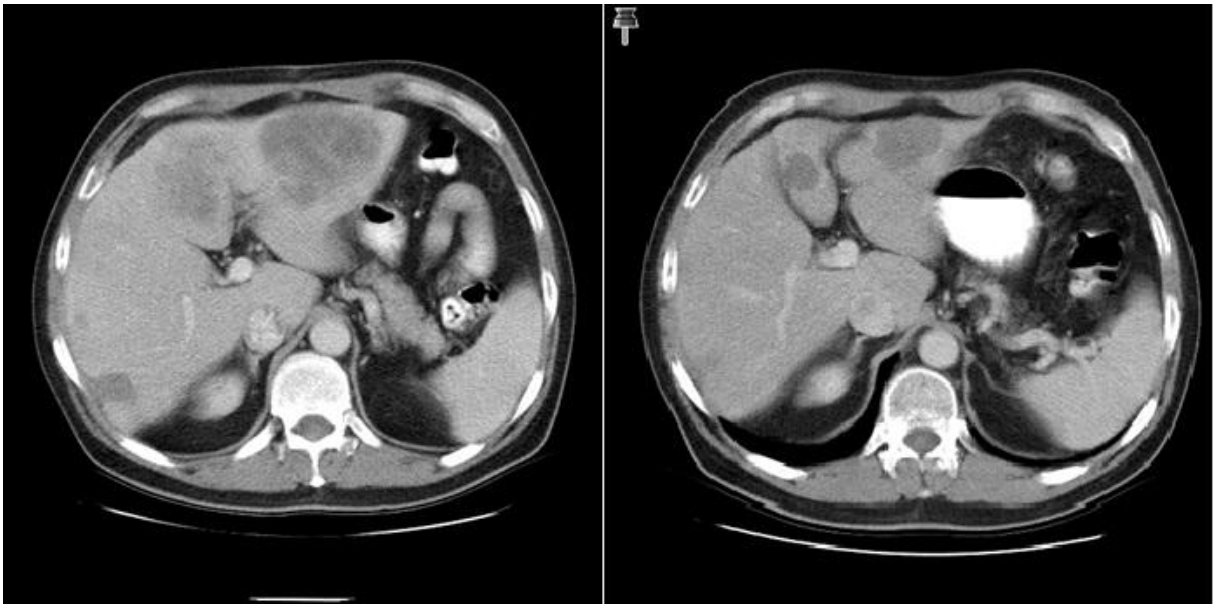
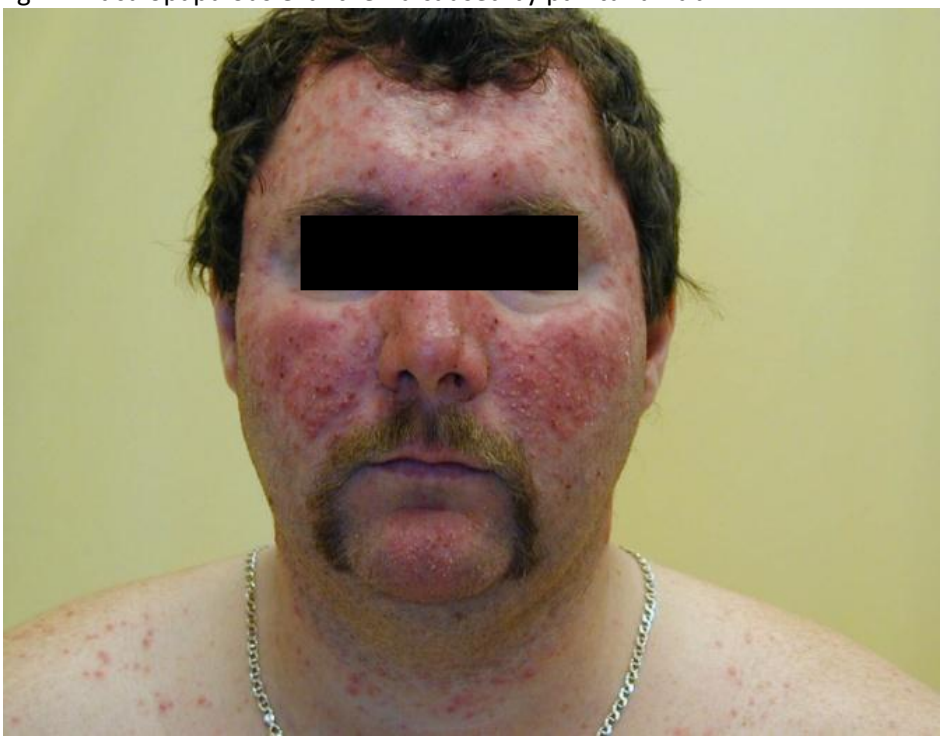


Fig. 2: Maculopapulous exanthema caused by panitunumab



Case No. 2

A 58-year-old woman without any serious comorbidities was referred to colonoscopy due to rectal bleeding and tenesmus. The examination revealed tumorous infiltration at 7 cm from the ano-cutaneous line, its lumen was permeable to the endoscope. There was no other pathology detected in the colon. Biopsy was taken and the patient was diagnosed with G2 adenocarcinoma. Transrectal ultrasonography (TRUS) was performed to complete the local staging and demonstrated regional lymph node involvement. CT scan of the chest, abdomen and pelvis did not show distant metastasis.

What treatment strategy would you recommend?

To achieve downstaging and downsizing of the tumour, the patient was indicated for neoadjuvant radiotherapy of rectum and regional lymph nodes with concurrent chemotherapy with capecitabine. After finishing the 5-week outpatient treatment, restaging with CT scan and TRUS was performed (Fig. 3).

What results would you expect?

There was a marked regression of the tumour, which allowed for a sphincter-preserving surgery. Only a fibrotic residue was macroscopically visible in the resection specimen (Figure 4). Histopathology revealed complete remission of the tumour (ypT0, N0).

Fig. 3: TRUS picture prior to treatment (locally advanced rectal carcinoma with pathological regional lymph node involvement) and after treatment (lymph node of normal echogenicity)

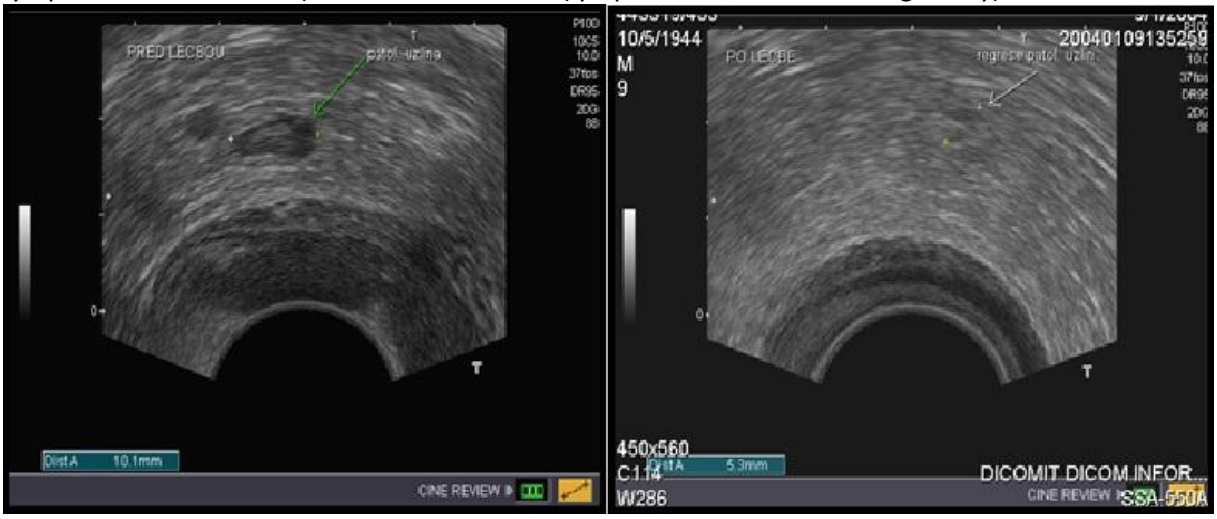
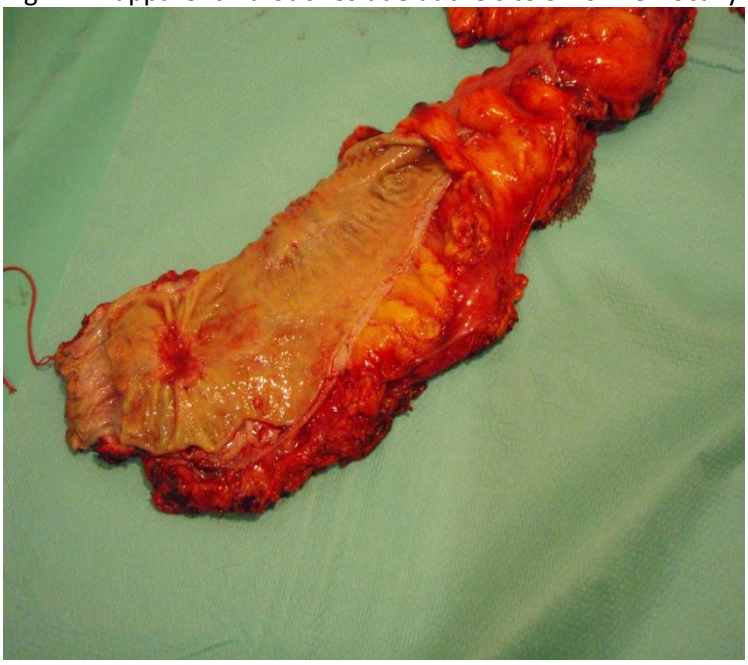


Fig.4: An apparent fibrotic residue at the site of former locally advanced rectal tumour



Anal carcinoma

I. Kiss, I. Kocáková, P. Šlampa

Epidemiology

Anal carcinoma comprises 1-2 % of all malignancies of the digestive tract. It occurs mainly in people aged 50 years and over. There are two types of anal cancer distinguished based on its relationship to the dentate line –mucosal-lined carcinoma of the anal margin or epidermis-covered anal canal carcinoma.

Aetiology

A particular role in the aetiology of anal cancer is attributed to HSV-2, HPV-16,18 and HIV infections. Other risk factors include anogenital condylomata, chronic immunosuppression after organ transplantation, prior pelvic radiotherapy, chronic perianal diseases (anal fistulas and fissures) and intraepithelial precanceroses such as Bowen's disease, Paget's disease or carcinoma in situ. Some studies also indicate the relation between anal cancer and receptive anal intercourse in males before the age of 30 years, prior treatment of cervical neoplasia in women or a history of sexually transmitted disease (gonorrhoea, syphilis, herpes genitalis). An important role in pathogenesis is assigned to a decrease in p53 activity (an E6 oncoprotein, which is produced by HPV virus, inactivates p53). There is also an evidence of the impact of cigarette smoking on the development of anal cancer.

The most common type of anal cancer is squamous cell carcinoma (ASCC), which accounts for 70 % of all anal cancers, basaloid carcinoma representing 20-25 % of all cases of anal cancers and muco-epidermoid carcinoma. Rare types of tumours include basalioma, anal adenocarcinoma, melanoma (3 %), small cell carcinoma, lymphoma and Kaposi's sarcoma (often associated with AIDS), undifferentiated carcinoma and carcinoid.

Clinical presentation

Anal cancer manifestation is similar to symptoms associated with rectal tumours: rectal bleeding, painful mass or ulceration, faecal incontinence, pruritus, signs of local tumour expansion. Anal carcinoma usually develops slowly and can be often mistaken for benign processes such as haemorrhoids or anal fissures. Lymphatic spread is more common than haematogenous dissemination. Metastatic liver involvement is reported in 5-8 % of all cases, spread to lungs and bones occurs in 4 % and 2 % of cancers, respectively.

Diagnostic methods and staging

Basic work-up comprises physical examination including DRE, gynaecological examination in women and past medical history focused on above-mentioned risk factors. Every patient with suspicious anorectal lesion should undergo biopsy for definitive histological diagnosis. Other necessary investigations include ultrasound of inguinal lymph nodes, anoscopy, transrectal sonography (TRUS), chest X-ray, abdominal and pelvic CT scan (or MRI), CBC, blood chemistry and SCC tumour marker examination in case of squamous cell carcinoma.

Prognostic factors:

- clinical stage (in T1 and T2 tumours, the 5-year survival rate is over 80 %)
- nodal status (5-year survival in patients with positive lymph nodes is 40%, whereas in N0 disease it approaches 100 %)
- grading (low grade tumours are reported to have 5-year survival of more than 75 %)
- gender (women have a more favourable prognosis)
- tumour localization (anal margin carcinoma has better prognosis)
- histology (cloacogenic carcinoma has better prognosis than squamous cell carcinoma)
- the dose of radiotherapy delivered to the tumour and regional lymph nodes

Treatment options

Prior to the introduction of standard concomitant chemoradiotherapy, 90% of patients with ASCC were treated with mutilating abdominoperineal anorectal amputation necessitating a permanent colostomy. Five-year survival of patients after radical abdominoperineal resection was 40-75 % depending on the clinical stage of the disease. Currently, **concomitant chemoradiotherapy** (with cisplatin + mitomycin) is the mainstay of ASCC treatment (especially in T2-T4 stages, sometimes also in T1 stage). In most cases, sphincter function is preserved (in about 80% of patients) and treatment outcomes are comparable to surgical management. Five-year survival after chemoradiotherapy is 32-90 % depending on the stage of the disease. At present, surgery is usually reserved for patients with recurrent cancer or persistent disease after chemoradiotherapy. Surgical or endoscopic excision is indicated only in very small surface lesions (1-2 cm) that do not invade the sphincter (Tis stages).

Treatment of anal adenocarcinomas is similar to the treatment of rectal adenocarcinomas and it is based on abdominoperineal resection and preoperative or postoperative radiotherapy or chemoradiation.

Radiotherapy as a standalone modality is indicated only exceptionally in patients whose general health condition does not allow for chemotherapy, such as elderly patients or HIV-positive patients in the AIDS stage who are expected to have lower tolerance to combination therapy.

Adverse effects of concomitant chemoradiotherapy

Systemic toxicity is primarily related to the impairment of haematopoiesis (leukopenia, thrombocytopenia, anaemia). Local gastrointestinal toxicity includes diarrhoea, pain, proctitis, tenesmus, bloody and mucous discharge. About 10-15% of patients report dysuria during the pelvic irradiation (due to actinic cystitis). Skin toxicity is very common, especially in the area of skin folds (inguinal, genital area, inter-gluteal cleft). Overall toxicity of multimodal therapy is often serious and requires specialized supportive treatment.

Follow-up recommendations

- Patients who achieved a complete remission should be seen for follow-up every 3-6 months for the first 2 years and then every 6-12 months up to 5 years after treatment.
- Physical examination including DRE and palpation of inguinal nodes is indicated. Alternatively, anoscopy or rectoscopy might be performed, however, the examination may not be tolerated well by the patients due to post-radiation pain syndrome.
- Liver ultrasound should be performed every 6 months in the first 3 years. Chest and abdominal CT scan is preferred in high-risk patients in the first 3 years.
- Annual chest X-ray should be obtained in five consecutive years.
- Tumour marker SCC should be taken every 3-6 months for 3 years, then every 6-12 months up to 5 years, if the pre-treatment value was increased.

Primary malignant tumours of the liver, gall bladder and biliary tract

I. Kiss, T. Andrašina

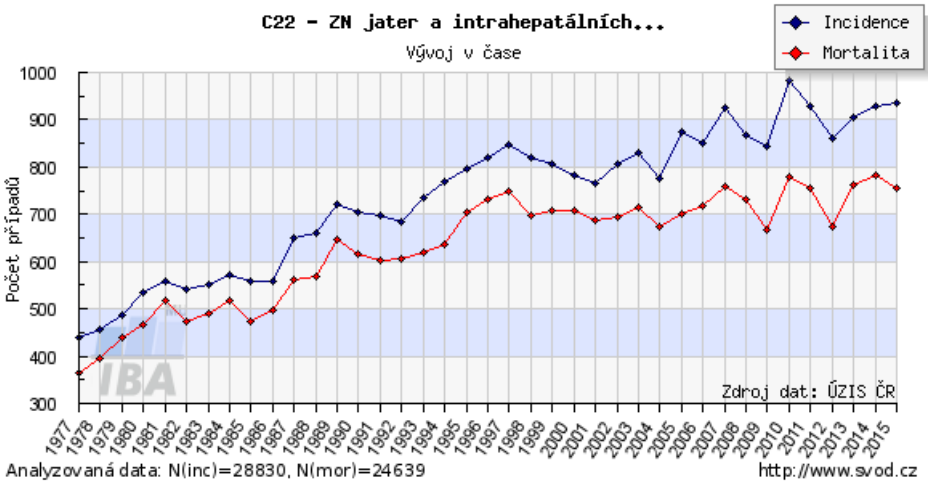
Introduction

Hepatocellular carcinoma accounts for 90% of all primary malignant liver tumours. The remaining 10 % include cholangiocellular carcinoma and mixed hepato-cholangiocellular carcinoma, and hepatoblastoma in children.

Hepatocellular carcinoma (HCC)

Epidemiology

HCC is a malignant tumour that displays the features of hepatocellular differentiation. There is a significant geographic variation described with the incidence of HCC, with highest incidence rates reported in East Asia (due to high prevalence of hepatitis B and C). Incidence and mortality of HCC in the Czech Republic is demonstrated in graph no. 1.



Risk factors

The major risk factor for developing HCC is chronic liver disease, usually alcoholic cirrhosis or due to HBV and HCV infection. Other risk factors include exposure to carcinogens (aflatoxin, castor oil, hydrazine, trichlorethylene, vinyl chloride) and certain drugs (steroid hormones, phenobarbital), less commonly hemochromatosis, Wilson's disease or porphyria cutanea tarda.

Screening and prevention

In contrast to the population-based screening programs for some cancers, HCC screening concerns only a narrowly defined group of at-risk patients. This target population includes: 1. patients with hepatic cirrhosis of any aetiology, 2. patients with chronic HBV infection (HBsAg positive), 3. patients

with chronic HCV infection and significant (stage 3) fibrosis or 4.hepatic fibrosis in patients with non-alcoholic steatohepatitis (NASH). Liver ultrasound is the primary screening examination that should be performed every 6 months. Given the limited possibilities of curative treatment of hepatocellular carcinoma, its prevention appears of key importance. This includes, in particular, the prevention and treatment of viral hepatitis B and C, alcohol addiction therapy and early detection and management of metabolic liver diseases.

Clinical presentation

Besides non-specific cancer-associated symptoms like anorexia, weight loss, abdominal pain, feeling of fullness or abdominal discomfort, HCC often presents with signs of decompensated liver cirrhosis. In non-cirrhotic patients, the first manifestation may be cholangitis due to tumorous invasion to bile ducts or Budd-Chiari syndrome due to hepatic vein or the inferior vena cava thrombosis.

Diagnostic workup

Findings on liver ultrasound and Doppler examination should be confirmed by CT, or, in case of doubt, by liver MRI. HCC usually has a **characteristic appearance pattern on a CT scan**, therefore a biopsy is not always necessary for its diagnosis (unlike in the vast majority of other solid tumours). Laboratory evaluation includes alpha-fetoprotein (**AFP**) determination (the sensitivity is about 60%). Extrahepatic metastatic involvement should be ruled out by abdominal CT scan, chest X-ray and bone scintigraphy. Metastases are most commonly found in the lungs, adrenal glands or bones.

Therapy

Prior to treatment decisions, it is important to evaluate the baseline characteristics of the tumour as well as the extent of liver disease. There are several staging systems including TNM classification or **Child Pugh** score (see Table no. 1). The most widely used staging system in clinical practice is the **Barcelona Clinic Liver Cancer system** (**BCLC system)** integrating both tumour and liver parenchyma assessment.

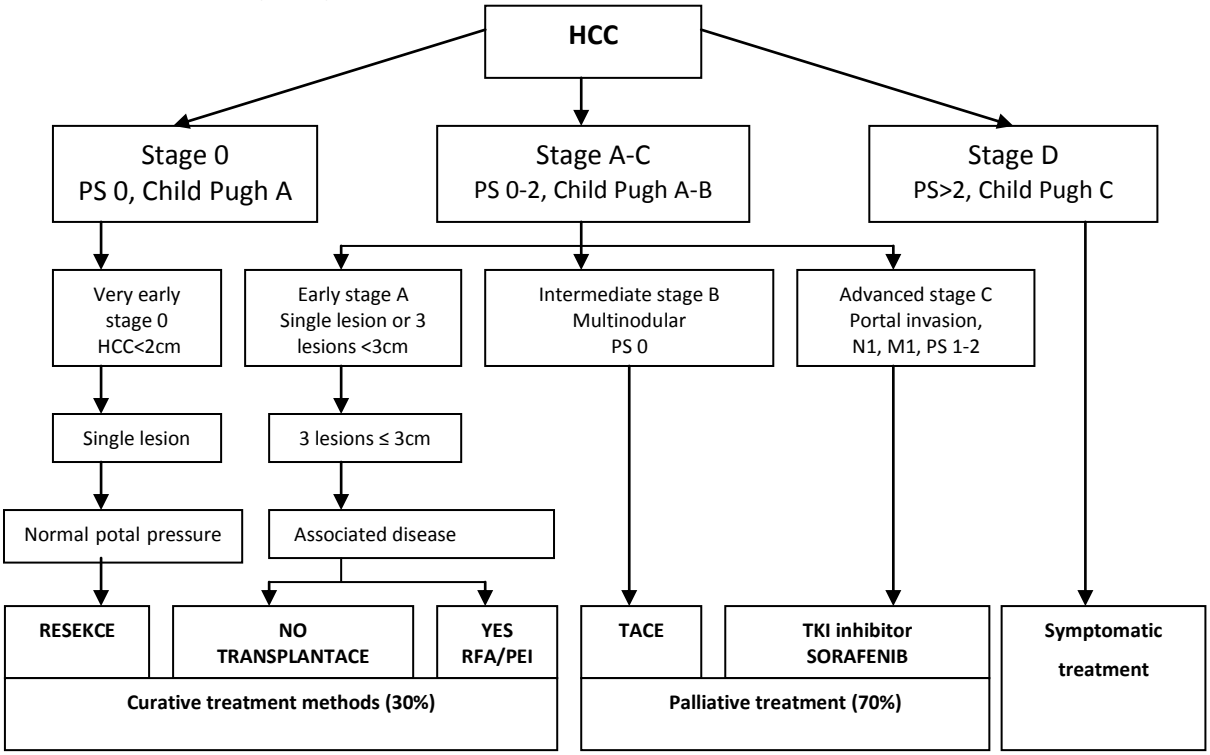
Table: **Child-Pugh** classification of liver cirrhosis

points	1	2	3
bilirubin (µmol / l)	<35	35-50	> 50
albumin (g / l)	> 35	28-35	<28
Ascites	0	reversible	irreversible

encephalopathy	0	mild	severe
INR	<1.7	1.71-2.20	> 2.20

Results: Class A: 5-6 points / class B: 7-9 points / class C: 10-15 points

The HCC treatment schedule, with respect to the clinical stage, functional liver reserve and expected treatment outcomes (BCLC)



Surgical treatment (liver resection or transplantation) is the only potentially curative method. Non-operative therapy options include local ablative methods such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation, cryoablation or laser ablation. The disadvantage of these techniques is a high recurrence rate and the necessity of repeated interventions. The most commonly used therapy is TACE, in which a vaso-occlusive material or a high local dose of cytostatic agent (usually **doxorubicin)** is delivered to the tumour through its feeding artery. Radiofrequency ablation (RFA) induces thermal coagulation necrosis by introducing a radio-frequency probe into the tumour tissue. Alternatively, percutaneous ethanol injection (PEI) might be used to destroy HCC lesions using a 96% ethanol, which causes denaturation of proteins and dehydration and necrosis of tumour cells.

In metastatic disease, treatment with targeted agents (e.g. tyrosine kinase inhibitor **sorafenib**) may be considered, however, the overall survival benefit is modest (a few months) compared to best supportive care. Given the chemoresistance of HCC, systemic chemotherapy has a minimal impact on survival compared to surgical methods and local ablation techniques.

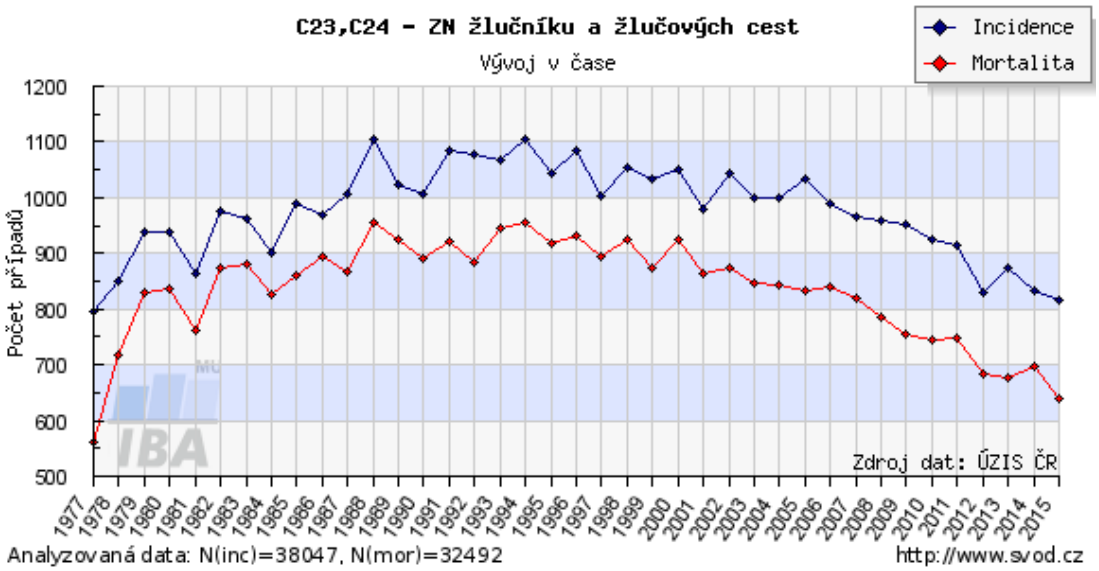
Prognosis and dispensarization

Unfortunately, the recurrence rate of HCC continues to be very high. Despite advances in diagnosis and treatment, 5-year overall survival of patients with HCC does not exceed 2%. The median survival in an untreated patient ranges from 1 month to 1 year.

After liver resection, ultrasound should be performed every 3 to 6 months for the first 2 years. In the case of pre-operative AFP elevation, serum measurements should be obtained every 3 months for the first 2 years, and then every 6 months. If a recurrence of the disease is detected, the investigations should proceed as in the case of primary disease.

Tumours of biliary tract and gall bladder

Cholangiocarcinoma (CCA) is the second most common primary liver tumour that stems from the epithelial cells of intrahepatic bile ducts. Depending on their location, CCAs are classified as intrahepatic carcinomas (proximal to hepatic duct bifurcation), extrahepatic carcinomas and gallbladder carcinomas. Extrahepatic CCAs have a predilection for the confluence of hepatic bile ducts (so-called Klatskin tumour). The most common biliary tract cancer is gallbladder cancer, which, however, accounts for only 2% of all malignant tumours.



Aetiology and pathogenesis

Several risk factors have been identified in the etiopathogenesis of CCA. Most common underlying conditions include chronic cholestasis, hepatolithiasis, primary sclerosing cholangitis, biliary tract anomalies and parasitic infections. More than 70% of patients with gallbladder cancer are diagnosed with cholecystolithiasis. A so-called porcelain gallbladder (presence of calcifications) is considered a precancerous condition. Benign polyps might progress to a malignant cancer as well.

Clinical presentation

Clinical manifestation is similar to those of hepatocellular carcinoma, in addition, obstructive jaundice accompanied by fever and rigors due to cholangitis are frequent presenting symptoms. Gallbladder cancer is often an incidental finding during an elective surgery due to cholecystolithiasis.

Besides jaundice, patients often present with enlarged and painless gall bladder (so-called Courvoisier's sign) supposing the obstruction is situated below the cystic duct. The typical combination of fever, jaundice and abdominal pain is referred to as Charcot's triad.

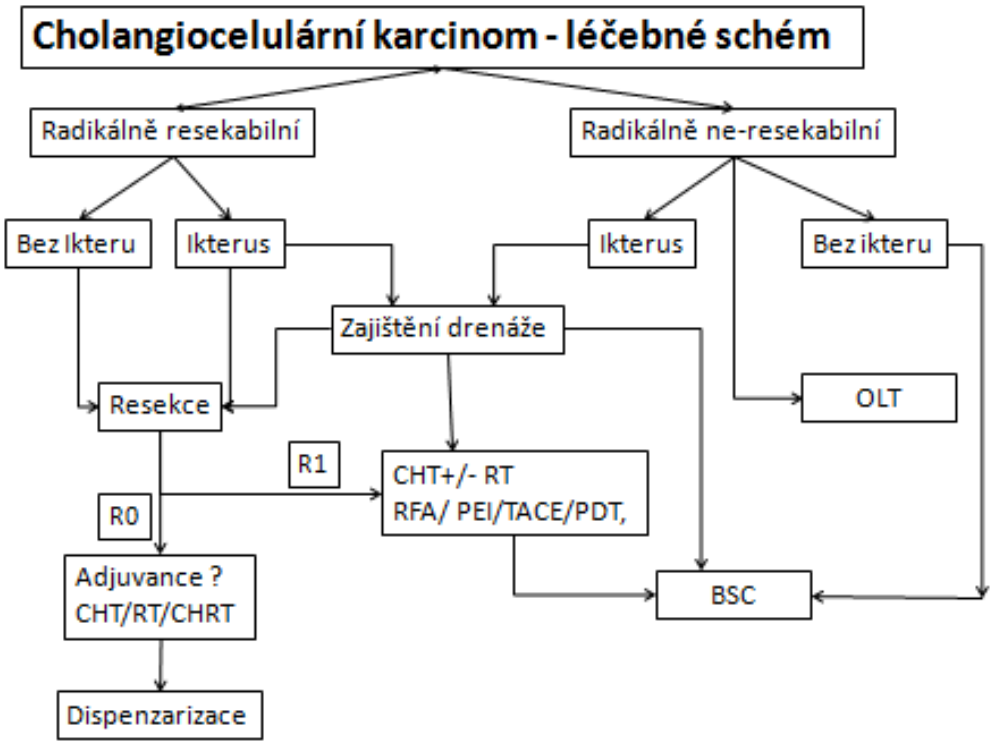
Diagnostic workup

Diagnostic imaging studies involve ultrasound, abdominal CT scan, endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC). Alternatively, novel non-invasive methods such as MRCP- MRI cholangiopancreatography are available. CEA and CA19-9 tumour markers might be elevated and used for disease monitoring. However, the levels are often influenced by benign cholestasis and their elevation must not always indicate a malignancy.

Therapy

Radical resection is the therapeutic method of choice, however, late diagnosis usually precludes patients from curative treatment and most of them eventually receive systemic therapy. Of note, CCA is intrinsically a chemoresistant disease and chemotherapy is of limited efficacy. Combination chemotherapy with 5-fluorouracil, leucovorin and cisplatin, or cisplatin and gemcitabine, or monotherapy with gemcitabine in elderly or compromised patients is often used.

Symptomatic therapy includes endoscopic techniques to relieve biliary obstruction, such as duodeno-biliary stenting provided by ERCP, or percutaneous transhepatic drainage (PTD) in which a radiologist introduces a catheter into the obstructed hepatic duct through an incision in the abdominal wall and if possible, establishes an internal drainage (to the intestine) or external drainage into a collection bag. In any case, stents and catheters have to be changed at particular intervals depending on their type. Brachytherapy, in which a radiation source is introduced intraluminally to the stent can prolong its lifetime period and provide a better symptom relief. Photodynamic therapy (PDT) is also being tested in clinical trials.



Prognosis

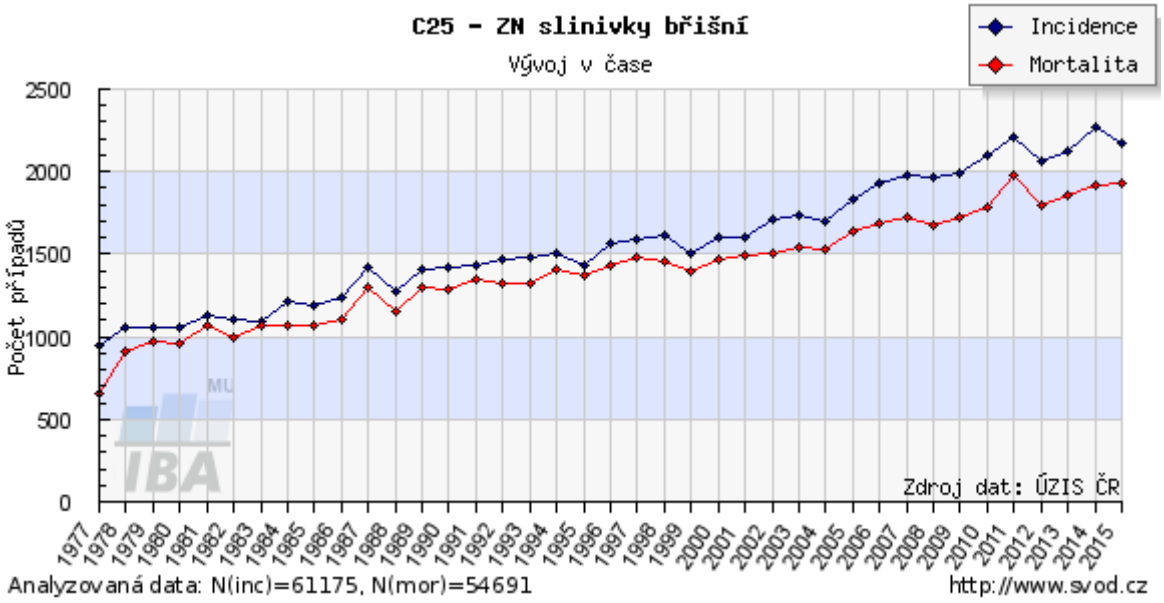
The prognosis of patients with cholangiogenic carcinoma is generally poor and surgical procedures are associated with high mortality rates. Five-year survival after radical liver resection ranges from 25 to 55%.

Pancreatic tumours

R. Němeček, P. Karásek

Epidemiology

Pancreatic carcinoma (PC) is the fourth most common cause of cancer death worldwide, and the Czech Republic has the second highest incidence of this disease, with as many as 2200 new PC cases diagnosed each year. The incidence of PC over the past 20-30 years has been steadily rising. Mortality closely reflects the incidence with about 1900 PC deaths reported annually.



The vast majority of pancreatic tumours (70-90 %) are diagnosed in an advanced inoperable or disseminated stage. The most common histological type is **adenocarcinoma** derived from epithelial cells of pancreatic ducts. **Pancreatic neuroendocrine tumours (pNET)** account for less than 5 %. In contrast to adenocarcinomas, their prognosis is significantly better (one-year survival in adenocarcinoma is below 20 %, while in pNETs it is about 80 %).

Risk factors

Most cases of PC occur sporadically. In some patients, development of PC is associated with hereditary conditions such as BRCA2 and BRCA1 mutations, Peutz-Jeghers syndrome, Lynch syndrome, familial adenomatous polyposis and others. A higher risk of PC is also reported with hereditary pancreatitis. A particular role in the etiopathogenesis is also attributed to chronic pancreatitis and there is an increased risk of PC found in patients with diabetes mellitus. The relationship between PC and diabetes is also reverse, i.e., PC is often associated with the onset of diabetes. Typical preventable risk factors include smoking, alcohol consumption, obesity. The role of vitamin D deficiency remains elusive.

Screening and prevention

There is not any population-based screening for PC. The most effective prevention of PC is related to the above-mentioned avoidable lifestyle factors.

Clinical presentation

One of the biggest pitfalls of PC is its long period of **asymptomatic growth**, which makes an early diagnosis practically impossible. Most patients with pancreatic head carcinoma present with **obstructive jaundice**. Another typical sign of an advanced disease is severe pain in the epigastrium radiating into the back, which is caused by the **infiltration of plexus coeliacus**. PC is also associated with loss of appetite and significant weight loss, meteorism and postprandial abdominal pain or vomiting (due to insufficient exocrine pancreatic function), fatigue and weakness. Most of the patients have new-onset glucose intolerance or diabetes at the time of diagnosis.

Diagnostic methods and staging

For initial imaging, abdominal CT is the most appropriate method. In the case of biliary obstruction being the first presenting symptom, ERCP is the primary diagnostic technique, which allows for stent insertion and brush cytology sampling for histopathology confirmation. If possible, endosonography with fine-needle aspiration biopsy (FNAB) is the preferred diagnostic method. For complete staging information, chest X-ray or CT scan and examination of tumour markers (typically CA 19-9 and CEA) should be performed.

Staging (according to TNM classification):

Stage I - Tumour limited to pancreas.

Stage II – locally advanced disease including nodal involvement, without invasion to superior mesenteric artery or celiac axis. (i.e. the disease is potentially operable).

Stage III - the tumour invades coeliac axis or mesenteric artery (unresectable disease).

Stage IV – metastatic disease

Principles of treatment

Patients with stage I and II disease with favourable overall health status and no significant comorbidities are candidates to radical surgery. The most common surgical procedure, known as **Whipple procedure** or **HPDE (hemipancreatoduodenectomy)** is suitable for patients with pancreatic head cancer. Tumours of the pancreatic body might be managed by total pancreatectomy, while distal pancreatectomy is indicated in patients with pancreatic tail tumours. All the procedures are associated with significant risks and perioperative mortality, long operative time (usually up to 7

hours) and subsequent pancreatic insufficiency. Due to high recurrence rates, adjuvant chemotherapy based on gemcitabine or 5-fluorouracil (5-FU) is recommended in most of the patients. Recent data favour the use of intensified **FOLFIRINOX regimen** in adjuvant as well as palliative setting.

Patients with stage III and metastatic (stage IV) PC are treated with systemic palliative chemotherapy with 5-FU or gemcitabine, which if used in monotherapy, offers a survival benefit of approximately 6 months. Best results can be achieved with the administration of multi-agent regimens combining 5-FU, with irinotecan and oxaliplatin (**FOLFIRINOX** regimen), preferably in patients with good performance status who can tolerate such an intensive therapy. This combination has a 30% response rate and a 12-month survival advantage. Alternatively, the use of gemcitabine monotherapy or a combination of gemcitabine and paclitaxel might provide a reasonable clinical benefit. Response rates are reported to be approximately 25% and median overall survival is up to 9 months. Supposing a tumour regression is achieved in a patient with locally advanced PC after 3 moths of chemotherapy, the treatment may proceed with concomitant chemo-radiotherapy (with 5-FU or gemcitabine) or SBRT in particular cases. Still, potential risks of these palliative methods should be weighted with improved quality of life in every individual patient. Patients with poor performance status, who are unable to undergo chemotherapy, are indicated for symptomatic treatment.

The treatment approach to **pNET** is substantially different and its detailed description goes beyond the scope of this publication. Besides radical resection and chemotherapy, the use of **somatostatin analogues** and radionuclide therapy is a common treatment option.

Follow-up

In the first 2 years after curative and adjuvant treatment, follow-up visits are indicated every 3-6 months. Unfortunately, a vast majority of patients is diagnosed with a relapse of the disease in this period. Follow-up visits comprise physical examination, basic laboratory tests including tumour markers (CA 19-9 and CEA), abdominal CT can be obtained every 6 months. Follow-up of patients with pNET depends on the size, grade and the extent of tumour.

Prognosis

Prognosis of PC is dismal, evidenced by the fact that even after radical resection (which is possible in only 10-20 % of cases) most patients relapse within 1-2 years after the primary treatment. Median overall survival of these patients ranges from 24 to 54 months. In locally advanced disease (30% of patients), the overall survival is reported to be 8 - 24 months, while the median overall survival for metastatic PC (60% of patients) is from 6 to12 months.

Prognosis of patients with pancreatic NET is significantly more favourable, approximately 80 % of patients will survive for one and more years.

Tumours of the lungs, mediastinum and pleura

J. Skřičková, B. Kadlec. M. Šatánková

Lung cancer

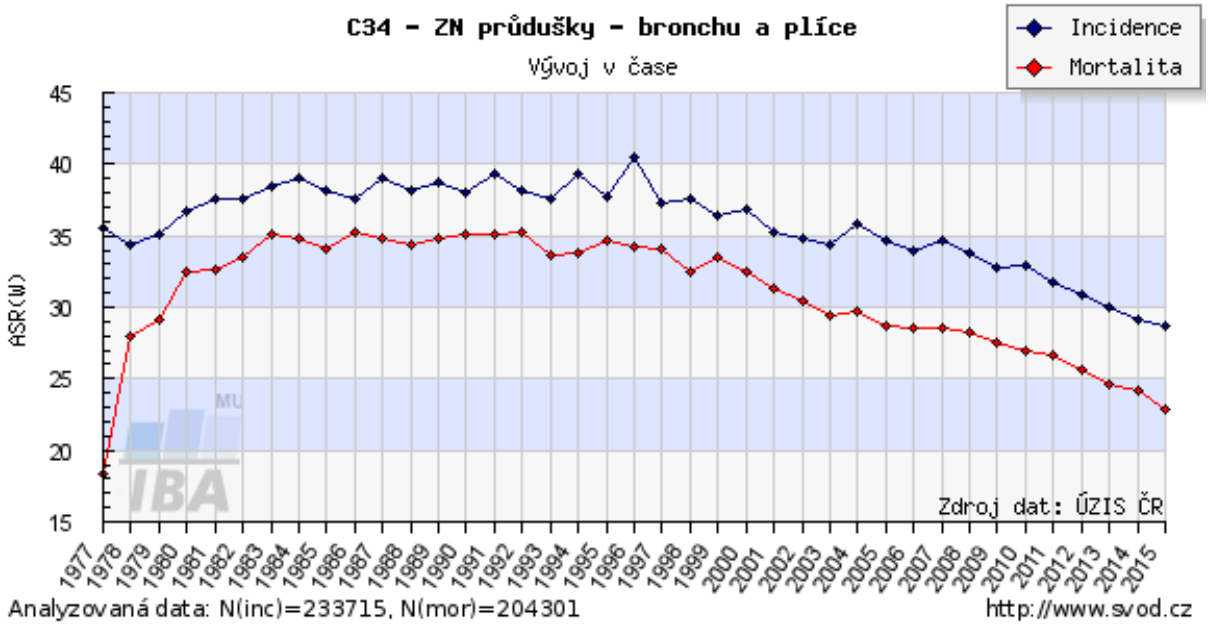
The term bronchogenic carcinoma (lung cancer) refers to a tumour arising in the central airways as well as pulmonary parenchyma. Generally, lung cancers are usually heterogeneous tumours comprising malignant cells with various degrees of differentiation or even distinct histological subtypes.

Types of lung cancer

In the clinical practice, there are two main types of bronchogenic carcinoma distinguished: **small cell lung carcinoma** (SCLC) and **non-small cell lung cancer** (NSCLC). SCLC accounts for 15-20% and non-small cell carcinomas for 80-85% of all lung tumours.

Epidemiology

According to national cancer registry, bronchogenic carcinoma is the second most common cancer in males and the leading cause of cancer-related death at the same time. In women, the incidence of lung cancer has significantly increased in the past few years and became the third most common cancer in women.



Aetiology

Endogenous risk factors include increased cytochrome P450 activity, which is responsible for higher susceptibility to tobacco-derived carcinogens, decreased activity of glutathione S-transferase, which plays a role in detoxification of aromatic hydrocarbons, and decreased activity of cellular DNA repair mechanisms. The 3p21 deletion, p53 suppressor gene mutation and other chromosomal aberrations underlying bronchogenic carcinoma have also been identified.

Tobacco smoking is the most significant **exogenous risk factor.** Lung cancer risk is about 20 times higher in individuals who have smoked more than 20 cigarettes per day for 20 years, compared to never-smokers (the lower limit associated with significant lung cancer risk is 200,000 cigarettes). Epidemiological studies have also showed an increased risk of developing bronchogenic carcinoma in **passive smokers.** Other risk factors include exposure to **radon**, **asbestos**, inorganic arsenic compounds, bischlormethylether, chromium, nickel and polyvinyl chloride compounds, **ionising radiation** and many others**.**

Screening and prevention

The main preventive measure is the **elimination of** external risk factors, especially **smoking cessation.** To date, there are no widely accepted guidelines for mass screening in high-risk individuals.

Clinical presentation

There are no specific warning signs that would allow for an early recognition of lung cancer and a vast majority of lung cancers are in advanced stage at the time of diagnosis. Presenting symptoms can be divided into three distinct groups:

Intrathoracic symptoms:

- Persistent cough in an individual without any history of chronic bronchitis or other respiratory disease.
- Change in the character of chronic cough in smokers (higher frequency, intensity, irritability, provoking factors).
- Haemoptysis (coughing up blood).
- Recurrent pneumonia confined to a specific part of lung.
- Chest pain.
- Hoarseness caused by recurrent laryngeal nerve compression and vocal cord paresis.
- Superior vena cava syndrome resulting from expansion of the tumour in the upper thoracic aperture, manifested by venous distension in the neck veins and later by facial and neck oedema (known as collar of Stokes) and cyanosis.
- Swallowing difficulties associated with central tumours causing compression of the oesophagus.

- Dyspnoea caused by the tumour itself and / or resulting from malignant pleural effusion

Non-respiratory symptoms are usually induced by distant metastases. Brain metastases underlie neurological or psychological disorders, bone metastases present with pain, pathological fractures or anaemia. By contrast, hepatic metastases, which are very frequent, may remain clinically silent for a long time.

Paraneoplastic symptoms are also very common in lung cancers and may be the first presenting symptom of the disease.

Diagnostic methods

- **Physical examination** findings do not usually reveal a pathology. Occasionally, we may encounter decreased or absent breath sounds, tubular breathing, or coarse rales.
- **Chest radiograph** often shows a mass shadow in the peripheral pulmonary parenchyma or centrally located lesions adjacent to mediastinal structures. Other associated findings may include pleural and pericardial effusions, atelectasis or pneumonia.
- **Contrast-enhanced CT scan of the chest** is crucial for the diagnosis of lung cancer. It is important for determining the exact range of the tumour itself and for the assessment of hilar and mediastinal lymph nodes. **Chest MRI** provides a more accurate delineation of tumour from adjacent soft tissues. This examination is particularly useful in tumours suspected from chest wall invasion or for assessment of Pancoast tumour (located in the pulmonary apex).
- **Positron emission tomography (PET)**, especially when combined with a CT scan can help to demarcate viable tumour tissue from surrounding atelectasis and detect pathologic activity in affected lymph nodes or distant metastases.
- **Abdominal sonography** is the most commonly used method to detect metastases in abdominal cavity (primarily in the liver) and the retroperitoneum.
- **Bone scintigraphy** is an imaging method that can be used for evaluating bone metastases. The indication depends on the type of bronchogenic carcinoma. In NSCLC, bone scan can be indicated in case of indeterminate CT findings.
- **CT scan of the brain** is a part of standard staging work-up in lung cancer patients. In a metastatic disease, clinical signs of brain involvement (dizziness, nausea, vomiting, neurological impairment, etc.) may warrant CT investigation.
- Endoscopy methods are invaluable in the evaluation of endobronchial tumour extension and for obtaining specimens for histological and / or cytological examination. These techniques involve bronchoscopy, endobronchial ultrasound (EBUS), video-assisted thoracoscopy (VATS), or mediastinoscopy. An alternative is a targeted transparietal biopsy under CT control.
- **Molecular genetics** is of particular importance in NSCLCs, used for the identification of EGFR, ALK, and ROS gene mutations.
- **PD-L1 expression** testing is used to predict the sensitivity of tumour to immunotherapy

The definitive diagnosis is based on **histopathological** findings. Lung cancers are divided into two main groups: **small cell** and **non-small cell lung carcinomas**, which comprises squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and non-specific/undifferentiated carcinoma.

Clinical stages

- **Non-small cell lung carcinoma**: the TNM system is used for NSCLC staging
- In clinical practice, **small cell lung cancer** is categorized as **limited disease** (LD) if the tumour is confined to one lung only with metastasis to ipsilateral mediastinal or supraclavicular lymph nodes or ipsilateral pleural effusion, which can be encompassed in a single radiation field. **Extensive disease** (ED) spreads beyond ipsilateral hemithorax.

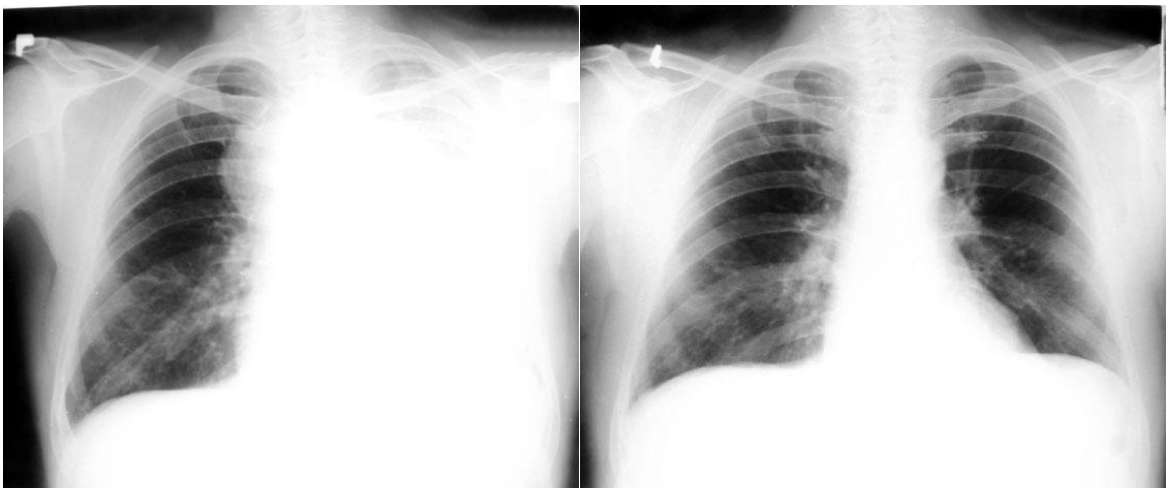
Therapy

Small Cell Lung Cancer (SCLC)

Patients with **limited disease,** with good performance status and usually younger than 65-70 years are indicated for **concomitant chemoradiotherapy**. The most commonly used regimen is a combination of cisplatin and etoposide or carboplatin with etoposide. **Sequential chemoradiotherapy** is an alternative for elderly patients or patients not suited for concurrent treatment. There is a response rate of 70-90% reported with the multimodal treatment. Median survival of patients with LD SCLC ranges from 14 to 20 months. An example of treatment efficacy is shown in Fig. 1.

Combined chemotherapy regimens also significantly prolong the overall survival in **patients with an extensive stage of small cell carcinoma.** The same cytotoxic agents as in the treatment of limited disease are used. Response rates are usually high, however short lived. If **SCLC recurrence** develops beyond 3 months of completing the initial treatment (so-called chemosensitive disease) the patient can be retreated with the original chemotherapy regimen. If a relapse occurs within 3 months (chemoresistant disease) topotecan can be used in monotherapy, however, the response rate is only 10%. Recent data favour the administration of palclitaxel in these patients.

Figure 1. Malignant bronchogenic carcinoma before and after concomitant chemo-radiotherapy



Non-small cell lung cancer (NSCLC)

The treatment options for NSCLC are based on the TNM stage and the type of tumour, as well as patient's characteristics such as lung function or overall health status. More than a half of patients with NSCLC are diagnosed with advanced stage disease (IIIB and IV).

Surgical resection remains the only curative treatment in patients with early-stage NSCLC (I and II) who are eligible for operation. Surgery might be considered also in some patients with stage IIIA tumours after neoadjuvant chemotherapy or chemoradiotherapy. In the Czech Republic, only 10-17% of NSCLC patients are eligible for curative surgery at the time of diagnosis.

The vast majority of patients present with an inoperable or metastatic disease. Chemotherapy is the preferred treatment modality in this case. **At clinical stage IIIB, subsequent or concurrent radiotherapy** might also be considered**.** The most commonly used cytostatics include cisplatin, carboplatin, paclitaxel, docetaxel, vinorelbine or gemcitabine. Lung adenocarcinoma and large-cell carcinomas may be treated with antifolate pemetrexed in combination with cisplatin. If a disease control has been achieved after four cycles of this combination therapy, monotherapy with pemetrexed might proceed until disease progression (**maintenance therapy).**

Patients with early-stage disease who are not amenable to surgery might be offered definitive chemoradiotherapy.

Targeted treatment of NSCLC

Patients with EGFR activating mutations can be treated with oral **EGFR tyrosine kinase inhibitors** - erlotinib, gefitinib, or afatinib. In clinical practice, treatment with tyrosine kinase inhibitors of EGFR is characterized by rapid onset of action and high response rate. The duration of response is approximately 10-11 months, and is often followed by a vigorous progression of the tumour. Several mechanisms of secondary resistance exist, the most common cause (up to 60%) being the T790M

mutation of the EGFR. A second-generation EGFR TK inhibitor osimertinib was developed to overcome this acquired resistance.

Another targeted agent used in the treatment of NSCLC is **bevacizumab** (antiVEGF antibody), which is indicated in combination with platinum-based chemotherapy in the 1st line treatment of patients with non-squamous NSCLC who do not have a history of haemoptysis (due to a higher risk of bleeding associated with bevacizumab).

In patients with **ALK–positive** lung cancer, **ALK** (anaplastic lymphoma kinase) **inhibitors** such as crizotinib, alectinib or ceritinib might be integrated into the treatment strategy.

Immunotherapy in NSCLC

NSCLC belongs to cancers with high mutational load, which is believed to be predictive of good response to immunotherapy. Recently, immunotherapy has become an important part of treatment algorithm, especially in patients without any driver mutations. Checkpoint inhibitors used in the treatment of NSCLC target either programmed death receptor (PD-1) – nivolumab and pembrolizumab or its ligand (PD-L1) - atezolizumab and durvalumab. The indication depends on the histology and extent of the tumour, the level of PD-L1 expression or patient's overall health.

Follow-up

Chest radiograph or CT scan, abdominal ultrasound and bronchoscopy are recommended every 3 months in the first year after completing the initial treatment and every 6 months thereafter. Every sudden change in chronic respiratory symptoms should warrant further investigation.

Prognosis

Trends of 5-year survival rates over time in patients by clinical stages are summarized in the table below.

Clinical stage	**5-year survival of lung cancer patients in different time periods / months (%, 95% confidence intervals)**				
	1990-1994	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2013**
I	23.5 (21.1-26.1)	33.7 (30.9-36.6)	43.4 (40.3-46.4)	52.2 (49.5-54.8)	61.2 (58.3-63.9)
II	9.4 (7,6-11,4)	16.7 (14.3-19.3)	21.6 (19.1-24.2)	25.9 (23.3-28.5)	33.5 (30.2-36.8)
III	6.1 (5.0-7.4)	8.6 (7.6-9.6)	8,9 (7,9-9,8)	10.7 (9.7-11.6)	13.9 (12.7-15.1)
IV	2.0 (1.4-2.8)	2,3 (1,8-2,9)	2.7 (2.2-3.3)	4.0 (3.5-4.5)	4.9 (4.4-5.5)
Total	9.2 (8.5-10.0)	11.0 (10.4-11.7)	12.0 (11.4-12.6)	14.4 (13.8-15.0)	17.1 (16.5-17.8)

Carcinoid

Carcinoid is a rare bronchopulmonary neuroendocrine tumour (NET), which accounts for approximately 1% of all lung cancers. According to the 2010 WHO classification, lung NETs can be classified as well-differentiated - typical carcinoids (low-grade NET), intermediate-grade atypical carcinoids and poorly differentiated large or small cell carcinomas.

Klasifikace plicních karcinoidů	Dobře diferencované		Špatně diferencované
Grade	**G1 (typický karcinoid)**	**G2 (atypický karcinoid)**	**G3 (karcinom - SCLC)**
Ki-67 index (mitotický index)	<=2	3 --20	>20
Funkční zobrazení	Octreoscan + SPECT PET (5-HTTP, 68-Gadolinium)		FDG PET
Prognóza	Příznivá	Méně příznivá, koreluje s diferenciací	Špatná
Léčba	chirurgická pro lokalizované onemocnění	chirurgická léčba chemoterapie somatostatinová analoga everolimus	chemoterapie, radioterapie

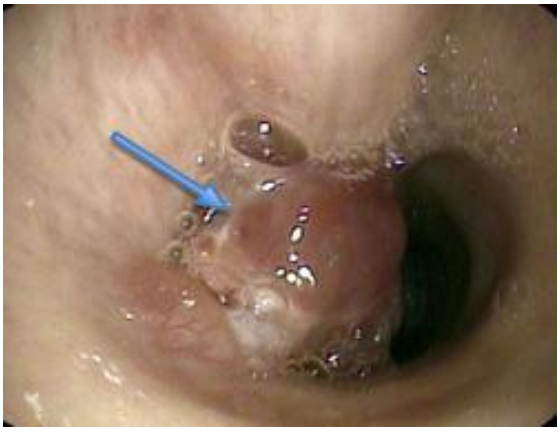
Lung NETs are of entodermal origin and their clinical presentation may range from indolent behaviour (in typical carcinoid) to an aggressive high-grade malignancy such as large-cell neuroendocrine carcinoma. A particular role in the etiopathogenesis is attributed to derangement of **PI3K / Alt / mTOR** signalling cascade and its associated transduction pathways such as IGF-1 or VEGF receptor pathway.

Carcinoids have significantly better prognosis compared to lung carcinomas (typical carcinoid has a 5-year survival of 90-98%, for atypical carcinoid it ranges from 40 to 65 %).

Carcinoids often grow endobronchially, and typical presenting symptoms include **haemoptysis** and **signs of bronchial obstruction** (recurrent obstructive pneumonitis, wheezing, dyspnoea), while **carcinoid syndrome** (manifested by diarrhoea, flushing or bronchospasm) is more typical in gastrointestinal carcinoids. Patients may sometimes present with symptoms associated with ectopic hormone production.

Lung carcinoid is the most common epithelial bronchial tumour in children and adolescents and it is often manifested as recurrent spastic bronchitis or recurrent obstructive pneumonitis and can be mistaken for bronchial asthma.

Fig. 2. Bronchoscopic image of carcinoid in the main bronchus



Diagnostic workup:

Laboratory evidence of 5-hydroxyindole acetic acid (5-HIOK) - a breakdown product of serotonin in urine may help to establish a diagnosis of carcinoid. Another tumour markers include chromogranin or neuron-specific enolase (NSE).

The most important immune-histochemical features of carcinoid are positive chromogranin A, synaptophysine and NSE staining, which are common to all neuroendocrine tumours.

Imaging methods used to determine the localization and the extent of carcinoid are HRCT of the chest or PET/CT. On the other hand, octreoscan (targeting somatostatin receptors that are expressed in some carcinoids) appears to be more sensitive for low-grade carcinoids. Bronchoscopy is another commonly used diagnostic method that allows for tissue sampling at the same time.

Treatment

Treatment of choice in localized carcinoids is surgical resection. Endobronchial removal is recommended only in particular cases (management of symptomatic endobronchial obstruction prior to curative surgery, treatment of tumours without an extension through bronchial cartilage). Systemic therapy is reserved for patients with advanced, inoperable carcinoid and includes chemotherapy and somatostatin analogue therapy, or relatively new agents combining peptide receptor radionuclide therapy with somatostatin analogues. Several cytostatic agents were investigated in patients with advanced carcinoid such as etoposide, platinum derivatives, capecitabine, doxorubicin, cyclophosphamide, temozolomide and 5-fluorouracil, however, they showed only limited efficacy. Due to their low proliferative activity, carcinoids display a high level of chemo- and radioresistance. More promising results were reported with the use of mTOR inhibitor everolimus. Currently, antiangiogenic agents and drugs involved in the PI3K / Akt / mTOR cascade are under investigation.

Benign lung tumours

The most common benign lung tumours include **chondrohamarthomas** and tumours of mesenchymal origin such as **fibromas, lipomas, myxomas, papillomas, myoblast myomas** and others. They are rarely symptomatic and most lesions are diagnosed incidentally. They are often **located peripherally within lung parenchyma,** whereas endobronchial involvement is uncommon. The course of the disease is indolent also due to longer doubling time of these tumours, which is counted in the order of years. Plain chest radiograph usually demonstrates a well-circumscribed lesion, but it fails to detect endobronchial tumours. They mostly manifest with signs of endobronchial obstruction (cough, dyspnoea) and bronchoscopy is the superior diagnostic method in these cases. Treatment of symptomatic tumours is chiefly surgical, endobronchial removal (with laser or electrocautery) is appropriate in symptomatic intraluminally growing tumours.

Mediastinal tumours

Epidemiology

Mediastinal tumours account for 90% of all mediastinal masses. A variety of tumours may develop in this location, representing about 3% of all thoracic malignancies. In adult patients, the most common types are lymphomas, thymic malignancies, germ cell tumours and thyroid cancer.

Clinical presentation (mediastinal syndromes)

Anatomically, mediastinum is divided into anterior, middle and posterior compartment. The location of a mass underlies a specific set of symptoms, reported as mediastinal syndromes, caused by direct mass effect on the anatomic structures of the particular compartment.

- ***Anterior mediastinal syndrome*** is often associated with superior vena cava syndrome.
- ***Middle mediastinal syndrome*** is characterized by respiratory insufficiency, stridor, dyspnoea, cough, and atelectasis in the corresponding lung segment. Hoarseness develops as a result of recurrent nerve compression. Imaging methods can show diaphragmatic elevation, clinically patients can suffer persistent hiccups due to phrenic nerve irritation. The affliction of the vagus nerve can result in dry irritant cough, dyspnoea, tachy- or bradycardia, or swallowing difficulties.
- ***Posterior mediastinal syndrome*** is most often manifested by neurological symptoms resulting from cancer invasion to the spine and spinal cord. Typically, Horner's triad (miosis, enopthalmus and ptosis) may occur as a result of cervical sympathetic trunk involvement. Pancoast-Tobias syndrome is indicative of brachial plexus compression and includes shoulder pain and upper limb muscular atrophy.

- ***Diffuse mediastinal syndrome*** occurs in case massive involvement of mediastinal structures with an extensive tumour or diffuse mediastinitis and presents with a combination of the symptoms mentioned above.

Diagnostic workup and differential diagnoses

Physical examination findings are determined by the extent and location of the mediastinal mass. *Chest radiography* is often the initial imaging method, which may show mediastinal shadow enlargement and pathological changes in its configuration. However, *CT of the chest* is essential for detailed evaluation of a mediastinal mass. In the case of suspected spinal cord involvement, *MRI* is recommended. Echocardiography or transoesophageal echocardiography are used to rule out cardiac tamponade or compression, angiography might be used to diagnose vascular compression. In patients who present with dysphagia, *barium swallow fluoroscopy* might be indicated to examine oesophageal patency. Invasive techniques used for tissue sampling are *bronchoscopy, endobronchial ultrasonography* (*EBUS*), or *surgical procedures* like mediastinoscopy and thoracoscopy.

Differential diagnoses include mediastinal pseudotumours (mediastinal cysts, meningocele), inflammatory conditions (mediastinal lymph node tuberculosis, chronic mediastinitis or absceses), oesophageal defects (diverticulitis, hiatal hernia), vascular abnormalities, sarcoidosis, Castleman's disease, etc.

Mediastinal tumours by their origin

Mediastinal tumours ca be classified based on their histological nature. We recognize:

- Tumours of the heart
- Thymus tumours (thymoma, carcinoid of thymus)
- Goiter (thyroid adenoma, carcinoma)
- Tumours of mediastinal soft tissues (sarcomas)
- Neurogenic tumours (neurinoma, neurofibrosarcoma, ganglioneuroma, pheochromocytoma, etc.)
- Malignant lymphomas
- Extragonadal germ cell tumours (seminoma, teratoma, choriocarcinoma, yolk-sac tumour)

Thymoma

Thymoma is the most common tumour of the upper anterior mediastinum. It accounts for 20-25% of all mediastinal tumours and 50% of all tumours of the anterior mediastinum. Its incidence is 0.25-0.32 / 100,000. Besides anterior mediastinal syndrome, about a half of patients present with paraneoplastic symptoms, most often secondary ***myasthenia gravis.***

Treatment of thymoma varies according to the clinical stage of the disease:

- *Stage I:* Treatment of choice for non-metastatic thymoma and thymic carcinoma, even locally advanced, is complete surgical resection.
- *Stages II-III:* Complete surgical resection should be followed by postoperative radiotherapy to reduce chances of local relapse. Concomitant chemotherapy is indicated in stage III disease.
- *Stages IVa and IVb:* Surgical reduction of tumour mass (debulking), radiotherapy and chemotherapy can be used with palliative intent.

Recurrences may be encountered even several years after the initial treatment, therefore, long-term follow-up is recommended.

Intrathoracic thyroid goiter

The tumour originates in the thyroid gland and often extends to anterior mediastinum. Though goiter is largely benign condition, an occult malignancy such as follicular, papillary or anaplastic carcinoma can be present in the enlarged gland.

Malignant mesenchymal tumours of the mediastinum

Soft tissue tumours represent 10-15% of all mediastinal tumours, with *sarcomas* being the most prevalent type. It is a heterogeneous group of tumours with aggressive behaviour and high tendency for haematogenic metastasis, particularly to the lungs and liver. The backbone of treatment is surgery, other treatment modalities are of limited efficacy.

Prognosis of mediastinal tumours

The prognosis of this wide range of tumours varies greatly. In patients with thymoma, radicality of surgical resection, clinical stage and histological type of tumour are the most important prognostic factors. Thymoma associated with myasthenia gravis is considered to have a better prognosis and to be less invasive. The prognosis of extragonadal germinal tumours is always worse than in tumours of testicular primary. In the case of neurogenic tumours, lower age at diagnosis is associated with better prognosis.

Malignant pleural mesothelioma

Mesotheliomas are malignant tumours that arise from mesothelial surfaces of the pleura, peritoneum, pericardium, tunica albuginea of testis and ovary. Up to 80% of malignant mesotheliomas occur in the pleural cavity. Malignant pleural mesothelioma (MPM) is one of the most aggressive tumours and despite advances in treatment options, it remains a major therapeutic challenge.

Epidemiology

The incidence of malignant pleural mesothelioma in women is 1-2.5 / 1 000 000 annually and 10-66 / 1 000 000 in males. It is often associated with occupational **asbestos exposure**. Also individuals living in areas where asbestos occurs naturally are at higher risk of developing MPM. The crucial role in pathogenesis of MPM is attributed to the inhalation of asbestos fibres, which are deposited in pleura where they induce a local inflammatory reaction underlying the development of cancer. The latency of MPM manifestation after the asbestos exposure is usually several decades. Although asbestos has already ceased to be used in our industry, we can still expect an upward trend in the incidence of malignant pleural mesothelioma (MPM).

Clinical manifestation and diagnostic procedures

Patients often present with dyspnoea, pleural pain or dry irritable cough. In the later course of the disease fatigue and weight loss are often encountered. In medical history, it is important to focus on environmental factors including asbestos exposure. Physical examination findings include dull percussion and decreased or absent breath sounds at the site of MPM or pleural effusion.

The basic imaging method is a chest radiograph and CT scan, which usually demonstrate pleural effusion and pleural thickening. An MRI of the chest can be helpful if chest wall, diaphragm or mediastinal invasion is suspected. PET / CT is advantageous in patients with distant metastases.

Samples for histopathological examination can be obtained either from thoracentesis (for cytological examination), by CT-guided percutaneous needle biopsy or by exploratory thoracoscopy. Immunohistochemical examination of the sample is often necessary for accurate diagnosis. Mesothelioma is staged according to TNM classification based on the imaging methods and histopathological findings.

Therapy

The mainstay of treatment of an unresectable disease is **chemotherapy** based on a combination of **cisplatin** and **pemetrexed**. There is no general agreement concerning second-line treatment. So far, immunotherapy, targeted agents, dendritic cell vaccines, or intrapleural interferon administration have not been proven superior to chemotherapy. Pleurodesis can be used for palliative management of recurrent pleural effusions.

Prognosis

Generally, MPM has a poor prognosis. The median overall survival is about 5-8 months in untreated patients, with chemotherapy survival can be prolonged up to 13 months.

Secondary pleural tumours

Most common primaries metastasizing to pleura are bronchogenic carcinoma, breast cancer and lymphoma. Clinical manifestation and diagnostic approach is the same as in primary pleural tumours. Treatment is based on the management of the underlying disease. In general, the presence of malignant pleural effusion is associated with a worse prognosis of the disease.

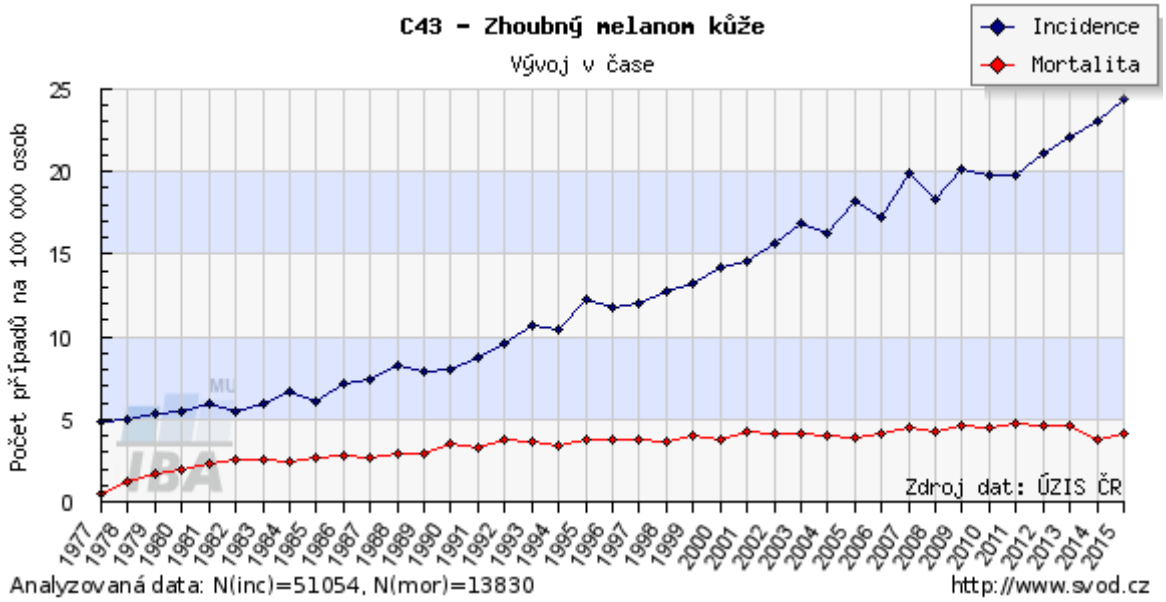
Skin tumours

R. Lakomy, A. Poprach, T. Kazda

Malignant melanoma

Epidemiology

Malignant melanoma is a tumour arising from melanocytes. Most commonly, it is located on the skin, though some melanomas might occasionally develop on mucous membranes or in the eye. Melanoma incidence shows a steady upward trend. Incidence rates are highest in Australia and New Zealand, which reflects its association with UV radiation exposure. Incidence and mortality of malignant melanoma in the Czech Republic is shown in Figure 1.



Risk factors

Both genetic and environmental factors are involved in the development of melanoma. Hereditary conditions associated with an increased risk of MM include cyclin-dependent kinase mutations (CDKN2A, CDK4), BRCA2, or p16 mutation. A major exogenous risk factor is UV radiation. Individuals with type I and II skin phototype, multiple pigmented nevi (> 50) or dysplastic nevi (> 5) are at particular risk of MM due to sunlight overexposure. Another important factor is the dose of UV radiation obtained in childhood, intermittent sun overexposure and sunburn, as well as the older age, which reflects the accumulating character of UV-induced DNA damages.

Screening and prevention

High-risk individuals should be seen by a dermatologist at least once a year. Skin self-examination and protection from UV radiation are of paramount importance.

Clinical presentation

Melanoma may occur de novo on sun-exposed skin or in already existing pigmented nevus (about 1/3 cases). Melanocytic nevi can be differentiated from dysplastic nevi according to so-called ABCD criteria (asymmetry, border, colour, and dermoscopic structures). In contrast to benign nevi, MM may also be associated with itching or bleeding due to ulcerations. Clinically, we distinguish several subtypes of MM- **superficial melanoma (SSM, most common), nodular melanoma, lentigo maligna and acrolentiginous melanoma.** Early in the course of disease, melanoma cells spreads mainly through the lymphatic vessels, haematogenous dissemination to distal organs occurs later and presenting symptoms may be related to the location metastases.

Fig. 1. Surface-spreading melanoma on upper limb

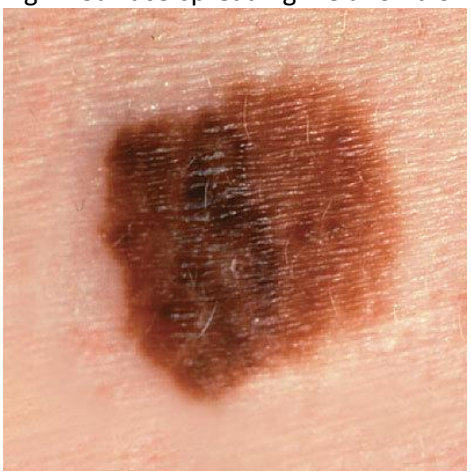
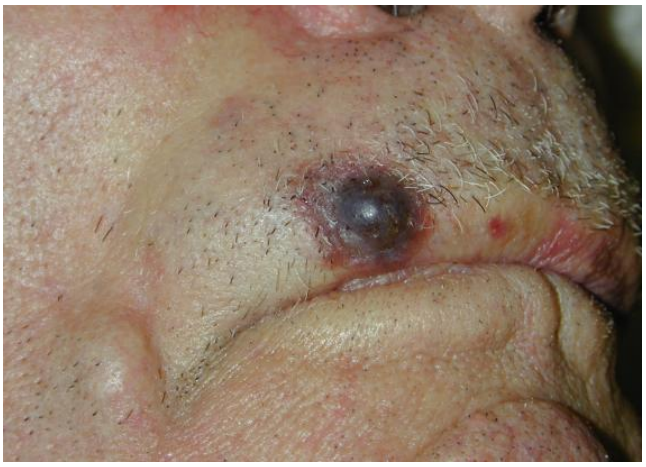


Fig. 2. Nodular melanoma on the upper lip



Diagnostic approach and staging

Every suspicious lesion is indicated for radical excision. Subsequent histopathology examination provides an information on Clark and Breslow staging (addressing the depth of skin invasion and

thickness of MM, respectively), the number of mitoses, presence of ulceration and other factors important for therapeutic decision-making. With the introduction of targeted treatment, mutations in *BRAF, NRAS*, or *cKIT oncogenes* are routinely investigated. Clinical staging procedures include chest radiograph, ultrasound of regional lymph nodes and the liver. In advanced disease, whole-body PET / CT is the imaging method of choice.

Treatment overview by clinical stages

The backbone of treatment is surgery. For stage 1B and stage 2 melanoma, sentinel node biopsy should be performed, and in the case of its positivity, surgical procedure should also encompass lymph node dissection. High-risk patients (stage 2B-3) may be considered for postoperative immunotherapy with interferon alpha, however, it the era of check-point inhibitors, the importance of interferon is declining. In advanced disease (inoperable stage 3 and 4 melanoma), targeted agents and immunotherapy have become the benchmark for melanoma treatment in recent years. Targeted treatment with **BRAF inhibitors** (dabrafenib, vemurafenib) usually in combination with **MEK inhibitors** (dabrafenib + trametinib, vemurafenib + cobimetinib) is indicated in patients with a mutation in the *BRAF V600* oncogene (positive in about 40-50% of patients). Immunotherapy is currently represented mainly by check-point inhibitors, i.e. monoclonal antibodies blocking the inhibitory receptors on T-cells: **anti-PD-1 antibodies** nivolumab and pembrolizumab, and the **anti-CTLA-4** antibody ipilimumab. These agents have a potential of inducing a durable tumour remission even after treatment discontinuation irrespective of the reason. Limiting factor in the use of immunotherapy might be its specific toxicity profile (irAE - immune-related adverse effects). In severe irAE, treatment should be temporarily or permanently discontinued, and immunosuppressive therapy with corticosteroids or other immunosuppressive agents should be initiated as soon as possible. Patients who progressed on targeted agents or immunotherapy (or who are not suitable for this type of treatment) can be treated with palliative chemotherapy with dacarbazine, cisplatin, vinblastine, vincristine, nitrosurea derivatives or paclitaxel. However, response rates and the impact on overall survival is very limited, irrespective of the cytostatic agent used (maximum survival benefit is several months).

Prognosis by clinical stages

The chances of 10-year survival in tumours ≤ 1mm in Breslow thickness is 92 %, in melanoma between 1-2 mm 80%, in lesion between 2-4mm 63 % and in tumours > 4mm only about 50%. Patients with nodal involvement have a worse prognosis (5-year survival is 78%, 59% and 40% for stages 3A, 3B and 3C, respectively). The prognosis of patients with metastatic melanoma was unfavourable prior to the introduction of targeted treatment and immunotherapy, only about 10% of

patients survived longer than 5 years, however, the expansion of treatment armamentarium have brought a significant improvement in patient survival. Chemotherapy-naïve patients achieve better outcomes with both immunotherapy and targeted agents, compared to pre-treated individuals.

Follow up

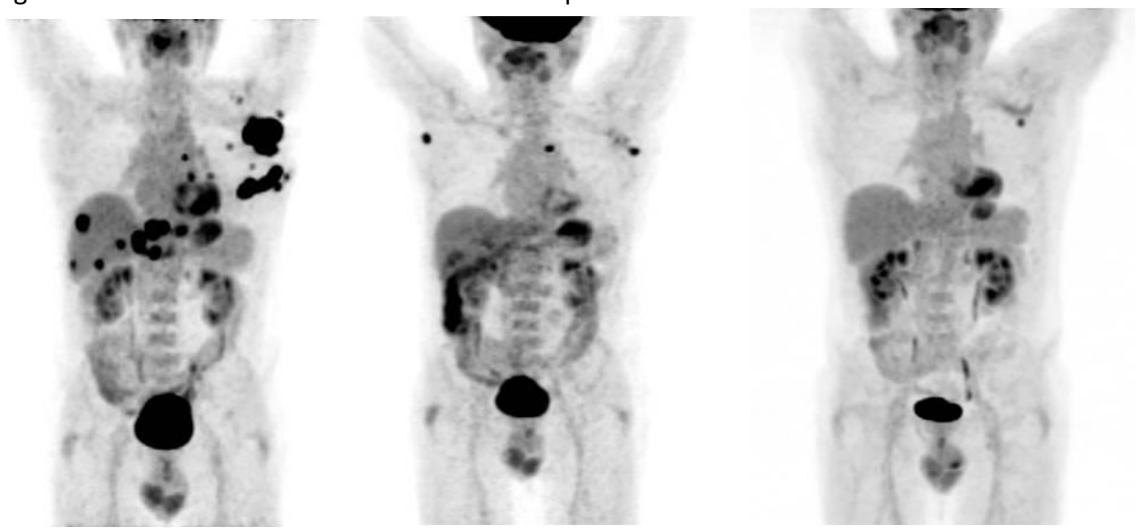
Regular oncology or dermatology check-ups are recommended every 3-6 months for the first 2 years and every 6-12 months for another 3 years. The imaging methods and lab tests are indicated individually depending on the stage of the disease and risk of relapse.

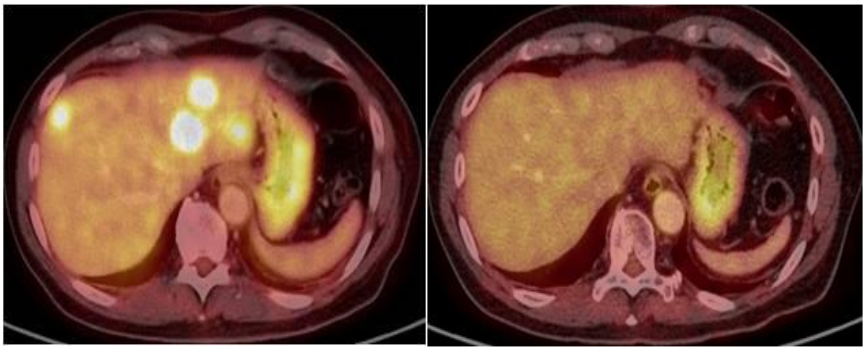
Case reports

Case No. 1

A 65-year-old man was diagnosed with ulcerated nodular malignant melanoma of the back, Clark V, with a Breslow thickness of 7.0 mm, with regional nodal involvement. The tumour was BRAF negative, stage 3C according to TNM classification and early after primary surgery, the patient presented with inoperable relapse in the skin and lymph nodes. He was started on palliative chemotherapy with dacarbazine, but on the treatment, the melanoma progressed to the liver, lungs and mediastinum. Subsequently, he was treated with four cycles of ipilimumab in the second line setting with the effect of long-term complete remission (Fig. 1).

Fig. 1 Massive tumour dissemination to the liver, mediastinum and lungs (PET and PET / CT), regression after 12 weeks of treatment and complete remission after 24 months of treatment.

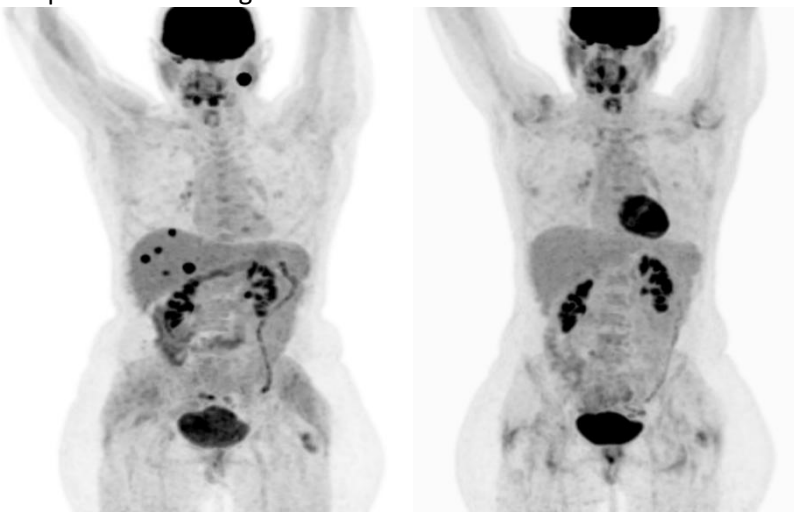




Case no. 2

A 56-year-old woman presented with nodular malignant melanoma of the scalp, pT4a and with dissemination to a left retromandibular lymph node and liver, BRAF negative. She was commenced on first line-ipilimumab, however, therapy had to be discontinued after 2 cycles due to serious adverse effects (autoimmune colitis with G3 diarrhoea). She was successfully treated with corticosteroids and after the gastrointestinal symptoms abated, second-line treatment with nivolumab was initiated because of a significant progression of liver metastases. The treatment was well-tolerated and after 6 months, complete tumour remission has been achieved. (Fig. 2).

Fig. 2 Dissemination of the tumour into the liver and the retromandibular lymph node (PET), complete durable regression of metastases after 6 months of treatment with nivolumab.

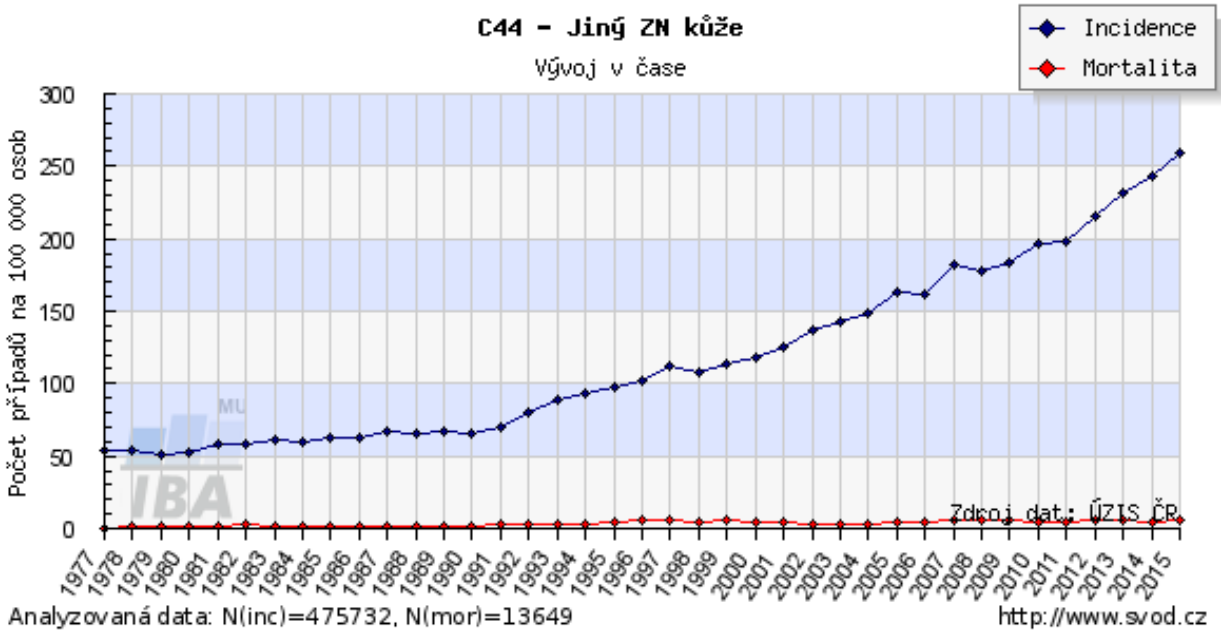


Non-melanoma skin cancers

Epidemiology

This is a heterogeneous group of diseases with different biological behaviour. The incidence of non-melanoma skin tumours is increasing worldwide and to date, they represent the most common

malignancy. **Basal cell** and **squamous cell skin cancer** comprise the majority of epithelial-origin skin cancers.



Risk factors

Major risk factors include chronic exposure to UV radiation, ionizing radiation, chronic immunosuppression, chemical carcinogens, genetic factors (xeroderma pigmentosum). Squamous cell skin cancer is also associated with scars and chronic skin affections such as ulcers or fissures and HPV infection (especially tumours in the anogenital area).

Screening and prevention

Regular preventative examination of the skin should be provided by GPs. High-risk individuals should be regularly seen by a dermatologist. Self-examination of the skin and protection from UV radiation are the most effective preventive measures. HPV vaccination might also confer protection against infection-associated squamous cell cancers.

Clinical manifestation

Basaliomas are mostly nodular lesions with a tendency to ulcerate, especially in the later course of the disease (ulcus rodens). **Squamous cell skin cancers** (SCSC) might initially appear as solid lumps that can ulcerate or, on the contrary, display exophytic growth pattern. Unlike basaliomas, SCSC have a higher tendency towards lymphatic spread and, in advanced states, SCSC might also spread by haematogenous route (most commonly into the lungs).

Diagnosis and staging

The diagnosis is based on clinical and histological findings. Due to higher propensity for lymphatic spread in SCSC, an ultrasound of regional lymph nodes should always be performed. In locally advanced lesions, clinical staging tests such as liver ultrasound, chest radiograph or CT scan should be obtained to rule out distant metastases.

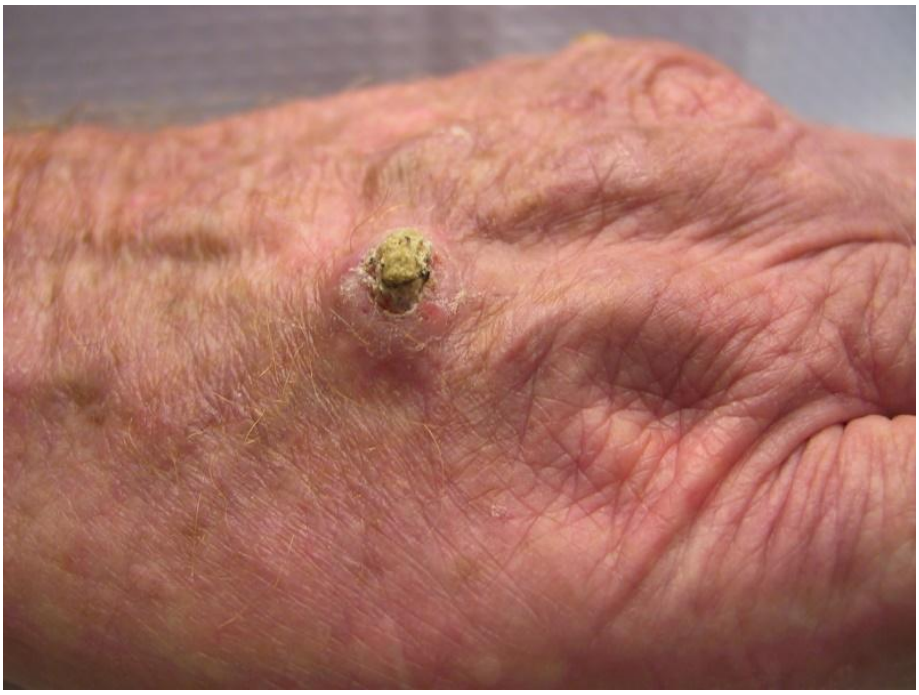
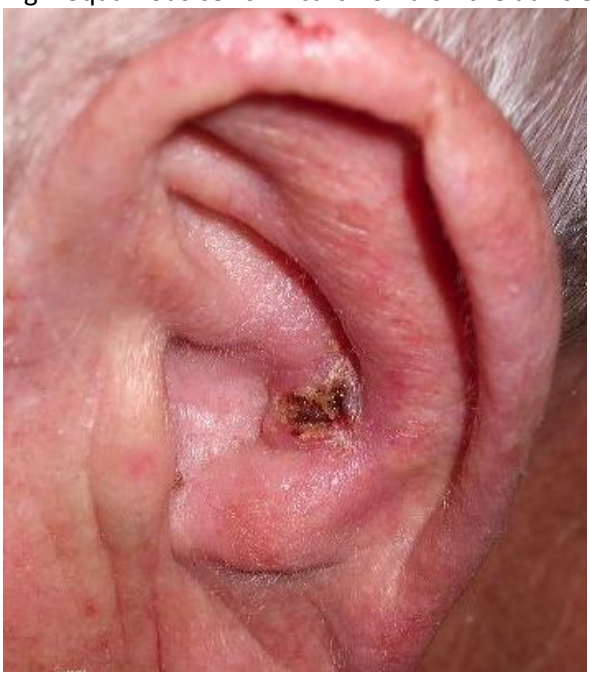


Fig. 1. Squamous cell carcinoma on the dorsum of the hand

Fig.2 Squamous cell skin carcinoma on the auricle



Basic principles of treatment according to clinical stages

Surgical resection is the preferred treatment modality. Small basaliomas not suitable for surgery (located in the face or multiple lesions) can be managed by cryotherapy with liquid nitrogen or curative radiotherapy. Less common methods include photodynamic therapy and local chemotherapy. Patients with unresectable locally advanced or metastatic basalioma who are not candidates for radiotherapy can be offered targeted treatment with vismodegib (inhibitor of hedgehog signalling pathway). Metastatic SCSC can be treated with palliative systemic chemotherapy based on cisplatin, 5-fluorouracil, paclitaxel, ifosfamide, or methotrexate.

Prognosis by clinical stages

The prognosis of early basaliomas and SCSC is extremely favourable. Radical excisions of SCSC yield a 90-95% cure rate. In the case of lymph node involvement, the 5-year overall survival is about 40-70%, with metastatic cancer, it decreases to 10%. Basaliomas rarely metastasize. Locally destructive growth is the major concern in afflicted individuals; cancer-related death is exceptional.

Follow-up

Each patient should be examined regularly by a dermatologist or an oncologist. Besides skin examination, it is important to check lymph nodes, particularly in SCSC. High-risk patients should also be examined for possible distant metastatic spread by chest radiograph. Patient education about skin self-examination and prevention of UV radiation is important.

Bone and soft tissue sarcomas

D. Adámková Krákorová, I. Kocáková

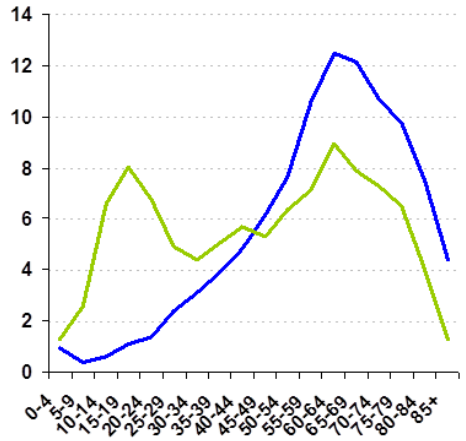
Bone tumours

Benign and secondary bone tumours account for the majority of bone affections. Primary bone tumours (sarcomas) are relatively rare and represent only 0.2-0.3% of all malignant tumours. There are about 100 new cases of bone sarcoma diagnosed in the Czech Republic annually. WHO Classification from 2013 distinguishes over 20 subtypes of bone sarcomas, the most common are **osteogenic sarcoma (OSA), Ewing sarcoma (ES)** and **chondrosarcoma (CSA).** Rare subtypes include poorly differentiated bone sarcoma, chordoma, adamantinoma, and semi-malignant giant cell bone tumour.

Epidemiology and biological behaviour

Osteosarcoma is the most common bone sarcoma of children and adolescents. It is predominantly located around the knee joint (i.e. distal femur, proximal tibia). Several histological subtypes are distinguished (e.g. highly malignant osteoblastic OSA, chondroblastic, fibroblastic, teleangiectatic, periosteal OSA or less malignant variants like, parosteal and central OSA). Early haematogenous spread similar to **Ewing sarcoma** (or Ewing sarcoma family tumours "ESFT") is a typical feature of OSA. ES is more prevalent in adolescents or adults; the incidence is slightly higher compared to OSA. ES is more often located in flat bones, pelvis and axial skeleton. It may also develop in soft tissues. ES is typically associated with a 11/22 chromosomal translocation. The most common adult age sarcoma is **chondrosarcoma,** affecting mainly the limbs and flat bones of the axial skeleton (pelvis, shoulder bone). Tumour cells often produce cartilaginous matrix.

Graph No.1: Age-related incidence (in the CR from 2006 to 2015), green: bone sarcomas, blue: soft tissue sarcomas, vertical axis: proportion of patients by age, horizontal axis: age



Risk factors

There are several predisposing factors, familial genetic syndromes and medical conditions that play an important role in the etiopathogenesis of sarcomas. An increased risk of OSA and ChoSa is associated with pre-existing benign bone lesion (Paget's disease, osteogenesis imperfecta, fibrous dysplasia, bone infarction, aneurysmal bone cyst, fibromas, etc.) or prior radiation therapy (RT). The incidence of OSA is up to 500x higher in patients with retinoblastoma (with Rb gene mutation) compared with the general population. Li-Fraumeni syndrome (caused by mutation of p53 tumour suppressor gene) is also associated with increased risk of OSA. Contrarily, no association with genetic predisposition syndrome was described with ES.

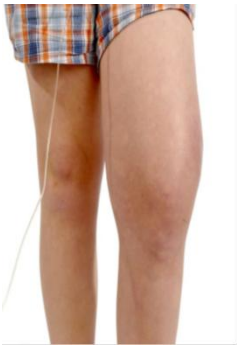
Screening and prevention

There are no particular screening recommendations for bone cancer and prevention follows general cancer preventive measures.

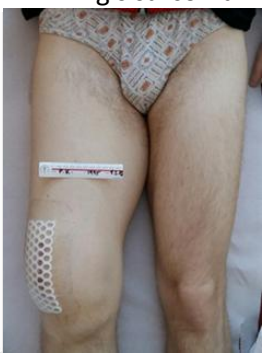
Clinical manifestation

Intermittent (mostly night-time) deep somatic pain is the most frequent presenting symptom. Swelling, erythema and palpable painful mass are seen in patients with locally advanced tumour. Pathological fracture or symptoms from distant metastases are also very common initial manifestations. Constitutional symptoms (fever, increased sedimentation rate, loss of appetite, weight loss) can be seen predominantly in patients with **ES**. Delayed presentation is characteristic of **ChoSa** (particularly of tumours located in the pelvis), which can thus become enormous at the time of diagnosis.

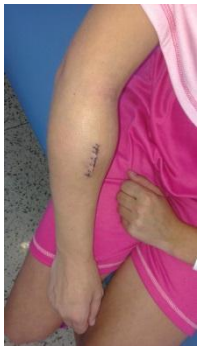
Osteosarcoma



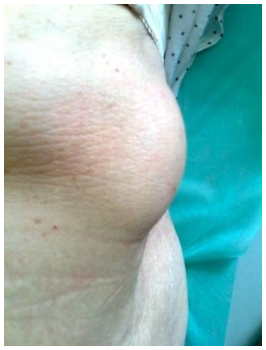
Ewing's sarcoma



Ewing-like sarcoma



Chondrosarcoma of ribs

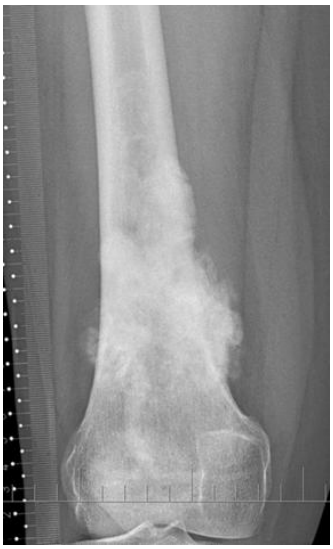


Diagnostic approach and staging

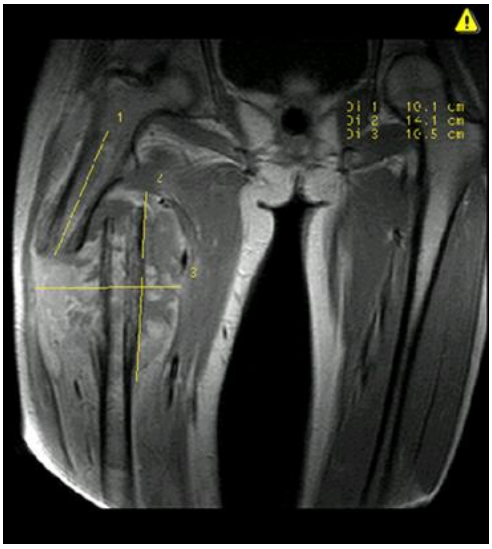
A comprehensive medical history, physical examination and plain bone X-ray followed by MRI, CT examination or bone scintigraphy are essential in the initial assessment of a patient presenting with a suspicious bone mass. An open biopsy is preferred to thru-cut needle biopsy since it provides more material for subsequent histological examination. Depending on histological findings, CT of the chest

may be required to rule out lung metastasis. The treatment approach and prognosis strongly depend on the extent of the disease, i.e. whether it is localized or metastatic.

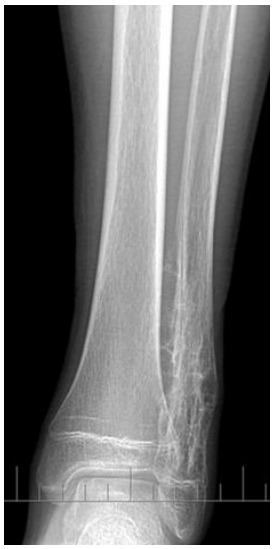
Osteosarcoma



Ewing sarcoma



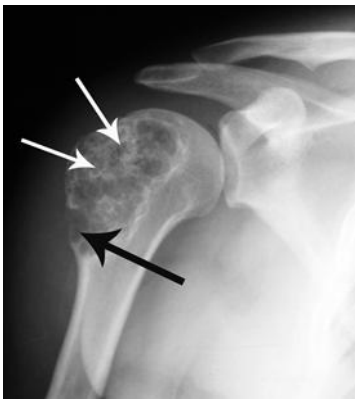
Ewing sarcoma with pathological fracture

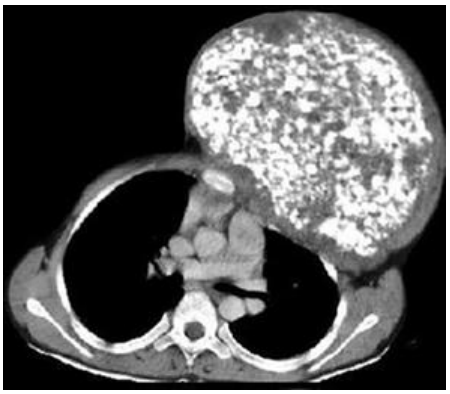


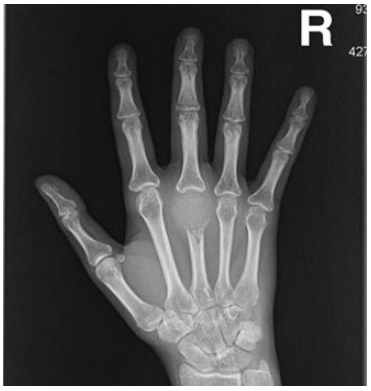
chondrosarcoma

extensive chest chondrosarcoma

large-cell bone tumour







Basic principles of treatment

Every patient with bone tumour or even a bone mass with indeterminate imaging findings should be referred to a specialized high-volume oncology centre. The treatment strategy should be decided at a multidisciplinary team board.

Osteogenic sarcoma - Radical surgery is the method of choice for localized low-grade OSA. Treatment of chemosensitive highly malignant OSA is always multimodal. Neoadjuvant chemotherapy is followed by definitive surgical resection (including metastasectomy in particular cases) and subsequent adjuvant chemotherapy. Chemotherapy regimens are based on adriamycin, cisplatin and high-dose methotrexate. Generally, limb-salvage surgery is a preferred technique, however, it should be noted that a radical resection with a negative margin is crucial for prevention of local recurrence. Supposing the tumour remains inoperable after neoadjuvant CHT, palliative irradiation may be used for local tumour management.

Ewing sarcoma is a highly chemo- and radiosensitive tumour and the initial treatment intention is always curative, irrespective of the extent of the disease. Combination chemotherapy (vincristine, etoposide, ifosfamide and adriamycin) is followed by local therapy (surgery is preferred to radiotherapy). Similarly to OSA, the pathological response to chemotherapy (measured by the proportion of tumour necrosis) strongly correlates with the overall survival. Local treatment is

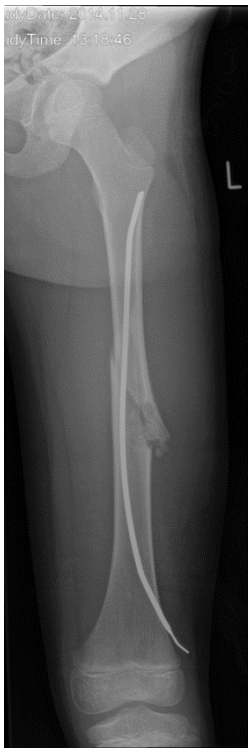
followed by consolidation therapy and its character is determined by the effect of the previous treatment modality (chemotherapy alone or in combination with radiotherapy).

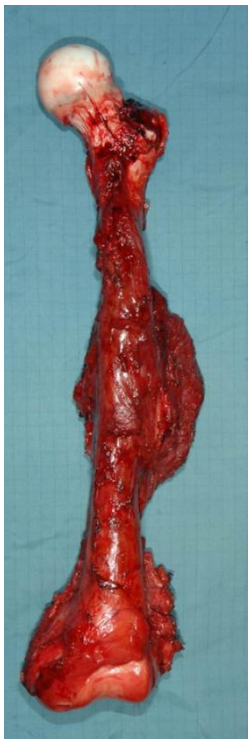
Chondrosarcoma is acknowledged as chemo- and radioresistant tumour, therefore the basis of treatment is surgery. If the patient or the disease is not amenable to resection, palliative irradiation or symptomatic care is recommended. The prognosis of a metastatic disease is extremely unfavourable.

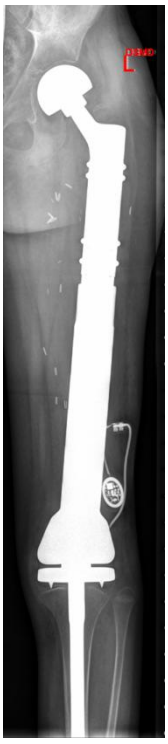
The prognosis of highly malignant OSA and ES has improved after the introduction of multimodal treatment approach. Basically, treatment protocols do not differ in children, adolescents and adults, however, the tolerance to chemotherapy usually decreases with age. Assuming the dose-intensity of systemic therapy is maintained, adult patients have outcomes comparable to childhood patients. Approximately 70-75% of patients with localized disease survive for 5 years or more, while metastatic disease carries a poor prognosis (only 30% of patients survive 3 years and more). Patients who progress during the initial systemic therapy or early after its completion and patients with bone metastases have the worst prognosis. On the contrary, long-term survival of low-grade malignant sarcomas after radical surgery is comparatively favourable.

Follow-up after treatment completion is lifelong, since the tumours may recur up to 20 years later. The frequency and character of clinical examinations depends on the type of tumour and its primary treatment.

Figure no.1: pathological fracture through a misdiagnosed osteogenic sarcoma in a 9-year-old boy with inappropriate osteosynthesis increasing the risk of early haematogenous dissemination
Figures no.2 and 3: Osteogenic sarcoma macroscopically and a metallic prosthesis after an adequate surgical treatment

1) 

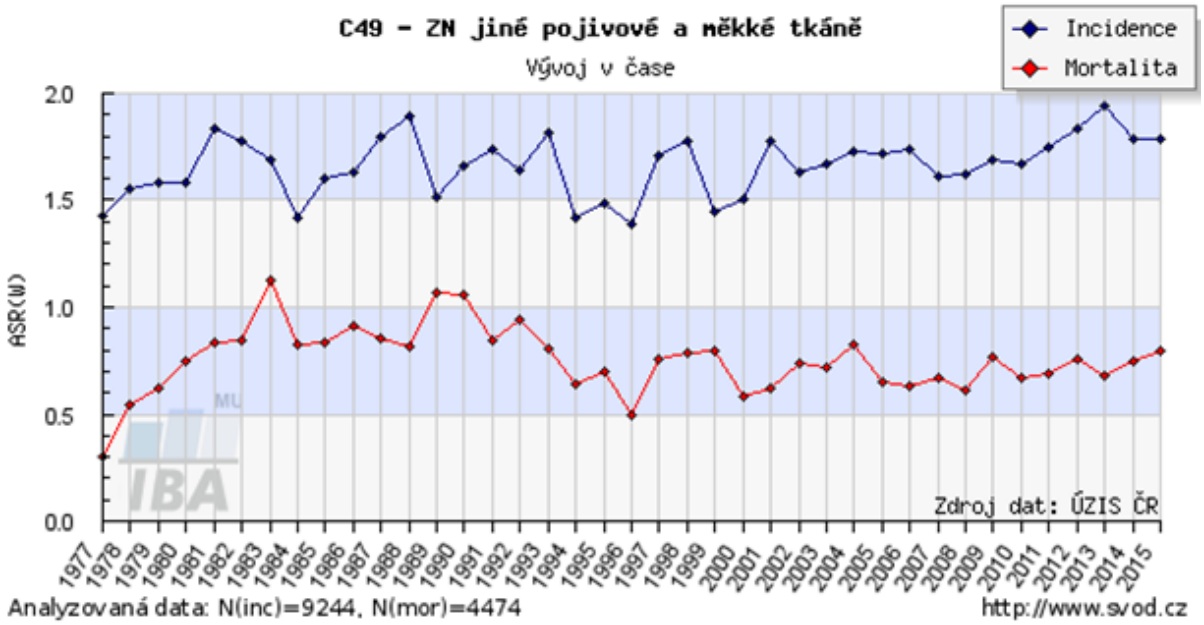
2) 

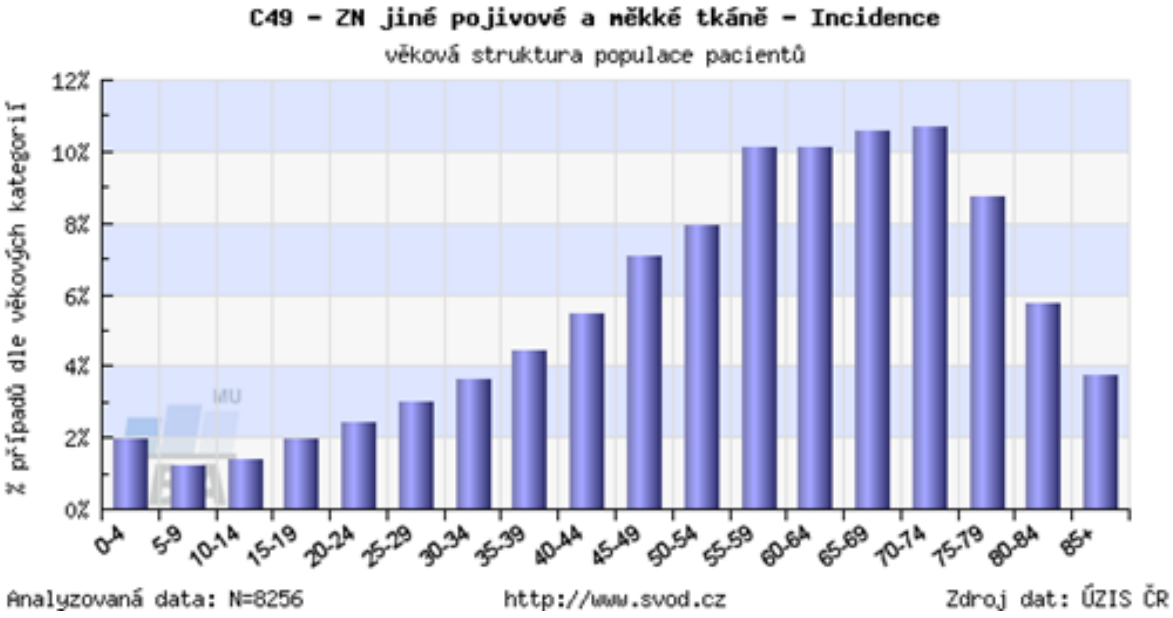
3) 

Soft tissue sarcomas

Epidemiology

Soft tissue sarcomas (STS) are rare tumours of mesenchymal origin. Along with bone sarcomas, they comprise less than 1% of all solid tumours. In the 2011-2015 period, approximately 512 soft-tissue sarcomas were diagnosed in the Czech Republic annually (an incidence of 5/100000). An embryonic mesenchymal cell may mature into a variety of tissues like muscle, bone, cartilage, connective or adipose tissue, and thus, STS is a very heterogeneous group of tumours. STS may arise in anywhere in the body and they may develop in any age group. A typical paediatric sarcoma is **rhabdomyosarcoma (RMS),** whereas adults most commonly present with so-called **non-rhabdomyosarcomas (NRSTS)**. Histopathological spectrum of STS is very broad; a WHO classification from 2013 distinguishes more than 50 subtypes of STS. Each subtype represents a specific disease with a distinct biological behaviour and sensitivity to treatment. Metastatic spread is primarily haematogenous.





Risk factors

Though most sarcomas are sporadic, there have been several predisposing genetic syndromes described with some STS subtypes (NF1, p53 mutations, APC mutations...). In addition, particular benign conditions (e.g. chronic lymphedema) may play an important role in the etiopathogenesis of sarcomas. Radiation-induced STS account for approximately 2.5% of all STS, but only less than 1% of patients who underwent radiotherapy for a primary tumour will develop secondary STS.

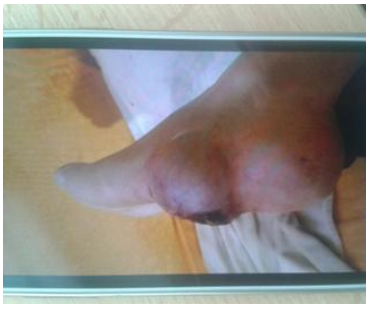
Screening and prevention

There are no particular screening guidelines or recommended preventative measures.

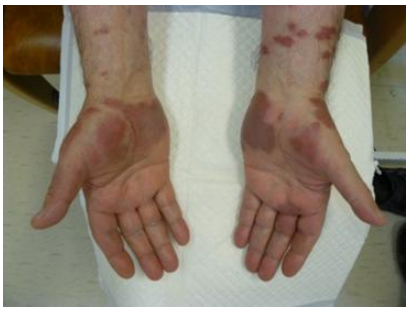
Clinical manifestation

Patients with STS generally present with a painless mass, which is increasing in size. Approximately 50% of STS arise in the extremities, 40% affect trunk and retroperitoneum, 10% occur in the head and neck area. A medical history of trauma in the affected limb may often lead to symptom underestimation and delayed diagnosis. STS located in the abdomen or the chest may first present with symptoms related to organ compression.

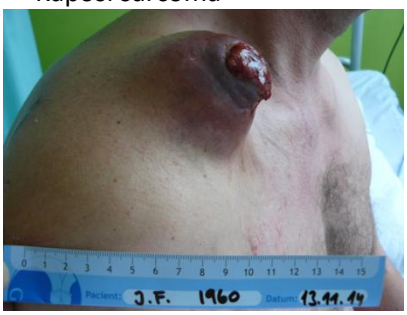
Clear-cell sarcoma



Pleiomorphic rhabdomyosarcoma



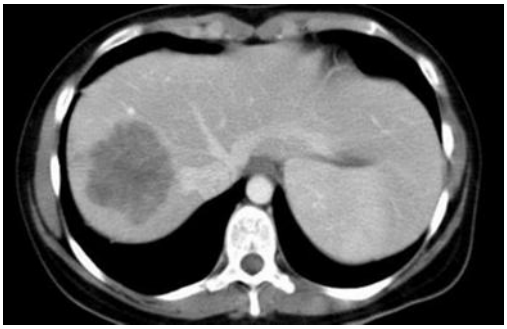
Kaposi sarcoma



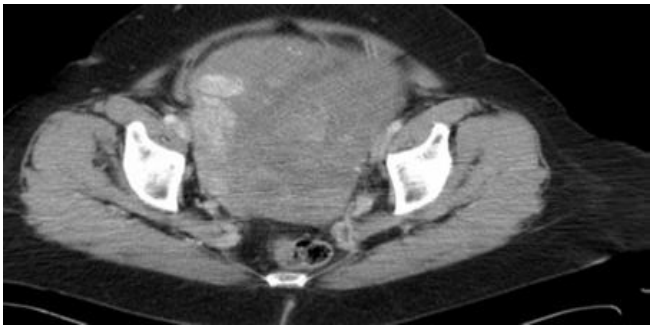
Diagnosis and staging

Every deeply located mass or a resistance larger than 5 cm (approx. golf-ball size) increasing in size **should be considered suspicious of STS** and the patient should be referred to a specialized high-volume oncology centre prior to any intervention. Histological verification from an open or tru-cut biopsy should be performed by a skilled surgeon and the specimen should be examined by an experienced pathologist. MRI is the primary imaging method for the evaluation of STS. A CT scan can provide valuable information on intralesional calcifications and potential changes of the adjacent bone. PET is not appropriate for STS evaluation because low-grade tumours can have a low FDG uptake leading to false negative results. Histopathological diagnosis usually warrants further staging methods.

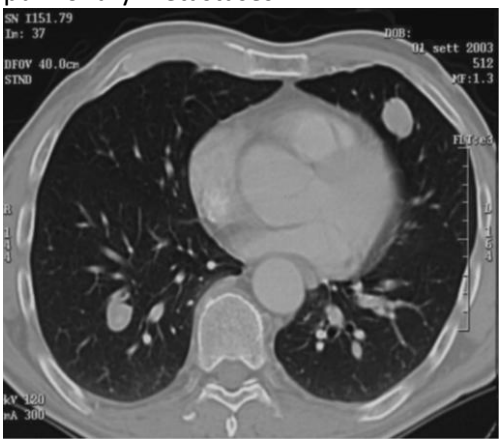
Leiomyosarcoma of the liver



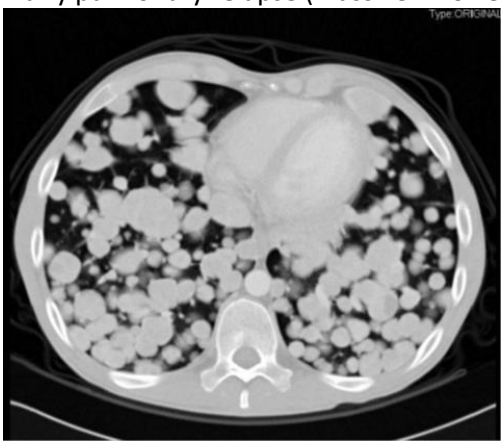
Dedifferentiated liposarcoma of the pelvis



pulmonary metastases



Early pulmonary relapse (massive involvement)

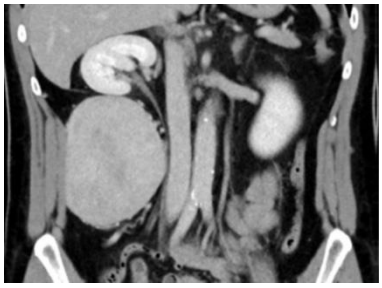
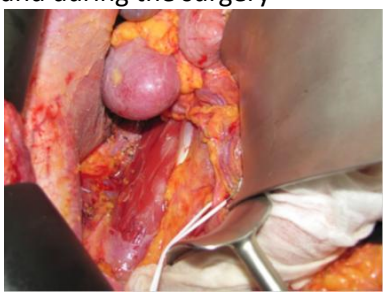


Basic principles of treatment

Treatment approach varies according to histologic type of sarcoma; it is different for the RMS and NRSTS group. Treatment of alveolar and embryonal RMS follows specific treatment protocols. **Elective surgical treatment with wide margins** is the mainstay of treatment for all STS. Adjuvant **radiation therapy** (RT) can be used to improve local control while maintaining function of the affected limb (especially in poorly differentiated tumours larger than 5 cm). It also has a role in palliative management of inoperable tumours. Currently, **adjuvant chemotherapy** is not recommended in adults, as it has not been proved to provide any survival benefit. An exception concerns patients with high-grade tumours of the extremities (synovial sarcoma, leiomyosarcoma, liposarcoma) with good performance status, who appear to benefit from the adjuvant chemotherapy. A variety of cytostatic agents has been used (***anthracyclines, ifosfamide*** *, pazopanib, dacarbazine, trabectedin, gemcitabine, docetaxel, eribulin, paclitaxel*). In treatment of unresectable/metastatic cancer (usually in lungs, bones, liver, occasionally lymph nodes), systemic **chemotherapy is administered with palliative intent**, however, the impact on overall survival is very limited. In elderly or compromised patients with chemoresistant STS, *watch and wait* strategy might be adopted. Generally, the management of STS should be discussed within a multidisciplinary tumour board. In particular cases, patients can be offered locoregional treatment techniques including

locoregional perfusion, combination of re-iradiation and regional hyperthermia, etc. Treatment of gastrointestinal stromal tumours is substantially different from the therapy of other STS and is presented elsewhere.

Liposarcoma weighing 8 kg Solitary fibrous tumour before and during the surgery

Prognosis

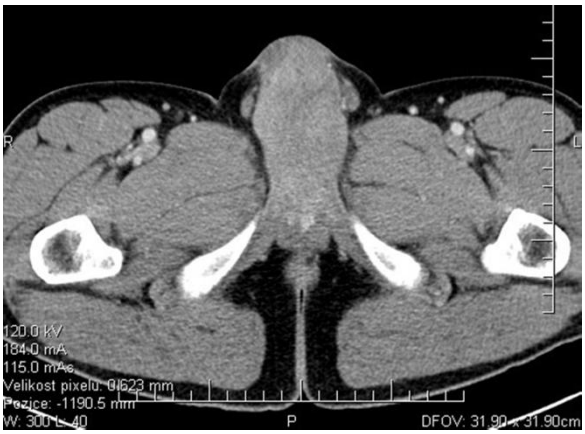
5-year survival in adult patients ranges from 60 to 65%, in children it is around 75% and correlates with tumour grade, size, depth, location and histologic type. Up to 30% of patients will experience local recurrence. Around one-fifth (15-20%) of patients present with metastatic disease at the time of diagnosis and almost half of patients will develop metastases within 5 years of diagnosis. Median overall survival in metastatic disease is 8-14 months. Only patients with limited lung involvement amenable for surgery have higher chances of long-term disease-free survival.

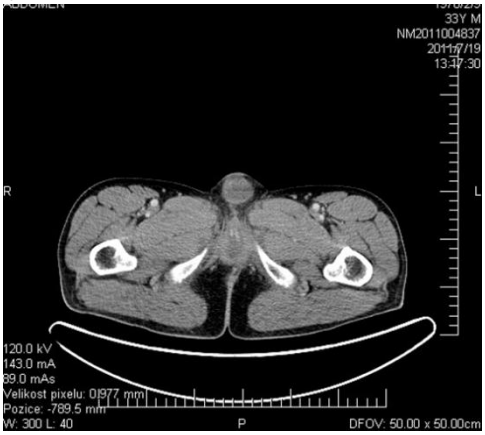
Follow-up recommendations are similar to those in bone sarcomas.

Case report

A 33-year-old man noticed a painless mass about the size of nut on his penis in December 2009. He was seen by a regional urologist and underwent a MRI in 4/2010, which revealed a 9x4.7x5cm large penile tumour that was believed to originate from urethra and invaded both cavernous bodies.

4/2010 7/2011





Histopathologic examination of a probatory excision specimen showed a small cell neuroendocrine tumour, which is very atypical in a young man and in this location. However, second opinion on the pathology diagnosis was not obtained. At the urology department, the patient underwent a mutilating surgery including amputation of the penis with perineal urostomy and left-side orchiectomy. Postoperative histopathology was consistent with extra-skeletal Ewing sarcoma, with high mitotic activity and perineural invasion. The resection margins were positive in the area adjacent to symphysis. The patient was referred to oncology. Restaging and genetic examination were performed. The patient was treated according to a modified Euro Ewing treatment protocol with chemotherapy and radiotherapy. He finished the treatment in May 2011 and achieved a complete remission of the tumour. In November 2013, he developed a pulmonary relapse in both lungs. He was treated with systemic therapy followed by thoracic surgery and subsequent postoperative chemotherapy and large-volume pulmonary irradiation. The 2nd complete remission was thereby achieved. A year later, the patient was diagnosed with a relapse in the mediastinum; he underwent surgery, systemic therapy and stereotactic irradiation. He died of progressive disease in May 2017, i.e. 7 years after the primary diagnosis. Throughout the course of disease, his quality of life has been greatly limited, mainly because of the initial surgery. Hopefully, an attentive reader has noticed shortcomings of the initial diagnostic evaluation and treatment of this young man. Ewing's sarcoma is a highly chemo- and radiosensitive tumour.

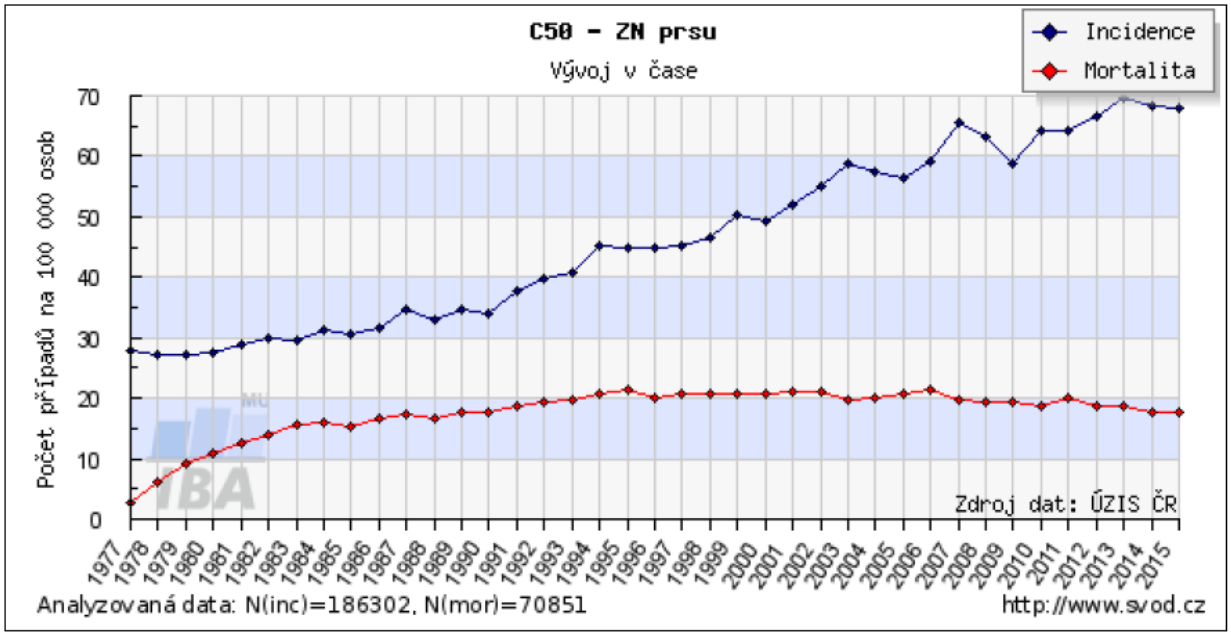
Breast cancer

K. Petráková

Epidemiology

Breast cancer is the most common malignancy in women worldwide. The incidence rates have been increasing, especially in developed countries of Western Europe and the US. The incidence increases with age, the highest rates are reported in the age group from 50 to 75 years. Mortality rate in the Czech Republic remains stable or has even slightly decreased in the past few years. This resulted in higher prevalence, i.e. the number of women living with the diagnosis of breast cancer, which is the highest of all solid tumours.

This favourable trend is mainly a result of early diagnosis and the availability of wider and more effective treatment armamentarium.



Aetiology

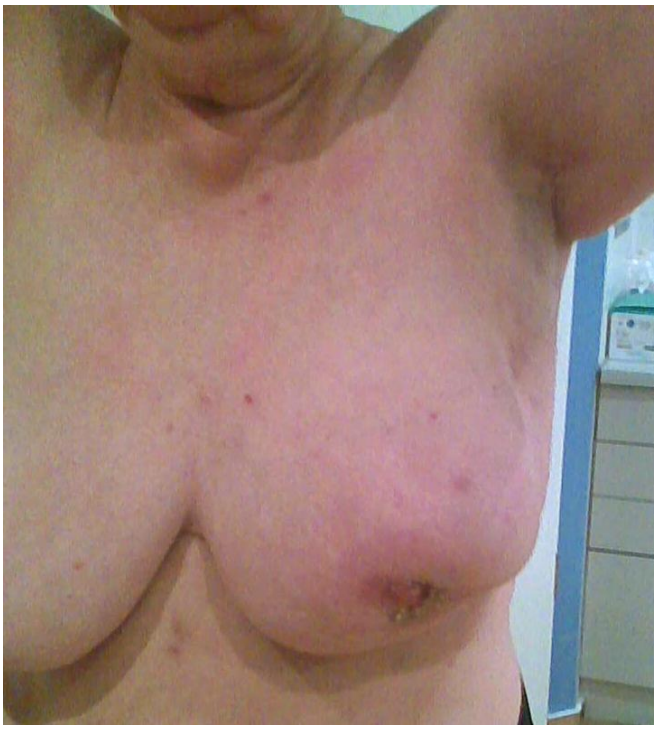
The etiopathogenesis of breast cancer (BC) is not entirely understood. Several risk factors for the development of breast cancer have been identified. Approximately **5-10 % of** BCs are associated with **genetic** predispositions, among which **BRCA1** and **BRCA2** mutations are the most frequent factors that confer higher risk of BC. Women with these mutations have an 84% chance of developing a BC in their lifetime. The risk of breast cancer is also increased in patients with a positive family history, especially in women with first-degree relative with breast cancer, irrespective of BRCAness. Other risk factors include history of irradiation (e.g. in patients who underwent treatment of Hodgkin's

lymphoma), early menarche and late onset of menopause (after the age of 50), premalignant changes in the breast, hormone replacement therapy (mainly estrogen + gestagen combined preparations), higher alcohol intake, obesity and lack of physical activity.

Clinical presentation

Symptoms indicative of BC are changes in breast size and shape, nipple or skin retraction, cutaneous oedema (peau d'orange appearance), erythema, nipple asymmetry, ulceration or eczema (*Paget's* disease), haemorrhagic discharge from nipples, breast pain, palpable lump in the breast, axillary or supraclavicular lymphadenopathy. Secondary upper extremity lymphedema may sometimes develop in an advanced BC with nodal involvement.

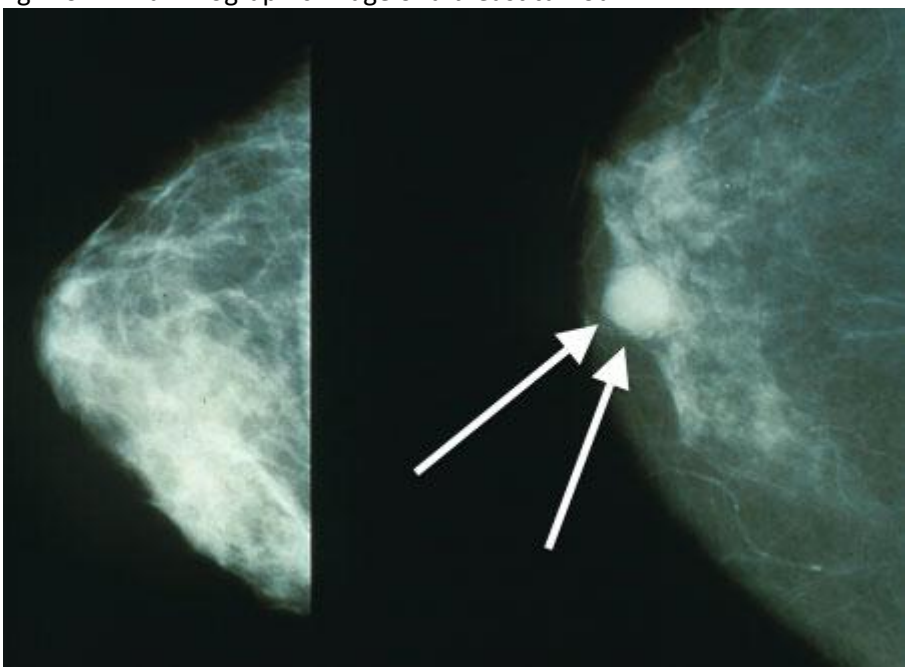
Fig. No. 1: locally advanced breast cancer with nipple retraction and incipient inflammatory skin reaction



Diagnostic evaluation and screening

Imaging methods: Mammography (MG) is an irreplaceable imaging method in breast cancer screening and diagnostics. Mammographic screening is indicated in women aged 45 years and older every 2 years. Dense breast tissue makes mammography less feasible and adjunctive ultrasound examination could be used in case of indeterminate findings. Breast ultrasound is also indicated in young, pregnant and *breastfeeding* women. MRI is part of a routine examination in high-risk women. Liver ultrasound and chest X-ray are used to evaluate distant metastases in patients at low risk of metastases. Otherwise, targeted CT scan or bone scintigraphy is indicated, if clinical signs of metastatic disease are present.

Fig. No.2 : Mammographic image of a breast tumour



Histopathology: Any suspicious lesion should be confirmed by histology. Tissue sampling is usually provided by a core-cut needle biopsy. For further treatment decision-making, the histopathologic report should convey information about the type of breast cancer, grade, oestrogen (ER) and progesterone receptor (PR) expression, proliferation and HER2 status.

Tumour markers such as carcinoembryonic antigen (CEA) a CA 15-3 have no place in the primary diagnosis of breast carcinoma, however, they might be used to monitor the dynamics of metastatic disease.

Prevention

The possibilities of primary prevention of breast cancer are rather limited. Preventable lifestyle factors include sufficient physical activity and healthy dietary habits. The use of long-term hormone replacement therapy and oral contraceptives should be avoided, especially in high-risk patients. Women with genetic burden should be offered prophylactic bilateral mastectomy with subsequent reconstruction. Regular breast self-examination as well as annual breast palpation exam by a treating gynaecologist or GP plays a crucial role in the early diagnosis of BC.

Therapy

Treatment of breast cancer is usually multimodal and includes locoregional methods, such as surgery and radiotherapy, as well as systemic treatment options like chemotherapy, hormone therapy and targeted agents. Treatment approach should be decided within a multidisciplinary tumour board,

based on tumour TNM stage, its phenotype, patient's age, co-morbidities and other predictive and prognostic factors.

Hormonal treatment

The main predictive factor for hormone treatment is the level of ER and PR expression, which is positive in approximately 75% of BC. Hormones binding to these receptors control the growth and activity of breast cancer cells, thus, by blocking the receptors or by decreasing hormone levels, we can influence tumour proliferation.

Types of hormone treatment

Depending on the mechanisms of action, there are three different types of hormone therapy:

Ablative: removal or inhibition of ovaries from producing oestrogens (by surgery or so-called chemical castration using LH-RH analogues)
Competitive: these agents work by blocking the binding site for oestrogen on the receptors (tamoxifen, fulvestrant)
Inhibitory: inhibition of aromatase enzyme, which is responsible for oestrogen biosynthesis in adipose tissue; these agents are used in postmenopausal patients only, i.e. in the absence of ovary function (anastrozole, letrozole, exemestane)

Chemotherapy

Chemotherapy is indicated in hormone negative, high-grade tumours with higher proliferation rate.

Targeted treatment

Approximately **15 %** of breast cancers carry **HER2 gene amplification**. These tumours are more aggressive and have a worse prognosis. Currently, there are several drugs available in clinical practice that affect HER2 receptor signal transduction. A groundbreaking drug used in the treatment of BC was a monoclonal antibody against HER2 receptor known as **trastuzumab,** which has dramatically improved the prognosis of HER2-positive BC. Other monoclonal antibodies include pertuzumab, lapatinib, and lately also T-DM1 (a combination of trastuzumab and emtansine - a strong cytostatic drug bound to the monoclonal antibody).

Surgery

The aim of surgical treatment is predominantly a complete tumour removal and it is therefore indicated in patients without any distant metastases. To date, breast-conserving procedures such as quadrantectomy (a partial or segmental mastectomy) or lumpectomy (removal of the tumour and normal tissue margin) are preferred. During the surgery, sentinel node biopsy (SNB) or lymph node sampling may be performed to rule out metastatic nodal spread. In case of positive results, surgery

will proceed with axillary dissection. After radical mastectomy, reconstructive breast surgery may be indicated, either using the patient's own tissue (autologous) or by inserting an implant (alloplastic).

Principles of treatment by cancer stage

Non-invasive carcinoma - carcinoma in situ (CIS) - stage 0

This is usually an incidental finding on screening mammography. Although malignant cells are present, they do not display infiltrative growth pattern and the tumour is confined to the breast. There are two histologic types of CIS - ductal (DCIS), which is more common and represents a true neoplasia that requires extirpation and adjuvant radiation in particular cases. Less frequently, an invasive lobular carcinoma in situ (LCIS) may be diagnosed. It is considered a precancerosis and requires active surveillance.

Clinical stages I, IIA, IIB

Preferred treatment in these patients is breast-conserving surgery followed by adjuvant radiotherapy. In case of presumptive N0 disease, per-operative examination of sentinel lymph node is indicated. For BC with nodal involvement, surgery is accompanied by axillary dissection removing at least 10 lymph nodes. There are three anatomical levels of axillary lymph nodes, in N1 disease, the dissection removes nodes in level I and II. Neoadjuvant chemotherapy is given only in large-size tumours, where tumour downsizing allows for breast-conserving surgery instead of a radical mastectomy.

Adjuvant systemic therapy and radiotherapy is the gold standard in most patients, as it was proved to reduce the risk of local BC recurrence by eradicating micrometastases after tumour excision. It has also resulted in overall survival prolongation and decreased risk of distant BC recurrence. The decision regarding adjuvant treatment is based on a risk-stratified approach taking account of several factors associated with increased cancer recurrence rates. Due to high curative potential of multimodal treatment, it is important to maintain appropriate dose-density of the chemotherapy even at the cost of higher toxicity.

Adjuvant chemotherapy is indicated in patients with receptor-negative aggressive tumours with higher proliferation rate. Most common regimens are FAC (5-fluorouracil, doxorubicin, cyclophosphamide), FEC (5-fluorouracil, epirubicin, cyclophosphamide), AC (doxorubicin, cyclophosphamide), CMF (cyclophosphamide, methotrexate, 5-fluorouracil) cyclophosphamide, paclitaxel), FEC-docetaxel or TC (docetaxel, cyclophosphamide).

Clinical stages IIIA and IIIB

Adjuvant chemotherapy is necessary in all these patients. Moreover, the addition of endocrine therapy is indicated in ER-positive BC patients. Chemotherapy regimens are similar to the treatments mentioned above. Neoadjuvant chemotherapy can be used as a part of treatment algorithm in certain patients with good overall health status. For patients not suitable for systemic therapy, surgery followed by adjuvant radiotherapy is an alternative.

Clinical Stage IV - Metastatic Breast Cancer (MBC)

Patients with MBC are incurable. The main objective of treatment is to prolong survival while maintaining a good quality of life. There is no "gold standard" for MBC management. The choice of treatment should be guided by BC phenotype, proliferation rate, patient age, co-morbidities and preferences. Generally, treatment effectiveness should be weighed against its risk in every individual case in order to help the patient lead an active life as long as possible.

In patients with ER-positive breast carcinoma with low proliferation rate, endocrine therapy is the treatment of choice. Chemotherapy is used after all the modalities of endocrine therapy were exhausted.

Patients with HER2-positive BC are likely to benefit from a combination of chemotherapy (most commonly a taxane) with trastuzumab and pertuzumab, especially when used as the first line treatment.

Treatment options in triple-negative breast cancer are currently very limited and they are based mainly on chemotherapy (anthracycline, taxane, capecitabine, eribulin, vinorelbine or gemcitabine monotherapy or in combination).

Dispensarization

Physical examination including breast palpation should be performed every 4-6 months after completion of curative treatment. Mammography should be obtained annually. Patients treated with tamoxifen are indicated for annual gynaecological examinations (due to higher risk of endometrial cancer). In accordance with international guidelines, routine ultrasound of liver, chest X-rays or bone scintigraphy are not recommended in BC survivors.

Case Report

A 28-year-old female was diagnosed with a 3cm mass in her right breast. The ultrasound revealed an enlarged axillary lymph node, the patient had no distant metastases, i.e. the stage was T2N1M0. The tumour was receptor and HER2-negative, Grade 3, with high proliferation rate. With regard to patient's age, genetic testing was indicated and proved a BRCA1 mutation. The patient underwent neoadjuvant systemic chemotherapy with 4 cycles of AC followed by 4 cycles of docetaxel. At

restaging, imaging methods did not show any residual disease. Due to the BRCA1 mutation, the patient opted for prophylactic bilateral mastectomy followed by autologous breast reconstruction. The histopathological examination confirmed complete remission in the breast as well as affected lymph nodes.

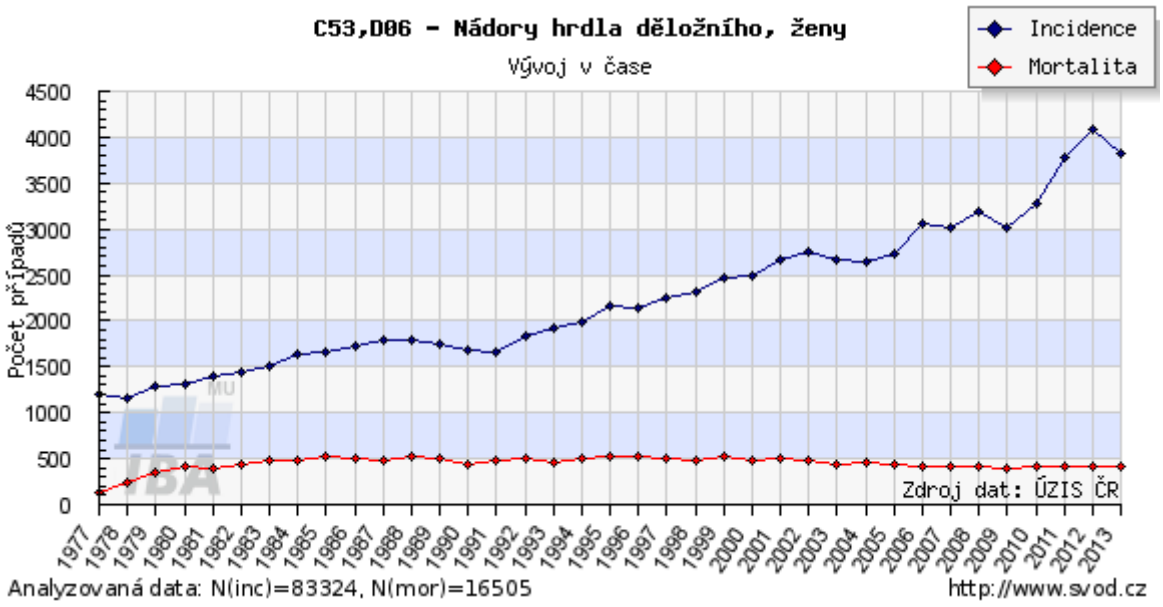
Gynaecological tumours

M. Zvaríková

Cervical carcinoma

Epidemiology

Almost 80% of cervical cancers are squamous cell carcinomas, while adenocarcinomas comprise only 15-20%. Other tumours like clear cell, small cell carcinomas, neuroendocrine carcinomas and sarcomas are rare, representing 1-2% of all cervical malignancies. Cervical carcinomas (CC) develop from premalignant lesions referred to as **cervical intraepithelial neoplasias** (CIN)**.** These precanceroses may be low-grade dysplasias (CIN I), which have a minimal malignant potential or high-grade dysplasias (moderate CINII, severe CIN III and carcinoma in situ), which are at significant risk of progression to malignancy.



Risk factors

A crucial role in the aetiology of CC is attributed to certain types of **HPV infection**. Low-risk HPV types (HPV6 and HPV11) cause genital warts and often clear spontaneously within several months. High-risk oncogenic viruses (HPV16 and HPV18) have the ability to integrate into normal cell genome and induce malignant transformation into precanceroses and subsequent carcinomas. HPV infection is acquired through sexual contact. Other factors associated with CC by increasing the chances of HPV exposure are early onset of sexual life and promiscuity, as well as HPV independent factors such as

multiparity, smoking, use of oral contraceptives and immunodeficiency (e.g. HIV, immunosuppression).

Screening and prevention

Annual screening for CC in sexually active women using a Pap smear is aimed at an early detection of precanceroses and prevention of their progression into malignancy. In some countries, screening cytology is also supplemented with HPV testing. Primary preventive measures include HPV vaccination of girls and women, preferably prior to the onset of sexual activity. There are 3 vaccines available to date - SILGARD (type 16,18, 6, 11), CERVARIX (type 16 and 18) and GARDASIL 9 (type 6,11,16,18,31,33,45,52,58) Vaccination before the recipient's exposure to HPV was proved to provide almost 100 % protection from HPV infection for at least 10 years. Vaccines help to prevent up to 70% of HPV-associated CC, however, they do not cover all HPV types.

Clinical presentation

Early stages of CC are often asymptomatic. Warning signs include postcoital vaginal bleeding or bleeding between periods. Abdominal pain, unpleasant vaginal discharge or symptomatology from distant metastases (ascites, fluidothorax, haematuria, rectal bleeding) are signs of advanced disease.

Diagnosis and staging

Pre-biopsy methods are used for evaluation of cervical disorders on the basis of morphologic signs. They include colposcopy and endocervical scraping for Pap test and HPV testing. Patients with abnormal findings suspected from malignancy should undergo cervical biopsy. There are several methods used to obtain cervical tissue samples, such as punch biopsy, cone biopsy or curettage. Clinical staging involves comprehensive gynaecological examination including pelvic ultrasound to assess local extent of the disease and regional nodal status. Pelvic MRI may be indicated in case of indeterminate findings. Abdominal ultrasound and chest X-ray are usually performed to rule out distant dissemination. Adjunctive methods used to assess the involvement of adjacent organs include urethrocystoscopy, colonoscopy or rectoscopy, intravenous urography, abdominal CT or whole-body PET scan, and the examination of tumour markers according to histological type of CC (SCC in squamous cell tumours, CA125 and CEA in adenocarcinomas).

Therapy

According to the FIGO classification system, CC can be divided into two groups: early stage CC (FIGO IA-IIA) and advanced-stage disease (FIGO IIB-IVB). In the early stage, surgery is the treatment method of choice. The extent of the procedure and surgical approach (laparoscopic, robotic or open

operation) depends on the extent of the disease. Stage IA1 tumours (with invasion lower than 3 mm) can be managed by conisation. Other early stages (IA2, IB1, IB2) are usually indicated for radical hysterectomy with systematic pelvic lymphadenectomy. An alternative method in women in fertile age is a fertility-preserving procedure known as radical trachelectomy, in which only uterine cervix with cranial part of the vagina and parametria are removed.

Radiotherapy

Radiotherapy is a highly effective method in the treatment of squamous cell CC. It might be used as a standalone curative method in patients with early-stage CC who are unfit or do not consent with surgery. For advanced CC (stage IIB and above), radiotherapy is the only curative method. In these cases, the treatment usually consists of external beam radiotherapy with concurrent chemotherapy (preferably with cisplatin, which acts as a radiosensitizer) and brachyradiotherapy.

Metastatic (stage IVB) or recurrent disease is often managed by palliative **chemotherapy**. Patients can be treated with monotherapy or a combined regimen. The primary cytostatic agent is cisplatin, which is considered the most effective cytostatic in monotherapy setting. Other cytotoxic agents used in CC include paclitaxel, topotecan, ifosfamide and carboplatin. Targeted therapy with bevacizumab can be used in combination with chemotherapy in particular cases.

Prognosis is dependent on the stage of the disease. Tumours confined to the cervix have a 90% cure rate, in advanced stages the cure rate decreases to 65-80 %, 35-45 % and 5 % for stage II, III and IV, respectively.

Follow-up

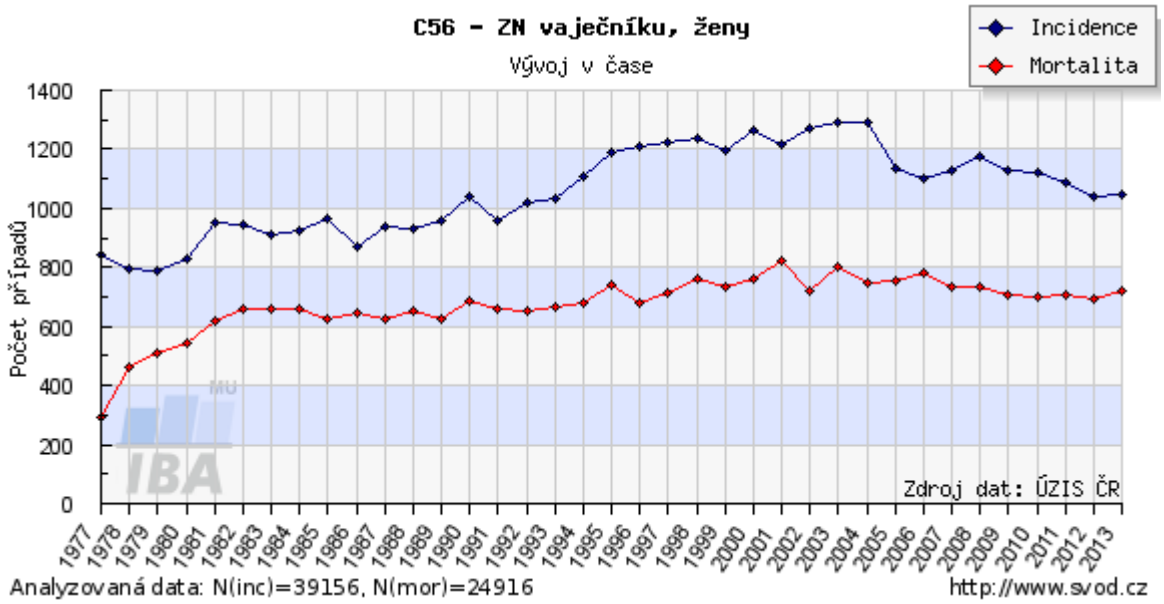
Post-treatment gynaecological examinations, CBC, basic blood chemistry and tumour marker examinations (in case of pre-treatment elevation) are recommended every 3 months for 2 years, every 6 months for another 3 to 5 years and then annually.

Ovarian cancer

Epidemiology

Ovarian cancer (OC) is the leading cause of death among gynaecological malignancies. The incidence of OC increases with age and the highest prevalence is in women aged 60-79. Malignancies arising in the ovaries represent a very heterogeneous group of diseases. Tumours may develop from a variety of cells present in ovarian tissue. **Epithelial** tumours are derived from surface epithelium and account for up to 90% of malignant OC. Less common ovarian histopathologies include **germ cell tumours** and sex cord- stromal tumours, which occur mainly in younger women and girls. Other types of malignant tumours are extremely rare.

Epithelial ovarian tumours are further divided into serous, endometrioid, mucinous, clear cell, undifferentiated and mixed carcinomas and benign Brenner tumours. However, in clinical practice and with regard to the pathogenesis and molecular genetics, two main groups of epithelial cancers are distinguished: **Type I** epithelial cancers include low grade serous and endometrioid carcinoma, mucinous, clear cell carcinoma and Brenner tumour. They are characterized by an indolent progression from pre-malignant lesions into low-grade tumours. The hallmark of these tumours is pathologic activation of KRAS and BRAF signalling pathways. Their proliferation rate is low and the 5-year survival rate is reported to be around 55%. **Type II** epithelial cancers have much worse prognosis. This group comprises mainly high-grade serous and endometrioid carcinomas or carcinosarcomas. Typical molecular characteristics of these malignancies include 1. high degree of chromosomal instability; 2. frequent mutations inTP53 proto-oncogene; and 3. low frequency of KRAS and BRAF activating mutations.



Risk factors

The development of sporadic OC is related to high frequency of ovulations (early menarche, late menopause, nuliparity). Other risk factors associated with OC include higher age, white race, hormone replacement therapy, history of infertility treatment and pelvic inflammatory disease (endometriosis, polycystic ovary syndrome, recurrent or chronic salpingitis). Approximately 10-15 % of ovarian cancers occur in women with BRCA1 and BRCA2 mutations, either as a part of breast and ovarian carcinoma syndrome, or as a site-specific ovarian cancer syndrome. Family history of hereditary non-polyposis colorectal cancer (HNPCC) known as Lynch syndrome resulting from MMR gene mutation is associated with a 10% chance of developing OC. The lifetime risk of ovarian

carcinoma in carriers of BRCA gene mutations is around 20-40 %, i.e. approximately 10-20 times higher compared to general population.

Clinical signs and symptoms

With regard to the location and biology of ovarian tumours, an early diagnosis of OC is rather uncommon. Early-stage disease is often asymptomatic. Only a small portion of OC is diagnosed during a regular gynaecological check-up. Occasionally, OC is an incidental finding during a surgery due to acute abdomen (resulting from abdominal bleeding, ovarian torsion or infection). Advanced tumours present with vague symptoms such as pelvic or abdominal discomfort, pain, bloating, urinary symptoms, nausea or heartburn. With an advancing tumour, abdominal distension, ascites, palpable intraabdominal resistance, anorexia and emesis or dyspnoea due to pleural effusion may occur.

Screening

To date, no screening method has been proven effective in ovarian cancer. Due to limited diagnostic methods, most women (up to 70%) are diagnosed at late stages of the disease. This corresponds to poor treatment outcomes in patients with OC.

Diagnosis

The initial work-up includes medical history, physical examination and comprehensive gynaecological examination. Laboratory tests such as CBC, blood chemistry and examination of tumour marker CA 125 and HE4 may be useful. Chest X-ray and abdominal ultrasound are basic clinical staging tests. In the case of indeterminate findings, a CT scan, MRI or PET might be appended. The use of cystoscopy, intravenous urography, rectoscopy or colonoscopy is indicated based on organ-specific symptomatology.

Surgical treatment

Surgery is the backbone of treatment in patients with both early and advanced stage of OC. A comprehensive surgical procedure should involve ascites evacuation, hysterectomy with bilateral oophorectomy, omentectomy, appendectomy, peritoneal lavage, peritoneal biopsy, and systemic pelvic and para-aortal lymphadenectomy. Advanced OC are indicated for debulking surgery, which should yield a minimal postoperative residual disease. An optimal cytoreduction technique might therefore include radical procedures, such as multiple bowel resection, diaphragmatic partial resection or peritoneal stripping, splenectomy, cholecystectomy, partial resection of the liver or pancreas. The extent of residual disease is one of the most important prognostic factors that significantly affects the time to progression and overall survival of the patient. Neoadjuvant

chemotherapy might be considered in patients with very advanced disease who are not suitable for debulking surgery or a resection to minimal residual disease is unlikely. If restaging after 3 or 4 cycles of chemotherapy demonstrates tumour regression, the treatment proceeds with a so-called interval debulking surgery followed by administration of postoperative chemotherapy.

Chemotherapy

Most of the patients are indicated for post-operative chemotherapy. Active surveillance after primary surgery is recommended only in low-grade stage IA and IB tumours.

Chemotherapy is based on **platinum derivatives** (cisplatin and carboplatin) and **taxanes** (paclitaxel and docetaxel). In addition to intravenous chemotherapy, younger patients with stage III OC and postoperative residue smaller than 1cm can be considered for a combination of intravenous and intraperitoneal chemotherapy. Patients with macroscopic residual disease larger than 1cm, or patients with metastatic OC are typically treated with a combination of chemotherapy with bevacizumab.

Treatment of relapses

Cancer, which has progressed during the course of chemotherapy is reported as platinum refractory and should be further managed with symptomatic care only. If complete remission is achieved with primary chemotherapy and the first relapse occurs within 6 months after treatment completion, the tumour is considered "platinum-resistant" and the patient might be offered non-platinum chemotherapy with palliative intent (e.g. topotecan, liposomal doxorubicin, gemcitabine, paclitaxel, etoposide). Currently, the combination of the paclitaxel with bevacizumab is also approved in this indication. A relapse of the tumour after more than 6 months is indicative of "platinum-sensitive" disease and a rechallenge of platinum-based chemotherapy is the preferred treatment option. Patients with BRCA1/2 mutation may be treated with PARP inhibitors. To date, olaparib is the only approved preparation in this setting.

Radiotherapy is used with palliative intent, especially due to its analgesic and haemostatic effect.

Hormone therapy might be employed in the treatment of certain types of ovarian cancer (e.g. low grade serous carcinomas) or as a treatment of last resort in patients who exhausted all other treatment possibilities. However, the impact on overall survival is very limited.

Prognosis

The prognosis of ovarian cancer depends on a number of factors. The most important is the stage of the disease, histological type, tumour grade, patient age, overall health status, the radicality of

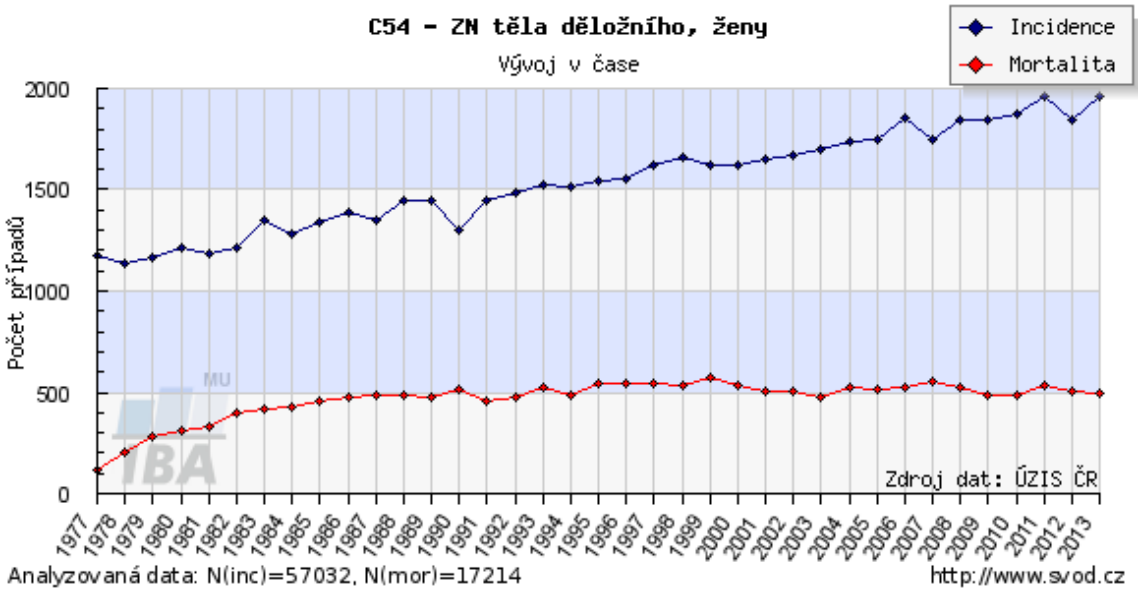
primary surgery and residual tumour size. Five-year survival is 70-80%, 60%, 23% and less than 10% for stages I, II, IIII and IV, respectively**.**

Dispensarization

Follow-up of patients treated for OC includes physical and gynaecological examination and blood tests with measurement of tumour markers obtained every 3 months for the first 2 years and every 6 months for years 3, 4 and 5. Beyond five years, annual follow-up is recommended. Imaging methods such as chest X-ray or abdominal US should be performed only if the findings are suggestive of disease recurrence.

Uterine cancer

Uterine cancer is the most common tumour of female genital tract representing more than 40% of all gynaecological malignancies. The incidence significantly increases after the age of 50. Depending on the site of origin, tumours are divided into **epithelial** (endometrioid, mucinous, clear cell, serous adenocarcinoma), **mesenchymal** (endometrial stromal sarcoma, leiomyosarcoma), **mixed** (carcinosarcoma) and **lymphoid tumours**. Endometrial tumour arising from the lining of uterus is the most common type of uterine cancer.



Risk factors

Most risk factors involved in the development of endometrial carcinoma are related to higher oestrogen exposure: longer menstrual lifespan, nulliparity, obesity (oestrogens produces by adipose tissue), the use of hormone replacement therapy, polycystic ovary syndrome, endometrial hyperplasia (precancerosis). Higher risk of endometrial cancer is also described with hereditary Lynch syndrome (HNPCC - hereditary non-polyposis colorectal carcinoma).

Clinical signs

The majority of patients presents with abnormal (postmenopausal) uterine bleeding of various intensity, ranging from weak spotting to serious bleeding. A purulent or haemorrhagic vaginal discharge, abdominal or pelvic pain are another symptoms indicative of malignancy. Occasionally, presenting symptoms may be related to distant metastases.

Screening and prevention

There is no specific screening method available for uterine cancer. Regular gynaecological examinations including transvaginal ultrasound are recommended.

Diagnostic approach

Women with suspected endometrial cancer should undergo a comprehensive gynaecological examination including transvaginal sonography. Laboratory evaluation should always include CBC (with regard to frequent uterine bleeding). Endometrial sampling for histopathology examination is crucial for the diagnosis of uterine cancer. This can be done either by endometrial curettage or hysteroscopy. Other staging examinations include CT of the abdomen and pelvis , chest X-ray, and cystoscopy or rectoscopy in select circumstances.

Surgical treatment

Surgery is the essential therapeutic modality. To date, laparoscopically assisted vaginal hysterectomy (LAVH) is preferred to abdominal hysterectomy, especially in early-stage disease. Robotic surgery may be used in indicated cases. In advanced disease, abdominal extrafascial hysterectomy with bilateral oophorectomy, abdominal cavity lavage and excision of all suspected lesions in the peritoneal cavity is necessary. Adjunctive lymphadenectomy may be indicated in high-risk tumours such as grade 3 endometrial carcinoma or other histological types with more than 50% myometrial invasion.

Radiotherapy

Adjuvant radiotherapy may be considered in high-risk early-stage (I and II) endometrial cancer with lymphangioinvasion, high-grade tumours or tumours with deep myometrial invasion (over 50%). Irradiation includes external beam radiotherapy with or without vaginal brachytherapy. Patients with advanced stages (III-IV) of the disease can be treated with chemoradiation or chemotherapy alone. Radiotherapy contributes to local control of the disease including lymph node metastases, whereas chemotherapy reduces the risk of developing distant metastases.

Chemotherapy

Chemotherapy is a critical modality in locally advanced, metastatic or recurrent disease. The most effective regimens include platinum derivatives (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel) and anthracyclines.

Hormone therapy

For patients with low-grade endometrioid carcinomas (grade 1 and 2) with positive oestrogen and progesterone receptors, treatment options include hormone therapy as well (including gestagens, tamoxifen and, exceptionally, aromatase inhibitors).

Prognosis

Survival is strongly related to stage of the tumour, histological type and patient age. Five-year survival rate for stage I tumours is 85%, stage II - 70%, stage III - 49% and stage IV only 19%.

Surveillance recommendations are similar to follow-up in ovarian cancer.

Penile and testicular cancer

R. Lakomy, A. Poprach, T. Kazda

Penile tumours

Epidemiology

Penile tumours are rare in Europe and other industrialized countries and they are more common in Africa, Asia and South America. Incidence rates in the Czech Republic have been steadily increasing; in 2015, the incidence was reported to be 2.43 / 100,000 and the annual mortality rate was 0.73 / 100,000.

Risk factors

The major risk factors are phimosis and poor hygiene (smegma retention). An increasingly important role is attributed to HPV16,18 and HPV33 infection. Higher incidence of penile cancer was also reported in association with asbestos exposure.

Screening and prevention

Routine screening is not performed. Patient education, good personal hygiene, self-examination and early diagnosis are of crucial importance. Protective vaccination against HPV infection may also be considered. Circumcision in children and adolescents showed to reduce the risk of penile cancer.

Clinical presentation

Tumour initially presents as an erythematous lesion, which subsequently either ulcerates or displays exophytic growth. Unpleasant discharge or bleeding may appear. Lymphatic spread is typical in early stages of the disease, enlarged lymph nodes may be palpable in the groin or above the symphysis. Advanced tumour may present with symptoms of haematogenous metastases to the liver, lung and bone.

Diagnosis and staging

Probationary excision and histological assessment (**squamous cell carcinoma**) are necessary to confirm the diagnosis. Staging examinations used to determine the extent of the disease include imaging methods such as chest X-ray, sonography of the abdomen and groin, CT, PET / CT, MRI or bone scintigraphy.

Basic principles of treatment by clinical stages

In stage I penile cancer, an organ-preserving approach is preferred, especially in young and sexually active men. Treatment methods comprise irradiation (external beam radiotherapy, brachytherapy), surgical excision, laser treatment, cryotherapy or local chemotherapy (topical 5-fluorouracil). Stage II cancer is managed by partial penectomy or radical amputation of the penis (Figures 1 and 2). Patients with stage III cancer or with very advanced tumours are indicated for so-called emasculation procedure, which involves radical amputation of the penis, perineal urethrostomy and removal of scrotum and testicles. Post-operative (adjuvant) radiotherapy is recommended in patients with metastatic nodal involvement. In case of inoperable tumours or in metastatic – stage IV disease, palliative radiotherapy and chemotherapy (cisplatin, 5-fluorouracil, methotrexate, bleomycin, vincristine or paclitaxel) is recommended. Treatment aims to control pain, ensure urine derivation, manage infections and other cancer-associated disorders.

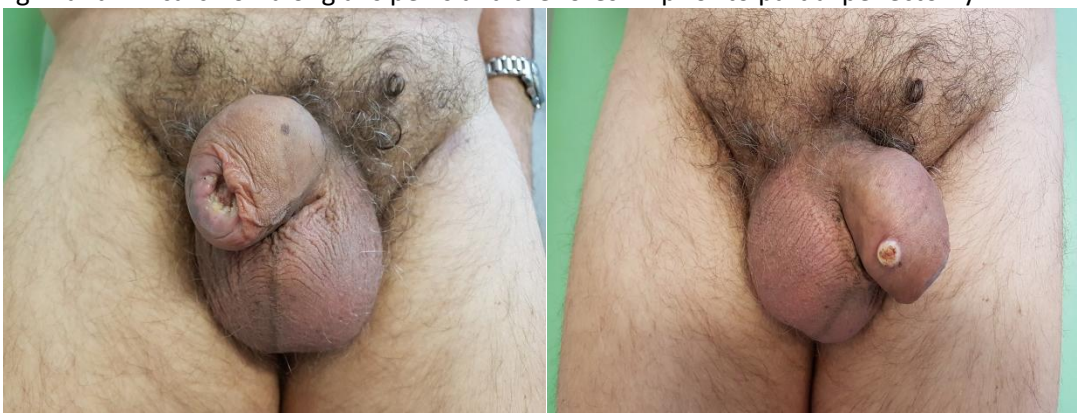
Prognosis by clinical stages

The prognosis depends on size of the tumour, depth of invasion and, above all, the number of affected regional lymph nodes. Three-year survival rate for stage I-II is 93 %, stage IIIA - 48%, Stage IIIB or IV - 0 %.

Follow up

Patients after curative treatment should undergo regular examinations at treating urologist or an oncologist. The primary aim is an early detection of locoregional disease recurrence.

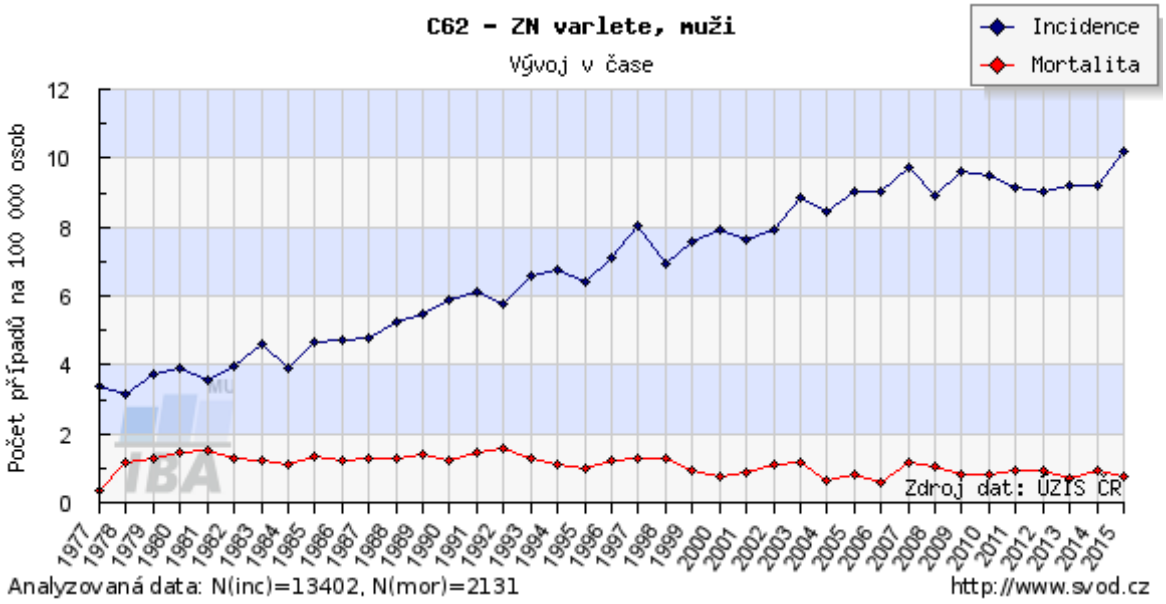
Fig. 1 and 2 – carcinoma of glans penis and the foreskin prior to partial penectomy



Testicular cancer

Epidemiology

Malignant testicular tumours account for 1-2 % of all malignancies in males. Incidence rates are higher in young white men between the ages of 20 and 45. Tumours are more common in industrialized countries (North America and Europe). Approximately 90-95 % of testicular tumours develop from transformed germ cell (**germ cell tumours - GCT**). There are two main histologic subtypes of GCT - **seminomas,** which constitute about a third of GCT and **non-seminomatous GCT,** which include **embryonic carcinoma, choriocarcinoma, yolk sac tumour, teratoma and teratocarcinoma.** Remaining 5% of testicular cancers comprise rare tumour types, such as sex cord **stromal tumours** (Leydig, Sertoli and granulosa cell tumours), exceptionally also testicular lymphomas or haemoblastoses. Testicular cancer incidence rates have remained stable over the last years in the Czech Republic.



Risk factors

Cryptorchidism and hereditary burden are cardinal risk factors for the development of testicular cancer. Patients with congenital anomalies of the urogenital tract, history of scrotal trauma and viral infections are at higher risk of testicular cancer. Preventable risk factors include smoking, alcohol consumption and exposure to chemicals (polychlorinated biphenyls, pesticides, phthalates, heavy metals).

Screening and prevention

There is no specific screening for testicular tumours. Patient education and self-examination is important for early detection of testicular cancers. Primary prevention includes early orchiopexy in children with cryptorchism (before the age of 2).

Clinical presentation

Presenting symptom of testicular cancer is most often a painless swelling of the scrotum or a testicular mass or induration. Some patients may complain of a heavy sensation and discomfort in the scrotum or present with orchitis. More advanced tumours are manifested with signs attributable to metastases, including venous thrombosis or pulmonary embolism. Retroperitoneal mass can cause lower back pain, lung involvement may result in dyspnoea and cough, neurological symptomatology is indicative of brain metastases. Gynecomastia is typical in hormone-producing tumours.

Diagnosis and staging

The initial workup should include physical examination and thorough medical history. Testicular ultrasound is the primary imaging method used to confirm the diagnosis. Baseline measurement of serum tumour markers (alpha-fetoprotein - AFP, β-human choriogonadotropin - βHCG and lactate dehydrogenase - LDH) is necessary for diagnostic, staging and prognostic purposes. Biopsies are not routinely performed and histopathological diagnosis is often obtained after the primary orchiectomy. To complete the staging, CT of the chest, abdomen and pelvis is usually performed. Sperm banking should always be discussed with patients prior to any treatment.

Basic principles of treatment by clinical stages

Radical inguinal orchiectomy is the mainstay of treatment for most patients with testicular cancer. Further management is determined by histological type and clinical stage of the cancer. Patients with stage IA and IB seminomas can be given 1 or 2 cycles of adjuvant chemotherapy with carboplatin or they can be offered active surveillance depending on particular risk factors, such as rete testis invasion or tumour size> 4 cm. In the case of NSGCT, standard post-orchiectomy options are surveillance or adjuvant chemotherapy with one or two cycles of BEP regimen (bleomycin, etoposide, cisplatin). Angioinvasion is considered the main risk factor in these patients. Stage II and III testicular cancer is treated with 3 or 4 cycles of curative chemotherapy with BEP. PET-negative residual disease in seminomas can be managed by active surveillance. Residual disease in NSGCT should always be treated with surgery. Inoperable residual NSGCT or viable residual seminomas are indicated for salvage chemotherapy with VeIP (vinblastine, ifosfamide, cisplatin) or TIP (paclitaxel, ifosfamide, cisplatin). Tumours refractory to salvage therapy have generally poor prognosis, third-line chemotherapy may be used with palliative intent in these patients (regimens based on taxanes,

gemcitabine, oxaliplatin). Radiotherapy can be indicated for management of tumour-associated symptoms related to bone, brain or lymph node metastasis.

Prognosis by clinical stages

GCTs are one of the most curable malignancies. The chances of long-term survival are very high, about 98% of patients with testicular GCT survive 10 years or more. Cure rates decrease with the stage of the disease, 5-year survival for stage I GCT is 98%, stage II (involvement of retroperitoneal lymph nodes) - 90%, stage III (patients with distant metastases) - 60 %.

Follow-up

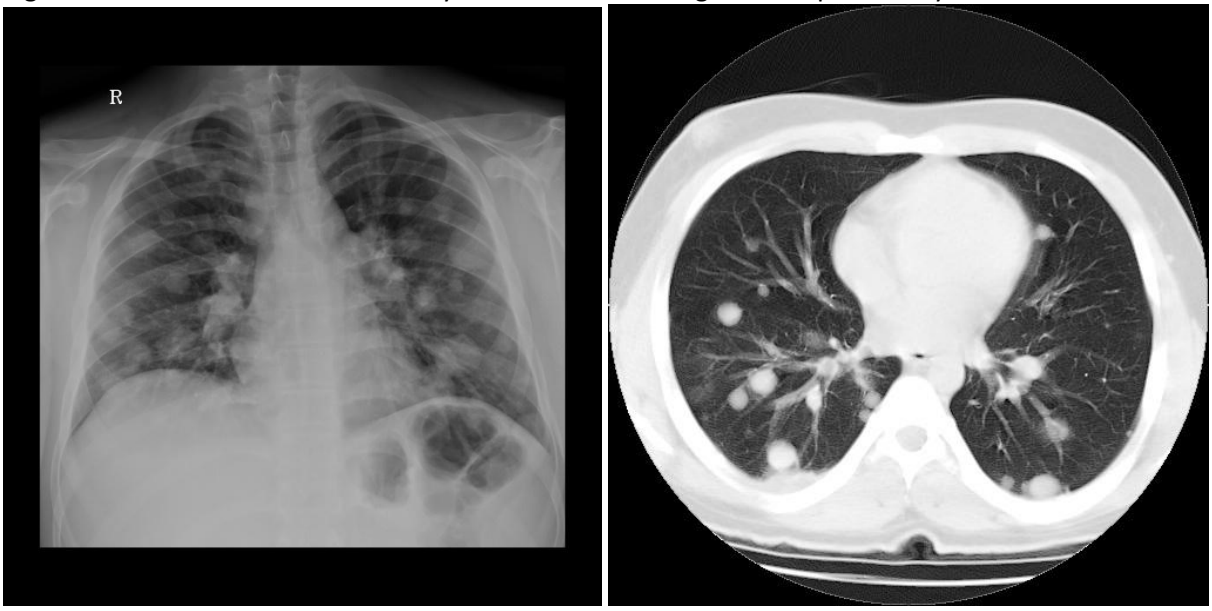
Long-term surveillance is usually provided by an oncologist. Follow-up includes physical examination, tumour marker measurement, chest X-ray, abdominal and pelvic CT scan and scrotal sonography. Relapses are most common in the first 2 years after treatment completion. (Check-ups are more frequent in this period).

Case Report

An 18-year-old man was diagnosed with a stage IIIC NSGCT of the left testicle, disseminated into retroperitoneum, liver, lung, mediastinum and brain, with high elevation of tumour markers. After two lines of systemic chemotherapy (BEP and VeIP regimen) and stereotactic radiosurgery of the solitary brain metastasis, a long-term complete remission (Figures 1-4) has been achieved.

Fig. No. 1 Advanced tumour of the right testis prior to orchiectomy

Fig. No. 2 and 3 – Baseline chest X-ray and CT scan showing massive pulmonary dissemination



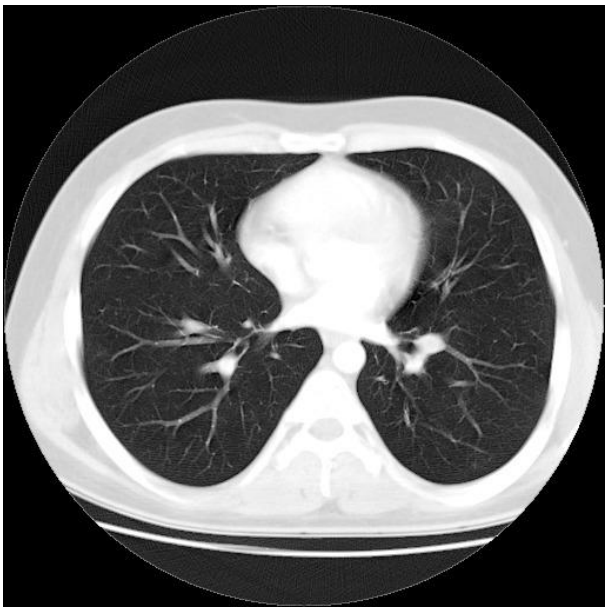


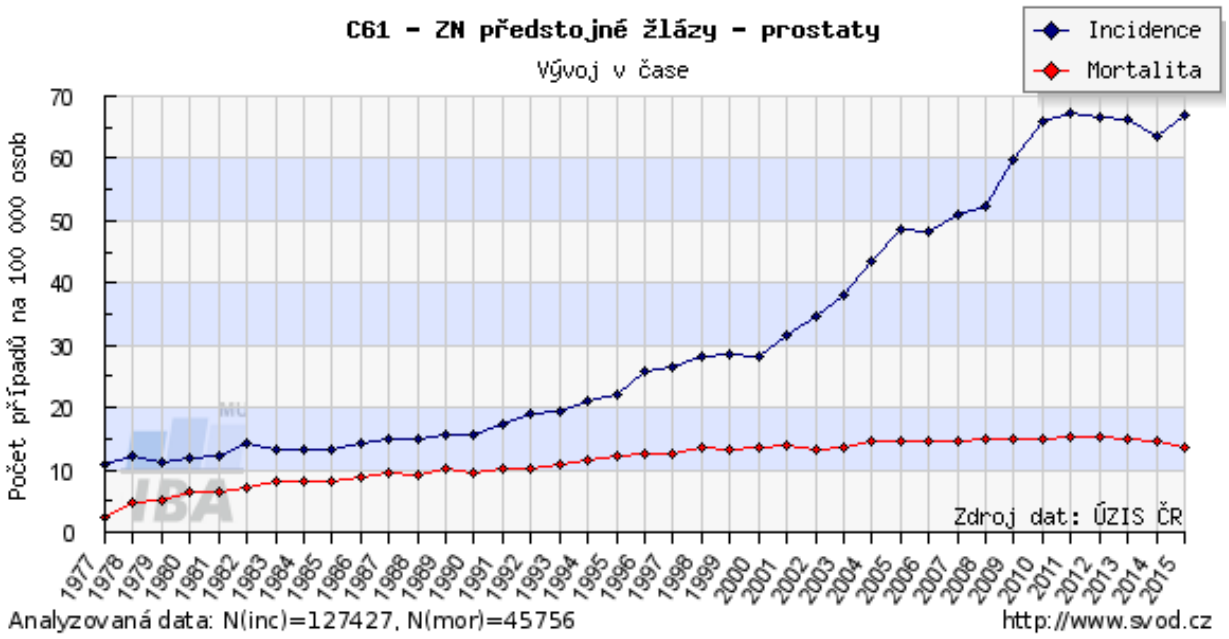
Fig. No. 4: Chest CT scan after 2 months of treatment - remission of metastases

Prostate cancer

I. Kocák, J. Navrátil

Epidemiology

Prostate cancer (PC) is the most common malignancy in men. There are almost 7,000 new PC cases diagnosed in the Czech Republic every year. Incidence increases with age, reaching its peak at the age of 70. Incidence and mortality rates are shown in the graph below:



Risk factors

Prostate tumour is predominantly sporadic and it is not linked to any specific risk factor. Only a small portion of cases (up to 10%) is related to an underlying genetic disorder. The most common inherited prostate cancer predisposition genes are BRCA1 and BRCA2. Preventable risk factors include high-fat diet, insufficient physical activity and obesity, vitamin deficiency and smoking.

Screening and prevention

Routine prostate cancer screening with PSA has not been implemented in the Czech Republic due to conflicting data regarding its efficacy. PSA testing is available to men from the age of 50 and is provided by general practitioners or treating urologists. Digital rectal examination is not recommended for routine prostate cancer screening due to its low sensitivity and specificity.

Clinical presentation

Prostate cancer develops most often on the periphery of the gland and early tumours may therefore remain clinically silent for quite a long time. Symptoms associated with locally advanced disease may resemble obstructive signs of benign prostatic hyperplasia, such as urinary urgency, higher urinary frequency and decreased urine stream. It is not uncommon that prostate carcinoma presents with symptoms of metastatic disease, such as back pain or pathological fracture.

Diagnostic approach and staging

The basic of initial prostate cancer assessment is digital rectal examination and PSA testing. Patients with abnormal findings are indicated for transrectal ultrasonography (TRUS) with prostate needle biopsy. By default, eight or more samples are obtained. Pathological grading is important in prostate cancer risk stratification. Specimens obtained from a needle biopsy are assigned two grades ranging from 1 to 5, based on the degree of tumour cell differentiation. The first grade represents the dominant cell morphology and the second value determines the highest grade. These values yield a so-called Gleason score, noted for example as GS 3+4 (the higher the number, the more aggressive the behaviour).

Once a histopathologic diagnosis of cancer is established, chest X-ray, CT of the abdomen and pelvis and bone scintigraphy are performed as a part of baseline staging. MRI might be useful if radiotherapy of prostate carcinoma is indicated. Clinical staging is based on TNM system. For treatment purposes, three basic categories are recognized: localized PC (tumour is confined to the prostate), locally advanced PC (the tumour extends outside the prostate and invades adjacent tissues) and metastatic PC (most often, PC spreads to lymph nodes and bones). Localized and locally advanced PC is further stratified to low, medium and high-risk group depending on clinical T stage, Gleason score and PSA levels.

Basic principles of treatment by clinical stages

Therapy of localized and locally advanced low and medium-risk PC (T1-2, GS 6-7, PSA up to 20 µg/l)

Since the disease is confined to the prostate, it can be managed with local treatment comprising radical prostatectomy with pelvic lymphadenectomy (RAPE) or curative radiotherapy (RT) combined with androgen deprivation therapy (ADT), most commonly using the LH-RH analogues (i.e., LH-RH agonists or antagonists). The choice of optimal treatment modality depends on the patient overall health status, co-morbidities and patient preferences. Elderly patients with lower PSA levels and expected survival shorter than 10 years may be offered active surveillance and delay the start of treatment until cancer-associated symptoms develop.

Therapy of locally advanced high-risk prostate cancer (T3, GS 8-10, PSA above 20 ug / l)

Cancers with extraprostatic extension can be cured with RAPE or external beam RT combined with androgen deprivation therapy. Due to high risk of cancer recurrence, postoperative management necessitates multimodal adjuvant treatment with radiotherapy or endocrine therapy, depending on definitive pathological staging (pT and pN stage).

Therapy of metastatic PC

Prostate cancer is considered a hormone-sensitive, or so-called castration-sensitive disease at the time of diagnosis. Thus, the initial approach to treatment of disseminated PC includes ADT (pharmacological LH-RH castration or bilateral orchiectomy or pulpetomy). Patients with high-volume disease (bone metastases outside the axial skeleton, visceral metastases) may benefit from the addition of 6 cycles of chemotherapy with docetaxel to ADT. However, within two or three years of ADT, most of patients develop castration-resistant prostate cancer (CRPC). This is usually manifested by progression during the treatment indicated by PSA elevation.

Treatment of castration-resistant disease (Table 1)

Even in castration-resistant disease, some form of castration should be continued, either as a pharmacological or surgical intervention. Other treatment options include systemic chemotherapy and next-generation androgen receptor-targeted agents (ARTA). Patients with extensive bone metastases can be offered supportive treatment with antiresorptive agents (bisphosphonates, denosumab), therapy with radioisotopes or palliative radiotherapy.

Tab. No.1 - Outline of treatment in patients with mCRPC

good general health condition, asymptomatic disease	ARTA drugs
good general health condition, symptomatic disease or visceral metastases	docetaxel
worse overall health status, symptomatic bone involvement, no evidence of visceral metastases	Radium ^{223}

Systemic chemotherapy

Chemotherapy is indicated in symptomatic patients, presenting most commonly with bone pain and in patients with visceral metastases. Chemotherapy confers a significant overall survival advantage in patients with generalized PC. Docetaxel is the most commonly used agent in the first-line setting. Patients who progress on docetaxel can be offered cabazitaxel as a second-line treatment.

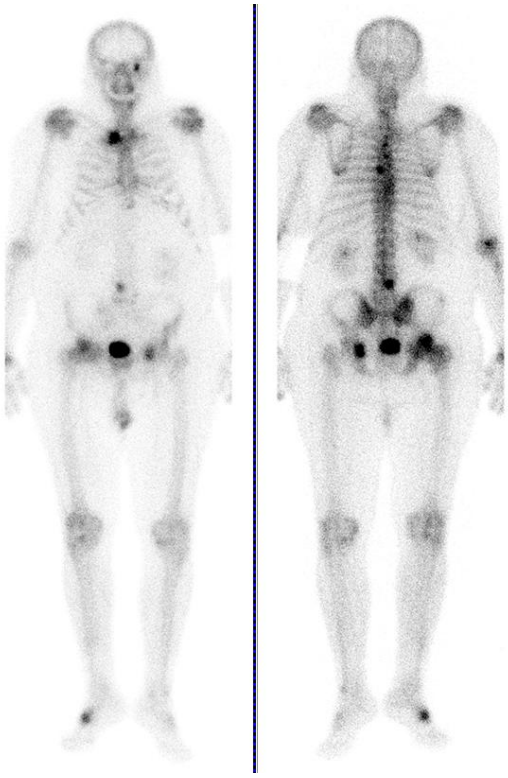
Androgen receptor-targeted agents (ARTA)

Recent introduction of ARTA into clinical practice has significantly improved the outcomes of patients with metastatic castration-resistant PC. These oral agents include abiraterone acetate and enzalutamide. The data from clinical trials suggest that these drugs are best used in patients with mildly symptomatic metastatic disease prior to taxane-based chemotherapy, in order to defer the administration of relatively toxic cytostatic agents. Moreover, sequential treatment with ARTA was associated with better survival outcomes in patients with mCRPC.

Treatment of bone metastases

Bone metastases are a major problem that contributes to impaired quality of life in men with advanced prostate cancer. Bone lesions can underlie pain syndromes and result in functional impairment and increased risk of skeletal-related events in affected patients (Figure 1, bone scintigraphy demonstrating PC generalisation to the orbit, thoracic and lumbar spine, pelvis and sternoclavicular joints. Other sites with higher FDG accumulation are found in the right hip joint and right leg - these may be of degenerative or inflammatory aetiology).

Fig. No. 1 massive skeletal dissemination



Supportive treatment in patients with bone metastases comprises antiresorptive agents, radioisotopes and external beam radiotherapy:

Antiresorptive agents

Antiresorptive agents affect bone metabolism by inhibiting osteoclast activity and reducing osteoclast- mediated bone resorption. The most commonly used drugs are bisphosphonates, mainly zoledronic acid and a monoclonal antibody - denosumab. These drugs significantly reduce the risk of pathological bone fractures and other skeletal complication.

Radioisotopes

Symptomatic bone metastases can be treated with radionuclides, preferably with novel agents, such as Radium-223. Since the isotope is similar to calcium, it is selectively absorbed by bones. Radium in an alpha-emitter, which means that it releases a high amount of energy within a very short range (100μm) with a minimal damage to adjacent healthy tissues. Due to its selective uptake by bones the drug is targeted only at skeletal metastases and it is not suitable for use in patients with visceral or nodal metastases. Radium-223 was proved to reduce the risk of pathological fractures, relieve bone pain and increase overall survival in patients with mCRPC.

Palliative radiotherapy

The goal of palliative external beam radiotherapy is to alleviate cancer-associated pain, to minimize complications such as pathological fractures or spinal compression and maintain a good quality of life.

Prognosis by clinical stages

Approximately 90% of patients with localized low-risk prostate cancer survive for 5 years or more. Five-year survival in patients with high-malignancy tumours is approximately 60%. Up to 70% of patients with locally advanced disease live for 5 years or more after the completion of treatment. Patients with metastatic disease have the worst prognosis, 5-year survival is about 30% in this group.

Follow up

Patients after radical treatment of prostate cancer are regularly monitored at 3 to 6-month intervals for 5 years. Surveillance includes regular PSA tests, digital rectal examinations and imaging methods guided by specific symptomatology. In the case of PSA elevation, complete restaging is necessary.

Case reports

Case No. 1:

A 65-year-old patient underwent a preventative oncology examination (as a retirement gift from his colleagues). Unfortunately, DRE revealed a suspicious prostate mass and lab tests showed a higher PSA levels (13.1ug/l). The patient was referred for TRUS with prostate needle biopsy. Subsequent histopathological examination confirmed a prostate adenocarcinoma GS 3 + 4 without lympho-vascular invasion. Clinical staging methods (abdominal and pelvic CT, chest X-ray and bone scintigraphy) did not show any distant metastatic spread. The tumour was staged cT2b cN0 M0 – i.e. clinical stage II, medium-risk prostate cancer. The patient was offered either curative surgery or radiotherapy, and opted for radiotherapy. Thus, he was started with neoadjuvant treatment with LHRH-agonists and after 4 months of endocrine therapy, the patient underwent outpatient prostate radiotherapy. The treatment was well-tolerated, side effects included only minor urinary urgencies by the end of radiotherapy. After completion of radiotherapy, the patient remained on hormone treatment for another two years. He has achieved a complete tumour remission and he has been regularly followed for more than 4 years up to now. He has no cancer-related symptoms and his PSA levels are negative.

Case No. 2:

A 74-year-old patient complained of lower back pain with increasing intensity in the past months. A plain X-ray detected metastasis of the lumbar spine. Abdominal CT abdomen and bone scintigraphy demonstrated multiple osteoplastic bone metastases, pelvic lymphadenopathy and enlarged prostate. Lab tests showed high PSA levels (390ug/l), hypercalcaemia and anaemia. Diagnostics proceeded with prostate biopsy, histopathology confirmed prostate adenocarcinoma, GS 4 + 4. Androgen deprivation therapy was initiated. The patient underwent orchiectomy and he was treated with zolendronic acid due to skeletal involvement and hypercalcaemia. After one month, his PSA levels dropped to 10ug/l, however, one year after the primary diagnosis, PSA levels began to rise and the patient was diagnosed with castration-resistant prostate cancer. Treatment with abirateron acetate was initiated and it was marked by another significant decrease in PSA levels. Progression free survival achieved with ARTA therapy was approximately 16 months. Afterwards, the patient complained of increasing back pain and bone scintigraphy confirmed disease progression. The treatment with ARTA has been discontinued. The patient was administered palliative chemotherapy with docetaxel every 3 weeks. In total, he underwent 10 cycles of chemotherapy resulting in regression of bone metastases, pain relief and PSA decline. Side effects included transient finger numbness and fatigue following the administration of chemotherapy. The patient was then indicated

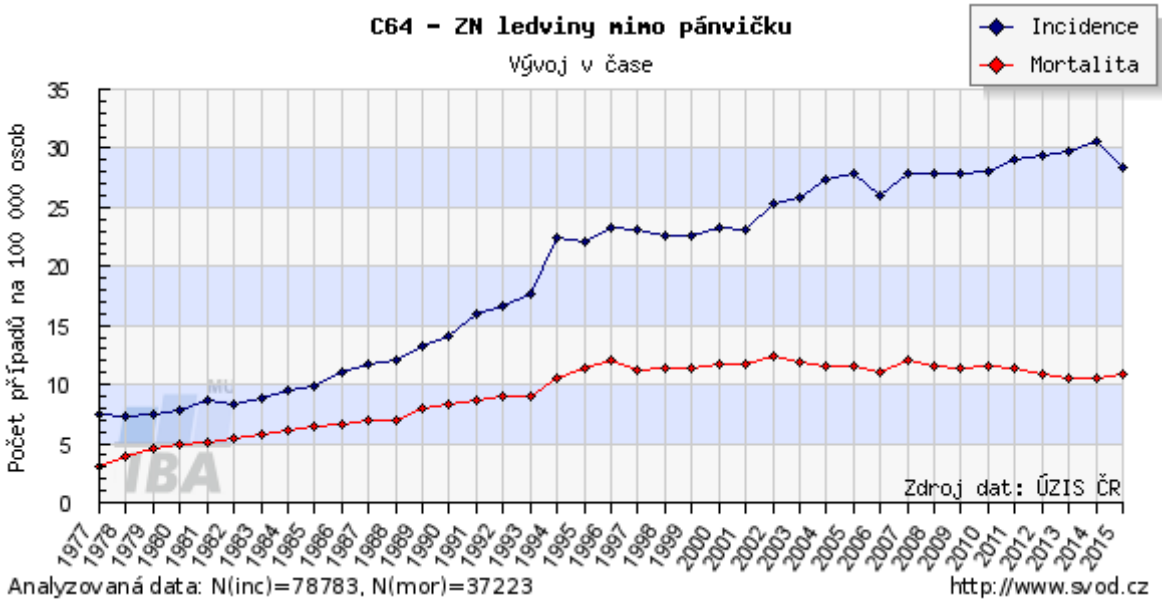
for surveillance. After 5 months, he developed new bone metastases. He was started on second-line treatment with cabazitaxel. Altogether, 8 series were administered with the effect of PSA decrease. Due to an imminent pathological fracture of the humerus and intermittent back pain the patient underwent a single irradiation of the affected sites. The disease progressed after another 6 months and patients overall health condition deteriorated. He suffered from severe right hip pain caused by extensive metastatic involvement. He was indicated for another series of palliative radiotherapy and he also required intensive treatment with opioid analgesics. The patient continued to be seen by a palliative care specialist, after 4 months he was referred to outpatient hospice services and one month thereafter he succumbed to the disease at home in his family circle.

Kidney cancer

A. Poprach, R. Lakomy

Epidemiology

Malignant kidney tumours represent approximately 2-3 % of all malignancies in adults and as many as 10% of childhood tumours (especially nephroblastoma and Wilms tumour). Renal cell carcinomas (RCC), which originate in the renal cortex, constitute up to 85% of primary renal tumours, other tumours arising in the kidney include transitional cell carcinoma or the renal pelvis, less commonly collecting duct tumours or sarcomas. The Czech Republic belongs to the countries with the highest incidence and mortality of renal cell cancer.



Aetiology and risk factors

Similarly to prostate cancer, the aetiology of kidney tumours has not been clearly understood yet. The vast majority of tumours occur sporadically. Two groups of risk factors associated with kidney cancer are distinguished: non-intrinsic (endogenous and exogenous) and intrinsic (genetic) factors. The most common exogenous risk factors are obesity, tobacco smoking and other lifestyle factors. Arterial hypertension and its treatment, end-stage chronic kidney disease and prolonged dialysis are considered partially modifiable endogenous risk factors. The group of intrinsic risk factors includes inherited genetic syndromes such as von Hippel-Lindau disease, Birt-Hogg-Dubé syndrome and others.

Screening and prevention

The most common preventable risk factors were mentioned above. Individuals with a strong family history of kidney cancer or with known genetic disorder should be monitored regularly; however, there is no general agreement on screening recommendations for this type of cancer.

Clinical manifestations

Kidney cancer often remains clinically silent until the disease is advanced. Nowadays, only few patients present with typical symptoms like pain, haematuria or palpable abdominal mass. Paraneoplastic syndromes such as polyglobulia, hypercalcaemia or high sedimentation rate are very rare. With the increasing availability of imaging methods, an incidental finding of early-stage kidney cancer has become more common, though, patients presenting with symptoms related to distant metastases (back pain, pathological fractures, ascites, fluidothorax, CNS involvement) are not an exception.

Diagnosis and staging

The initial assessment involves medical history, physical examination and laboratory studies including complete blood count, blood chemistry, coagulation and urine tests. Contrast-enhanced CT of the abdomen and pelvis is the preferred imaging procedure in clinical tumour staging. Chest X-ray should be also obtained to rule out lung metastases. If urothelial carcinoma is suspected, urine cytology and ureteroscopy are recommended. Percutaneous renal biopsy, bone scintigraphy, brain MRI or whole body PET / CT are not performed routinely and are indicated only in select cases.

Histopathological subtypes of RCC are classified according to the WHO system (2016). Approximately **75-80%** of RCC are **clear-cell carcinomas**, less common histologies include papillary or chromophobe carcinoma, other subtypes are very rare. Besides morphological features, tumour grading is important for the assessment of its malignancy. Among many different classifications, the most widely used grading system is by ISUP (International Society of Urological Pathology).

Basic principles of treatment by clinical stages

Stage I and II RCC (T1 or T2, N0 M0): Radical nephrectomy with or without lymphadenectomy and adrenalectomy is the backbone of treatment. In indicated cases (e.g. T1a or some T1b stages, especially in patients with hereditary kidney cancer who are at high risk of developing another kidney tumour; in patients with renal insufficiency, solitary kidney or bilateral RCC), partial nephrectomy might be preferred. Patients not amenable to surgery might be offered nephron-sparing procedures including thermal or radiofrequency ablation, cryosurgery, or various types of chemoembolization.

These modalities have been associated with favourable treatment outcomes, particularly in patients with localized tumours smaller than 4cm.

Stage II and III RCC (T1 or T2N1M0; T3 N0 or N1M0): Radical nephrectomy is the standard of treatment in these patients. Ablative techniques (mentioned above) can be used with palliative intent only. In addition, palliative radiotherapy may be considered to control cancer-associated symptoms like pain or bleeding. Patients with unresponsive haematuria may be offered palliative nephrectomy. Studies published to date have not proved any benefit of adjuvant chemotherapy or immunotherapy.

Stage IV RCC: The treatment is guided by prognostic models determined by various factors, such as serum haemoglobin level, patient performance status, histopathologic characteristics of the tumour, etc. Based on these characteristics, patients are classified into several prognostic groups (e.g. low, medium and high-risk patients according to Motzer).

Palliative systemic therapy is of paramount importance in patients with metastatic disease and it consists mainly of targeted agents. The most common preparations are tyrosine kinase inhibitors that affect vascular endothelial growth factor (VEGF) signalling pathways and mTOR inhibitors. **Pazopanib, sunitinib**, bevacizumab with interferon α, temsirolimus (mTOR inhibitor) and sorafenib are the available treatment options in the first-line setting. In the second line, **everolimus** (mTOR inhibitor), axitinib or sorafenib can be used, however, currently they have been eclipsed by novel agents like nivolumab or cabozantinib. Third-line treatment with everolimus, sorafenib or interferon can be considered in patients with good general health status, depending on the effect and character of prior therapy. To date, there is not an unequivocal consensus on the optimal treatment sequence in patients with metastatic RCC.

In addition to systemic treatment, select group of patients can benefit from **cytoreductive nephrectomy** (occasionally, a spontaneous regression of other metastases is described after the procedure). It is recommended in patients with potentially resectable RCC without brain or liver metastases and with good general health condition (PS 0-1). **Metastasectomy** is indicated in patients with oligometastatic disease, usually when no more than two organs are involved. **Palliative radiotherapy** is a measure of last resort in patients with symptomatic skeletal involvement and brain metastases.

Prognosis by clinical stages

Five-year survival rate in patients with stage I RCC is 80-85%, 75% in stage II, and about 53% and 15% in stage III and IV, respectively.

Follow-up

There is not a consensus regarding the most appropriate follow-up scheme in RCC survivors. Most relapses occur within the first 3 years after the initial diagnosis. The frequency and character of check-ups is based on every patient's individual risk factors, which are defined by SSIGN (stage-size-grade-necrosis) system. Laboratory tests and imaging techniques should be chosen based on the best clinical judgement.

Case Report

A 56-year-old patient presenting with macroscopic haematuria was diagnosed with a 12cm tumour of the left kidney with presumed retroperitoneal lymph node involvement. He underwent radical nephrectomy and lymphadenectomy, the histopathology findings were consistent with grade 3 clear-cell renal carcinoma, pT3a pN1. After 17 months of follow-up, metastasis in the lungs, mediastinum and retroperitoneum were detected on a CT scan. The patient was indicated for first-line palliative treatment with sunitinib, which was well-tolerated, however, there was disappointing lack of efficacy. After three months of treatment the patient became symptomatic, he suffered from dyspnoea and persistent cough due to progression of lung metastases. The patient was started on nivolumab, which was available under the EAP (expanded access program) at that time. At the first review, a significant regression of the disease was demonstrated on a CT scan (predominantly in the mediastinum - see Figure no. 1 and 2) and there was a sustained improvement of respiratory symptoms. The patient was treated with nivolumab for two years until the EAP was discontinued. Adverse effects comprised only of grade 1 fatigue, grade 2 arthralgia and clinically silent elevation of pancreatic amylase.

Fig. no 1: Mediastinal metastasis prior to nivolumab

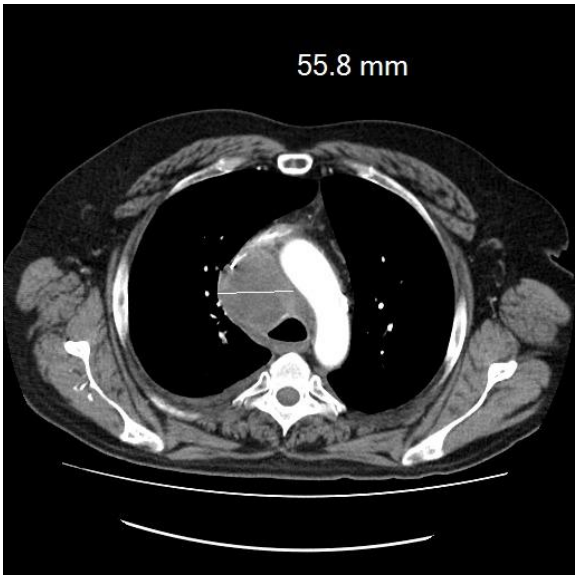
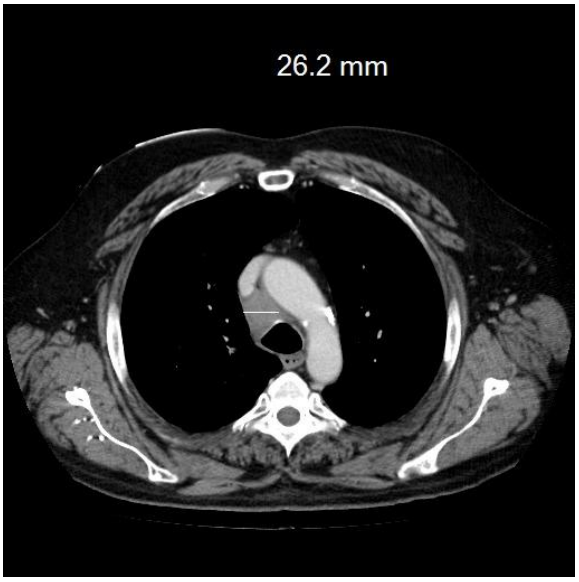


Fig. no 2: Mediastinal metastasis after 3 months of treatment

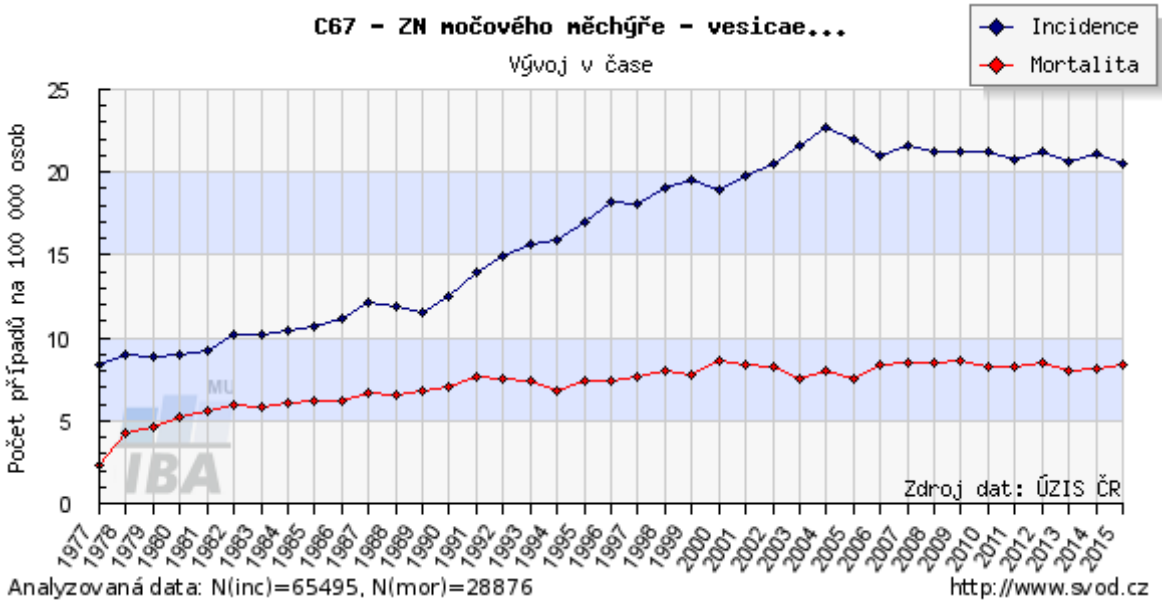


Bladder cancer

A. Poprach, R. Lakomy

Epidemiology

Incidence and mortality rates for bladder cancer in the Czech Republic reported in 2015 were 20.5 and 8.4/ 100 000, respectively. Approximately two-thirds of bladder cancers occur in people aged 65 and over, more commonly in males than in females (men to women ratio is approximately 3: 1).



Aetiology and risk factors

The aetiology of bladder cancer is multifactorial, however, there are several risk factors clearly linked to development of the tumour, such as smoking, occupational exposures to polycyclic aromatic hydrocarbons and amines, dietary factors (increased meat and fat intake) and chronic bladder infections. Intrinsic risk factors include a variety of genetic diseases and disorders (e.g. Lynch II and others).

Screening and prevention

There is no population-based screening available for this type of cancer. A large proportion of bladder tumours is preventable by avoiding the exogenous risk factors mentioned above.

Clinical picture

The cardinal presenting symptom of bladder cancer is **haematuria** (micro or macroscopic), urinary difficulties (dysuria or stranguria) and other symptoms that may resemble urinary tract infection or

renal colic. These conditions may often coexist, since malignant urinary tract obstruction can underlie superimposed infection. A palpable mass at abdominal physical examination is indicative of advanced disease, as well as symptoms associated with distant metastasis (cough, abdominal or bone pain).

Diagnosis and staging

Most common bladder cancer is **urothelial carcinoma**, less common histologies include **epidermoid carcinoma, adenocarcinoma, small cell carcinoma** and other rare subtypes. The initial workup comprises medical history, thorough physical examination. Besides standard laboratory investigations, urianalysis and voided urinary cytology might be helpful in the diagnostics. Nevertheless, primary modality for the assessment of bladder cancer is cystoscopy with urinary cytology, which is often followed by transurethral resection of the tumour (TURT). This procedure is both diagnostic and therapeutic in some cases (papillary localized tumours). During cystoscopy, biopsy of a suspicious lesion can be obtained for further histopathologic examination. Alternatively, so-called bladder mapping may be performed, in which multiple specimens are taken randomly from lateral walls, base, dome, and trigone of the bladder. Depending on tumour grade, primary location and extent, ascending pyelography or i. v. (or CT) urography is indicated. Abdominal and pelvic CT scan should be performed in sessile, high-grade or muscle-invasive tumours. Contrast-enhanced dynamic MRI of the bladder is an alternative method for determining tumour extension and depth of invasion. Bone scintigraphy, chest X-ray, or abdominal ultrasound should be obtained, if distant metastases are suspected.

For treatment purposes, bladder cancer (BC) is classified into:

1. non-muscle invasive (superficial) BC - Tis, Ta, T1
2. muscle invasive BC - T2-4a N0
3. metastatic BC - T4b / N + / M +

Basic principles of treatment by clinical stages

Superficial bladder carcinomas (Tis, Ta, T1)

The mainstay of treatment is sufficiently deep and radical transurethral resection of the tumour (**TURT**). Treatment usually proceeds with intravesical instillation of chemotherapy within 24 hours after the procedure in order to reduce the risk of recurrence (mitomycin C or intravesical immunotherapy with BCG vaccine is used). Recurrence risk stratification (based on the number, size, grade of the tumour, etc.) governs further treatment and surveillance decisions. High-risk patients might be offered secondary TURT with intravesical chemotherapy instillation or maintenance therapy with BCG vaccine.

Muscle invasive or infiltrating bladder cancer (T2, T3, cT4a)

The primary treatment modality is **radical cystectomy with lymphadenectomy.** Particular patients may be indicated for neoadjuvant chemotherapy with cisplatin and gemcitabine, less frequently, adjuvant chemotherapy may also be considered. Bladder-preservation procedures are increasingly used, among which a maximal TURT followed by concomitant chemoradiotherapy is the preferred approach. In select circumstances, partial cystectomy preceded by neoadjuvant chemotherapy represents an alternative option. Patients who are unfit for a major surgery might be offered TURT as a standalone treatment, concomitant chemoradiotherapy (CHT / RT), or radiotherapy alone, however, it should be noted that all these approaches are inferior to radical cystectomy and confer worse survival.

Advanced and disseminated disease (T4b or N1-3 or M1)

The intent of treatment is mostly palliative. Patients are usually treated with **chemotherapy** (cisplatin-based or carboplatin-based regimens with/without gemcitabine) or exceptionally with concomitant **chemoradiotherapy**. Checkpoint inhibitors such as pembrolizumab or atezolizumab may be indicated in patients unfit for cisplatin, however, they are not covered by Czech national health insurance yet. Checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab) used in the second-line setting have showed very promising results and reimbursement approval is expected. An alternative option in the second and higher lines includes taxanes, methotrexate, vinblastine or doxorubicin, however, these agents are of limited efficacy.

Prognosis according to clinical stages

5-year survival of patients with stage 0 cancer is about 98 %, in stage I disease it is approximately 88 %, and with increasing stages it drops to 63 %, 46 and 15 %.

Follow-up

Patients with early-stage disease managed by TURT are followed by regular cystoscopy. Laboratory investigations include renal function tests, basic blood chemistry, liver tests, CBC and voided urine cytology. They should be obtained every 3-6 months. Imaging modalities such as chest X- ray, CT of the abdomen and pelvis should be performed every 3-6 months in the first two years, then depending on individual patient's recurrence risk. Patients treated with bladder-preserving procedures require lifelong rigorous surveillance based mainly on regular cystoscopy and urine cytology examinations.

Case Report

A 54-year-old patient underwent neoadjuvant chemotherapy due to locally advanced high-grade bladder cancer (cT3 cN2 M0 stage) followed by radical cystectomy and subsequent adjuvant chemotherapy (indicated because of an excellent effect of neoadjuvant therapy confirmed by

histopathological results - the disease was classified as ypT0ypN0, which means a complete remission). Unfortunately, six months after adjuvant treatment completion, the patient developed multiple peritoneal metastases extending from the liver to the rectum. The tumour was largely symptomatic, the patient suffered from severe abdominal pain and tenesmus. He was given taxanes in order to reduce the tumour burden and control cancer-associated symptoms (cisplatin was not indicated since the patient relapsed within 6 months after prior treatment). The administration of paclitaxel was complicated by acute vestibular syndrome (brain MRI did not show any metastases). Symptoms resolved within a few days and they were concluded as an adverse effect of chemotherapy. The patient was subsequently started on nivolumab and achieved a complete remission of the disease after 3 months of treatment. Up to now, he remains free of cancer.

Fig.No.1: abdominal CT scan prior to treatment

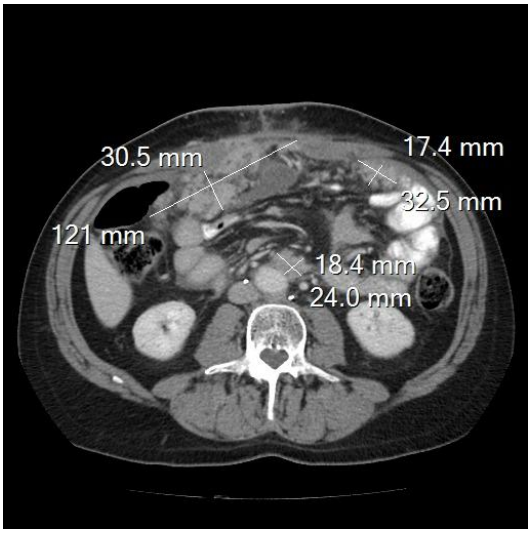
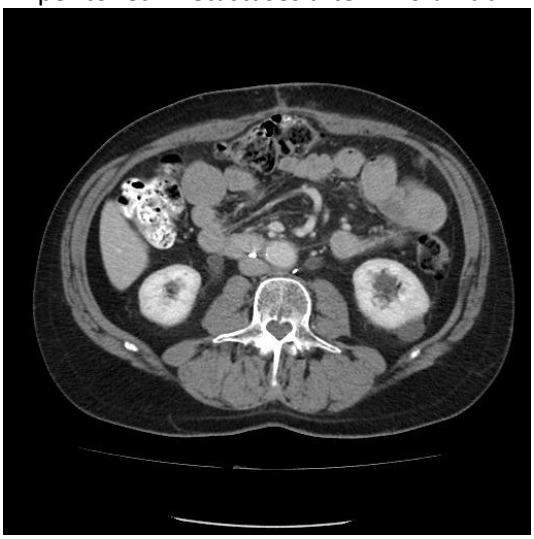


Fig.No.2: complete regression of peritoneal metastases after nivolumab

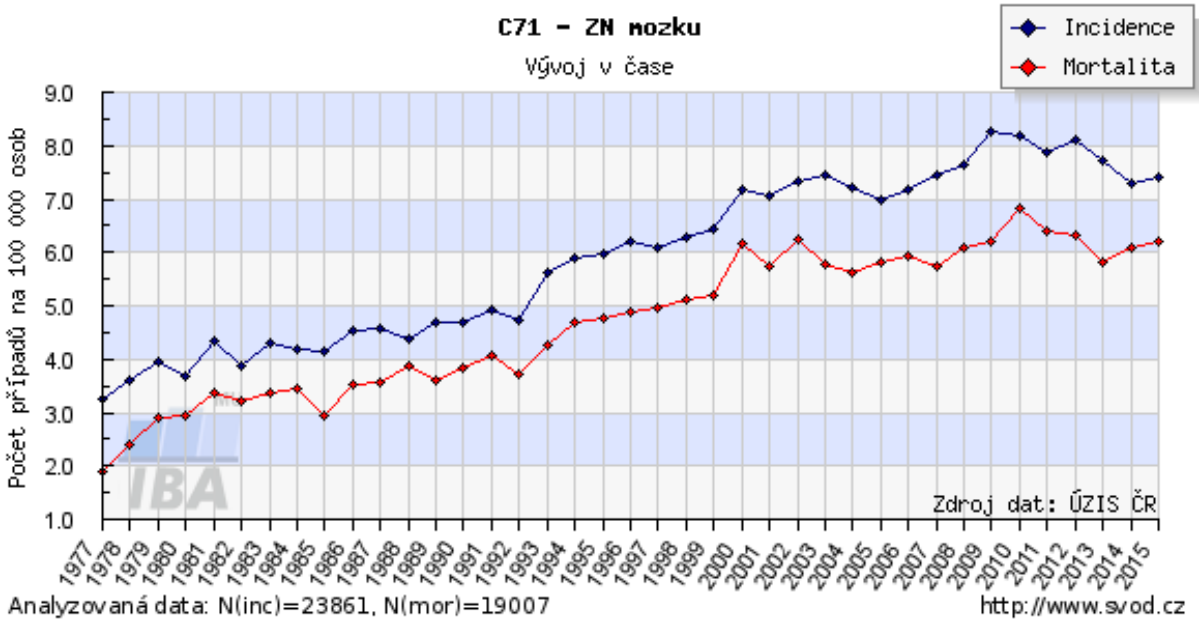


Central nervous system (CNS) tumours (primary and secondary)

R. Lakomy, T. Kazda, A. Poprach, P. Fadrus, P. Pospíšil, P. Šlampa

Epidemiology

Primary CNS tumours account for only about 2% of all tumours. The incidence shows a bimodal age distribution with peaks in children under 5 years of age and adults after their 6th decade of life. Secondary tumours (metastases) disseminate to brain from locations outside the CNS and are 10 times more common. The most common primaries with CNS spread include lung, breast, kidney cancer and malignant melanoma. The incidence and mortality of primary CNS tumours is presented in the figure below (adopted from Czech National Cancer Registry).



Risk factors

The aetiology of primary brain tumours is multifactorial. Ionizing radiation and long-term immunosuppression (HIV infection, immunosuppressive therapy), as well as exposure to polycyclic aromatic hydrocarbons are the most common well-established risk factors. Approximately 5% of tumours display familial occurrence. An estimated 1% of all cases is associated with hereditary syndromes (e.g., Li-Fraumeni syndrome, Turcot syndrome, type 1 neurofibromatosis).

Screening and prevention

Screening of brain tumours is not performed. Only high-risk patients (carriers of mutations associated with hereditary syndromes) are regularly monitored.

Clinical presentation

Clinical manifestations of brain tumours are related to their location, size and biological behaviour. In the case of **supratentorial** location, patients most commonly present with sensory-motor deficits, speech disorders, cognitive functions deterioration and epileptic seizures. **Infratentorial** tumours manifest by cerebellar and brainstem symptomatology including cranial nerve palsy. As tumours advance, an increase in intracranial pressure may result in intracranial hypertension syndrome, altered state of consciousness and even death (especially in cerebral herniation syndromes).

Diagnosis and staging

Magnetic resonance imaging (MRI) and its variants (diffuse MRI, spectral MRI, perfusion MRI, functional MRI) are essential in tumour diagnosis and further assessment. It provides a better view of brain structures in comparison with CT scan. Complementary diagnostic methods include dilated-pupil fundus examination, electroencephalography (EEG), positron emission tomography (PET) or angiography.

Histological examination of the tumour (its origin and level of differentiation, i.e. grading) including molecular and genetic profiling are essential for the diagnosis. Specific chromosomal aberrations and gene mutations provide diagnostic as well as prognostic information. The latest WHO classification of brain tumours from 2016 integrates histologic and molecular characteristics in order to improve the diagnostic accuracy, refine prognostication and enable reliable prediction of treatment response. Better patient stratification based on molecular biomarkers also contributes to greater homogeneity of patient populations within clinical studies. According to tissue of origin, brain tumours are divided into several groups: **neuroepithelial** tumours, **cranial and paraspinal nerve** tumours**, meningeal** tumours, **lymphomas and hematopoietic neoplasia, germ cell tumours,** tumours of the **sellar region** and **metastatic** tumours. Primary CNS tumours most commonly develop from **glial (supportive) tissue** of neuroectodermal origin and are referred to as **gliomas** (constitute more than 50% of CNS tumours).

Basic principles of treatment

Treatment strategy depends on the biological behaviour of a tumour (histological type, grade, molecular biomarkers), its size, location in the brain, patient age and general health condition. Therapy of brain tumours requires multidisciplinary approach. Brain metastases are usually managed in the context of the underlying disease (surgery, radiotherapy, chemotherapy, targeted treatment, immunotherapy, hormone therapy).

Surgery

The main objective of every neurosurgical procedure is to provide a radical tumour resection without any damage to functionally important brain structures. If a safe resection is not possible, a biopsy (for histopathologic diagnosis and grading) should be attempted. In malignant tumours with infiltrative type of growth (gliomas), the primary goal of surgery is to perform maximal safe tumour debulking (size reduction), obtain adequate material for histological examination and allow for further treatment modalities like radiotherapy or chemotherapy. Contrarily, in the case of metastases or localised and accessible tumours, surgery should achieve complete tumour resection (without compromising neurologic function). In lymphomas, the role of the surgery is mainly diagnostic (biopsy), the principal treatment modality is chemotherapy and radiotherapy.

Radiotherapy and radiosurgery

Radiotherapy (RT) is often indicated after primary resection or as a treatment of choice in tumours that are not amenable to surgery. Radiation dosing and treatment plan depends on the type of tumour and overall health condition of the patient. The basic irradiation method is a standard fractionated external beam radiotherapy of the tumour bed and a safety margin (to eradicate microscopic disease in surrounding tissue). The overall treatment duration counts in the order of several weeks (3-6 weeks). Patients with tumours prone to spread along the liquor pathway (e.g., medulloblastomas) are indicated for the entire cranio-spinal axis irradiation. Other radiation techniques used in the treatment of CNS tumours include **stereotactic radiosurgery** (single high-dose irradiation) and **stereotactic fractionated radiotherapy** (fractionated high-dose irradiation, the treatment takes about one week). Both methods are used to treat small or deep lesions inappropriate for surgery (maximum tumour size manageable by radiosurgery is 2-3 cm and 4-5cm for fractionated stereotactic radiotherapy). To date, photon radiation produced by linear accelerators or cobalt irradiators (gamma knife) is the most frequently used technique in the therapy of brain tumours. In select cases, novel radiation methods (such as proton radiotherapy) can be considered.

Chemotherapy and supportive treatment

Due to the restrictive character of the blood-brain barrier, lipophilic cytostatic agents are preferred in the treatment of brain tumours. **Temozolomide**, **nitrosourea derivatives** or procarbazine are used most often. Sensitivity to systemic treatment varies significantly accross brain tumours. Germ cell tumours and haematological malignancies belong to the most sensitive and curable tumours. On the other hand, gliomas typically present with very low chemosensitivity and the role of systemic treatment is mostly palliative. Chemotherapy can be given as a standalone treatment or concurrently with radiotherapy, in post-operative (adjuvant) setting or, in case of a recurrent tumour, as a

palliative monotherapy or in combined regimens. The role of targeted agents or checkpoint inhibitors has not been conclusively established yet. In some countries, bevacizumab is recommended for the treatment of recurrent high-grade astrocytomas, however, the impact on overall survival is dubious. Systemic treatment of brain metastasis is based on preparations used for the treatment of the primary tumour (including targeted treatment and advanced immunotherapy). Comprehensive oncological care also involves anti-oedema treatment of intracranial hypertension (dexamethasone, mannitol) and anti-seizure therapy in the case of secondary epilepsy.

Management of gliomas (the most common primary brain tumours in adults)

Low-grade infiltrative astrocytomas (grade II under the WHO system)

These tumours occur frequently in young adults (30-40 years). Primary surgery is usually followed by radiotherapy, though the optimal timing of RT is a matter of discussion (early postoperative RT vs. deferred RT in case of recurrent disease). There are several risk factors favouring early RT, such as residual tumour at postoperative MRI, neurological symptomatology, age > 40 years, positive molecular biomarkers. Chemotherapy can be started immediately after radiotherapy or it can be reserved for recurrent tumour after the exhaustion of other treatment modalities (surgery and radiotherapy). The use of chemotherapy as a substitute for postoperative RT (due to high risk of cognitive impairment after radiotherapy in young patients) is currently under investigation.

High-grade astrocytomas (grade III and IV)

High-grade glioma is the most common type of brain tumours, the incidence is highest in older people (mean age of 60 years). This group comprises anaplastic glioma (grade III) and more prevalent **glioblastoma multiforme** (grade IV), which is considered the most aggressive brain tumour. The mainstay of treatment is maximum safe resection followed by concomitant chemoradiotherapy and subsequent adjuvant chemotherapy with temozolomide. In elderly patients (> 70 years) or patients with poor performance status, sequential postoperative radiotherapy (often a hypofractionated regimen) and chemotherapy (given the methylation of MGMT- methylguanine-DNA methyltransferase promoter is detected) is the preferred option. A novel treatment modality uses TTF technique (Tumour Treating Fields), which involves a device attached to patient's scalp transducing ultra-low-intensity alternating electric fields into the tumour.

Oligodendrogliomas (grade II and III)

They are relatively rare tumours compared to astrocytomas. The backbone of treatment is surgery, whereas indications of postoperative radiotherapy are the same as in astrocytomas. Most of these tumours share distinct molecular characteristics, namely 1p/19q co-deletion and IDH (isocitrate

dehydrogenase) gene mutation, which are predictive of good treatment response and better overall survival. Due to higher chemosensitivity, the addition of adjuvant therapy with PCV-procarbazine, lomustine, vincristine or less toxic temozolomide is recommended in these patients.

Prognosis

The prognosis is influenced by many factors, mainly by histological type, grade and size of tumour, its biological behaviour (prognostic and predictive molecular biomarkers), age of the patient, associated co-morbidities, etc. In low-grade astrocytomas (grade II), median survival is reported to be around 7-8 years, in anaplastic astrocytoma (grade III) 2-3 years, in glioblastoma (grade IV) between 12-15 months. Median survival of oligodendroglioma is longer (5-10 years, sometimes even more). The prognosis of patients with brain metastases is dependent on their size and number, as well as the type and extent of the primary tumour and its sensitivity to treatment.

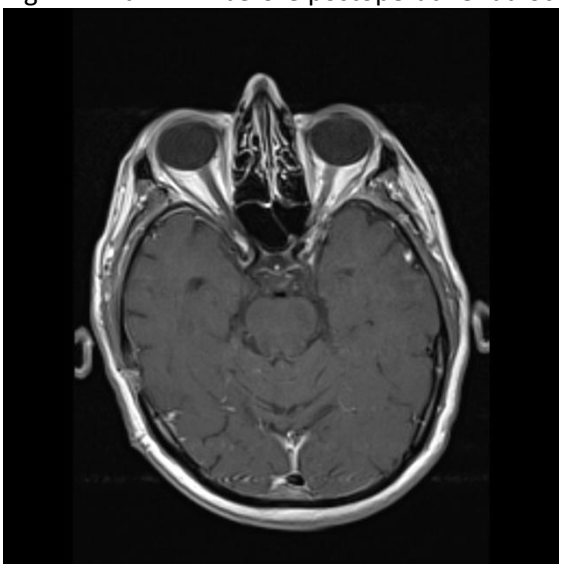
Follow-up

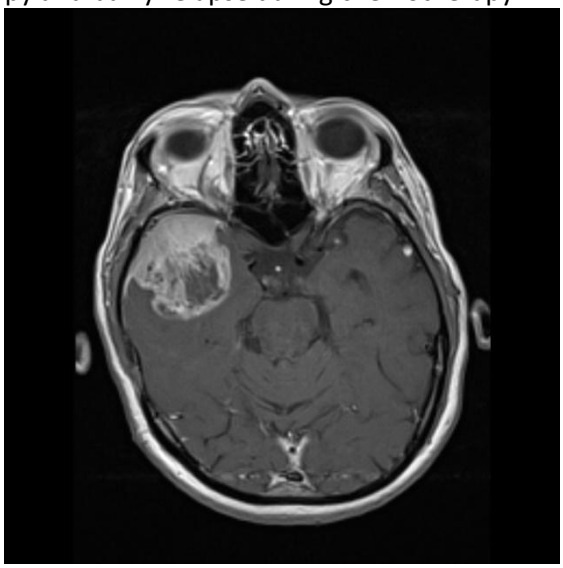
Surveillance is provided by a neurologist, oncologist or neurosurgeon. Brain MRI should be obtained every 3-6 months in the first 2-3 years, every 6-12 months up to 5 years after treatment completion and then annually. Given the patient presented with seizures at diagnosis or in the course of disease, EEG should be performed every 6 months.

Case Report

A 42-year-old man with glioblastoma in the right temporal lobe underwent partial tumour resection and subsequent concomitant chemoradiotherapy with temozolomide, followed by post-irradiation adjuvant temozolomide. After 5 cycles the therapy, he developed a tumour recurrence (Fig. 1-2). The disease progressed despite palliative chemotherapy with carmustine (nitrosourea derivative), patient's condition deteriorated and ultimately, he died 12 months after the primary surgery.

Fig. 1-2 Brain MRI before postoperative radiotherapy and bulky relapse during chemotherapy





Cancer of unknown primary site

M. Svoboda, J. Halámková, P. Fabian, O. Slabý

Introduction

Cancer of unknown primary site (CUP) is a histologically verified metastatic tumour, in which the primary location cannot be identified by standard diagnostic procedures. It accounts for approximately 1 - 2% of all newly diagnosed malignancies, afflicting about 600 patients in the Czech Republic every year. Despite the increasing number of tumours in general, the incidence of CUP has decreased by as much as 50% since the mid-1970s, which corresponds to the improvement of diagnostic methods, such as imaging, immunohistochemistry and molecular genetics in particular.

Diagnostics

Diagnostic process aims to identify the malignancy and determine its histological origin and presumed primary site. The initial evaluation comprises a detailed personal and family history, identification of exposure to established carcinogens, and thorough physical examination, including rectal, pelvic and breast examination. Laboratory investigations include complete blood count, basic blood chemistry (urea, creatinine, ions, bilirubin, and liver tests, LDH, uric acid, albumin, total protein, CRP), ESR and urinanalysis. The evaluation of tumour markers, such as PSA, hCG and TSH might provide useful diagnostic information, the role of AFP is controversial due to its lower specificity. Other tumour markers (CEA, CA19-9, CA15-3, CA-125) are expressed by a number of adenocarcinomas and cannot be used to establish a specific primary tumour site. On the other hand, a remarkable elevation of these markers may direct further investigations or assist in the evaluation of tumour response. Basic imaging studies are CT of the chest, abdomen and pelvis, as well as mammography in women. Nevertheless, extensive investigations should not be performed in patients without any prospect of anti-cancer treatment.

Classification of CUPs

CUPs can be classified into five categories based on morphologic and immunohistochemical analysis of the tumour biopsy specimen. Further investigations should be selected with regard to a particular type of CUP.

a) Well and moderately differentiated adenocarcinomas (approx. 70% of CUPs)
b) Poorly differentiated adenocarcinomas (approx. 15 to 20%)
c) Poorly differentiated cancers (approx. 5%)
d) Squamous cell carcinomas (approx. 5%)

(e) Neuroendocrine tumours/carcinomas, including mixed adeno-neuroendocrine carcinomas (approx. 5%).

a) Well and moderately differentiated adenocarcinomas. These tumours often affect the liver, lungs, lymph nodes and skeleton. In approximately 15-30% of cases, the primary site of tumour becomes identified during the disease trajectory. Positron emission tomography (PET) has increased this number up to 40%, whereas PET/CT is reported to identify the site of origin in 60% of cases. The initial evaluation of adenocarcinomas with unknown primary should predominantly aim to exclude treatable diagnoses, such as the breast cancer in women and the prostate cancer in men.

b) Poorly differentiated adenocarcinomas. A potentially treatable malignancy, such as extragonadal germ cell tumour, breast and prostate cancer, should be excluded in the first place.

c) Poorly differentiated cancers. This group of CUPs encompasses cases, in which morphologic evaluation of the tumour specimen fails to differentiate between carcinoma, sarcoma, melanoma, or haematological malignancy. More than a half of the cases is represented by Non-Hodgkin lymphomas. Due to high curability of lymphomas and the potential of favourable treatment response in other types of tumours belonging to this group (e.g., C-Kit negative gastrointestinal stromal tumour (GISTs), Ewing sarcoma and extragonadal germ cell tumour), specific immunohistochemical, cytogenetic and molecular testing as well as electron microscopy should be employed in order to obtain an accurate diagnosis.

d) Squamous cell carcinomas. Identification of the region drained by the involved lymph nodes is of crucial importance and may guide further diagnostic procedures. Patients with squamous cell carcinoma in the upper cervical lymph nodes should be referred for ENT examination, including direct laryngoscopy and nasopharyngoscopy to exclude a primary head and neck tumour. The involvement of lower cervical and supraclavicular lymph nodes might be indicative of lung cancer and these patients should undergo diagnostic bronchoscopy. Inguinal lymphadenopathy can be associated with a primary tumour in the anorectal and urogenital area, therefore a detailed pelvic examination, including rectoscopy, cystoscopy and gynaecological examination should be performed. If all these investigations remain inconclusive, PET scan could be considered. Given the high metabolic activity of these tumours, PET can detect the primary location of squamous cell carcinomas in up to 30% of the cases.

e) Neuroendocrine tumours, including mixed adeno-neuroendocrine carcinomas. Neuroendocrine tumours with occult primary can be divided into two basic subgroups. The first group is represented by well-differentiated (low-grade) neuroendocrine tumours (NETs) with low proliferation rate and indolent behaviour. These tumours were formerly referred to as carcinoids, and are usually located

in the terminal ileum, appendix, rectum, and pancreas, less often in the bronchi, ovaries, etc. Carcinoids have a low potential to metastasize and distant spread is a sign of very advanced disease, with predilection for dissemination to the liver, bones, and endocardium. Certain tumours are characterized by secretion of serotonin and can be diagnosed by the detection of increased excretion of its metabolite - 5-hydroxyindoleacetic acid (5-HIAA) in a 24-hour urine sample. A specific type of neuroendocrine tumour is a pheochromocytoma, which originates from chromaffin cells of the adrenal gland and typically produces catecholamines. The diagnosis is based on characteristic symptoms related to its endocrine activity and laboratory detection of vanillylmandelic acid (VMA) and other catecholamine products in urine.

The second group of neuroendocrine tumours of the unknown primary comprises poorly differentiated (high-grade) neuroendocrine carcinomas. These are often very aggressive tumours, which have already disseminated into several organs and lymphatic regions by the time of diagnosis.

Therapy

The treatment approach is determined by the presumed site of origin based on histological findings, character of dissemination and clinical manifestations of the tumour. If the potential primary site remains indeterminate, treatment is guided by the histological subtype of the tumour (see Table 1).

Similarly to other solid tumours, local therapies (e.g. surgery, radiotherapy, embolization, radiofrequency ablation) should be preferred to systemic treatment in localized tumours, especially if their chemosensitivity cannot be predicted. Appropriate local management is particularly important in solitary lesions of the brain. In select cases, local treatment can be followed by radiotherapy or systemic treatment. Patients with advanced CUP and unfavourable prognosis should not be treated with anticancer agents unless they have a good performance status (PS$\leq$1). Patients with poor performance status are more likely to benefit from comprehensive supportive care only.

Tab. 1 Recommended anticancer treatment in specific groups of CUPs

Histological type	**Clinical characteristics**	**Recommended treatment**
Adenocarcinoma	Female (less commonly a male) with unilateral axillary lymphadenopathy	Patients should be managed according to guidelines for stage II or III breast cancer
Adenocarcinoma	Involvement of inguinal lymph nodes (unilateral or bilateral)	Inguinal dissection followed by radiation therapy, if $\geq$ 2 nodes are involved or extra-capsular spread is detected, possibly with subsequent chemotherapy.
Adenocarcinoma	Male with high serum PSA and /	Treatment according to guidelines for

	or with skeletal metastases	metastatic prostate cancer
Adenocarcinoma	Women with peritoneal carcinomatosis without visceral involvement. Ascites and elevated serum CA-125 levels may be present.	Treatment should follow guidelines for stage III ovarian cancer including maximal surgical cytoreduction.
Adenocarcinoma with signet-ring cells	Metastatic disease in the abdominal cavity	management corresponding to gastric cancer therapy
Carcinoma	Solitary metastatic lesion	Local treatment (see text)
Squamous cell carcinoma	Cervical lymphadenopathy	Treatment following the guidelines for head and neck cancers (multimodal treatment based on surgery, radiotherapy, or concomitant chemotherapy).
Squamous cell carcinoma	Inguinal lymphadenopathy	Inguinal dissection. Concomitant chemoradiotherapy can be considered in women susceptive of advanced cervical cancer. Adjuvant radiotherapy given that 2 or more lymph nodes are afflicted.
Poorly-differentiated carcinoma	Male <50 years, metastases located in the midline (mediastinum, retroperitoneum) and / or metastatic lung disease, and / or elevated serum AFP, HCG or LDH levels	Tumour should be managed as extragonadal germ cell tumour.
Poorly-differentiated carcinoma	Male> 50 years, metastatic involvement of mediastinal and / or retroperitoneal lymph nodes	Treatment as in the case of non-small cell lung carcinoma
Poorly-differentiated carcinoma	Cases that do not fit to any of the groups mentioned above	Empiric chemotherapy based on the combination of platinum cytostatic and taxanes (most frequently paclitaxel)
Well-differentiated neuroendocrine tumour	All cases	Tumours should be managed as carcinoids. In the case of hepatic metastases, chemoembolization can be considered.
Poorly-differentiated neuroendocrine cancer	All cases	Treatment similar to small cell lung carcinoma therapy- a combination of platinum cytostatics with etoposide,

		optionally paclitaxel. In indicated cases, somatostatin analogues can be used.

Prognosis

CUPs with known histogenetic origin or those than fit into one of the categories outlined above, have the best prognosis when treated with corresponding therapy. In more than 40% of lymphomas and germ cell tumours, durable complete remission can be achieved by an appropriate treatment strategy. Tumours with presumed primary in the breast, ovary or prostate, as well as squamous cell carcinomas of the head and neck have relatively good prognosis with a 5-year survival rate of 10-20%. CUPs that are treated with empiric therapy have generally a dismal prognosis with the exception of localized tumours amenable to surgery or radiotherapy. A further improvement of treatment outcomes is expected with the implementation of novel molecular biomarkers, which might facilitate the identification of the site of origin.

Secondary tumours - metastases

J. Halámková

Introduction

In the clinical practice, patients might present with metastatic disease at the time of diagnosis (**synchronous** metastatic disease) or develop metastases during the treatment or follow-up period (**metachronous** metastatic disease). Occasionally, metastatic disease can be diagnosed in a patient without the identification of primary tumour site (see the chapter Cancer of unknown primary site).

The initial workup in patients with metastatic disease comprises thorough medical history, physical examination (including the examination of peripheral lymph nodes, breast, testicles and DRE), basic laboratory tests (CBC, blood chemistry, urianalysis, measurement of tumour markers with regard to presumed tumour primary). The assessment of synchronous metastases is usually a part of initial staging procedures. Tumours with metastatic spread are classified as stage IV disease and, generally, they carry a poor prognosis. Metachronous metastases are most commonly diagnosed during the post-treatment surveillance, less commonly in the course of anticancer treatment. Metastatic disease may be manifested by specific symptoms (e.g. localized pain at the site of metastasis) or non-specific constitutional symptoms such as loss of appetite, weight loss, weakness, fatigue or paraneoplastic syndromes (e.g. fever of unknown origin, deep venous thrombosis, migrating thrombophlebitis, hypercalcemia, polyglobulia or thrombocytosis).

Tumour metastases are always managed in the context of comprehensive oncology treatment of the primary tumour. The following text outlines the most common symptoms related to site-specific metastatic disease and the available treatment options.

Metastases to the liver

The liver is one of the most common sites of malignant metastatic spread. Tumours most likely to metastasize to the liver include digestive tract malignancies, breast, lung, kidney cancer and melanoma.

Fig.1: Multiple liver metastases (abdominal MRI)

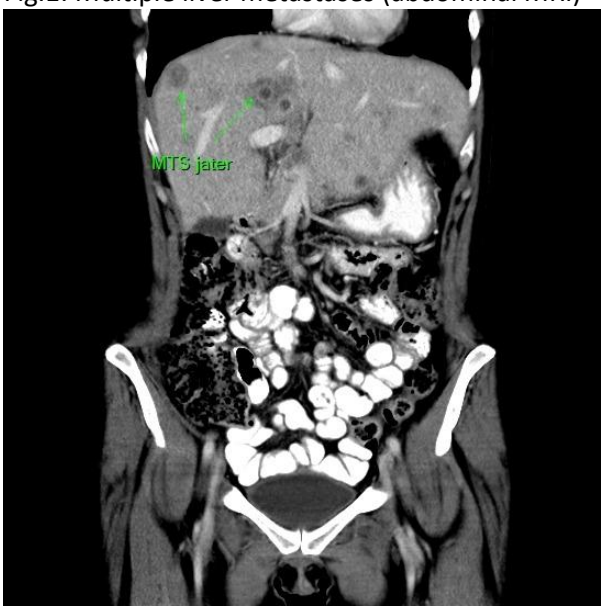
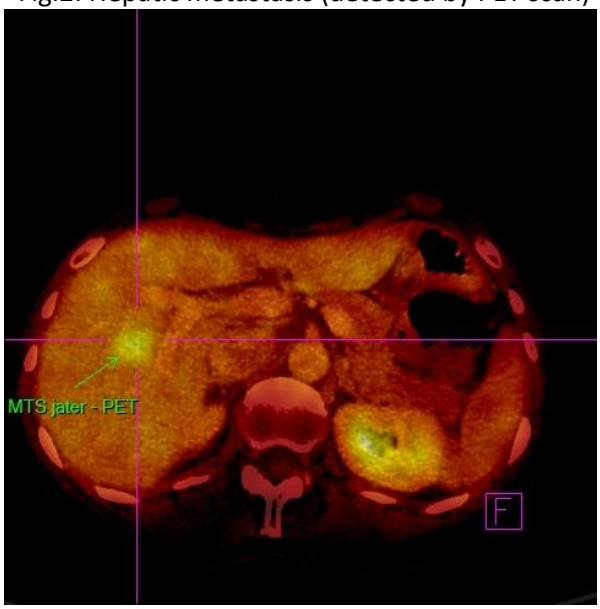


Fig.2: Hepatic metastasis (detected by PET scan)



Clinically, they can be manifested by abdominal pain in the right upper quadrant, however, usually they remain clinically silent for a long time and present as an incidental finding in most patients. Hepatomegaly is a sign of very advanced disease and it is often accompanied by symptoms of liver failure, such as jaundice, ascites, and portal hypertension. There are a number of conditions associated with hyperbilirubinemia and jaundice in cancer patients and a stepwise approach to the initial evaluation is necessary for accurate diagnosis. Depending on the underlying cause, three basic groups of jaundice are distinguished:

- **Prehepatic jaundice** – is a consequence of bilirubin overproduction marked by elevated unconjugated bilirubin levels, usually due to haemolysis, hematoma resorption or ineffective haematopoiesis. It is rather uncommon in oncology patients.
- **Hepatic icterus** - is indicative of hepatocyte disorder, most often as a result of massive liver infiltration. Both conjugated and unconjugated bilirubin levels are elevated, liver function tests are impaired (especially transaminases). Abdominal CT or ultrasound shows metastatic liver disease without any signs of cholestasis. Treatment approach is aimed at primary cancer management, which can be cumbersome, since a large number of cytostatics are metabolised by the liver and their administration is often contraindicated in patients with hepatic insufficiency. Thus, the expected treatment benefits should be weighed against potential risks in every individual patient.
- **Biliary obstruction** – this is the most common cause of jaundice in oncological patients, often accompanied by other clinical symptoms such as pruritus, dark urine and acholic stool. Abdominal ultrasound or CT demonstrates biliary tract dilatation (Fig. 3, Fig. 4); the hallmark laboratory abnormality is the elevation of obstructive liver enzymes, predominantly alkaline

phosphatase. The treatment method of choice is endoscopic (ERCP) or percutaneous biliary drainage (PTD). An alternative option is a biliary bypass surgery. Some patients may be indicated for biliary stenting followed by intraluminal brachytherapy in order to extend stent patency. If biliary obstruction cannot be managed by any of these procedures, the patient is indicated for symptomatic treatment of cholestasis-associated complications such as pain, pruritus (antihistamines, corticosteroids, local ointments) and hepatic encephalopathy.

Fig. 3. Dilated biliary tract in malignant intrahepatic obstruction (liver ultrasound)

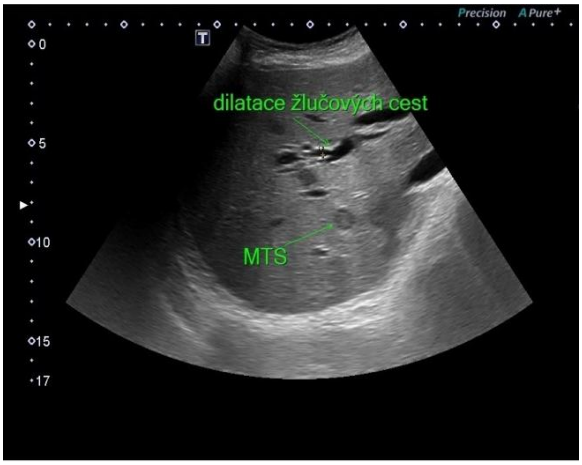
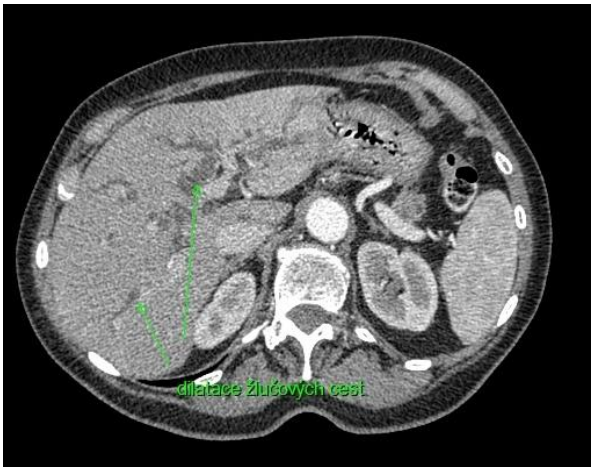


Fig. 4. Dilatation of intrahepatic bile ducts due to liver metastases (CT of the liver)



Hepatic insufficiency is often associated with portal hypertension and **ascites**, which is manifested by abdominal swelling, unpleasant sensation of abdominal pressure or pain, change in bowel habits, flatulence, nausea and emesis. Ascites associated with liver failure (sometimes referred to as central type) is a transudate and responds well to diuretics. A more common form is so-called peripheral type of ascites resulting from peritoneal metastatic involvement. It is exudative, characterised by high protein concentration and refractory to diuretic treatment. In clinical practice, these variants may overlap and patients may present with a combination of both types of ascites (for details on ascites management, see palliative care in oncology).

Management of liver metastases

In the case of oligometastatic chemosensitive tumours, liver metastases can be managed by surgical resection or local ablative techniques - radiofrequency ablation, chemoembolization, stereotactic radiotherapy, cryosurgery, etc. Radical resection is indicated with curative intent. In particular tumours (such as colorectal cancer), preoperative chemotherapy combined with targeted agents can be used to achieve operability. Radiofrequency ablation is a procedure, in which probes are introduced percutaneously or intraoperatively inside the tumour, and destroy the tissue using the heat generated from alternating current that passes through it. Correspondingly, cryotherapy uses a

probe through which a cryogen (most commonly liquid nitrogen) is circulated. During chemoembolization, microparticles coated with a cytostatic agent are used to restrict blood supply to the tumour destroy tumour cells by local cytotoxic effect. Other treatment options include radiotherapy techniques, such as Cyberknife, Leksell's gamma knife or stereotactic radiotherapy. Patients with multiple liver metastasis are treated with systemic treatment. Given the abundance of diagnostic and therapeutic procedures available, treatment decisions should be always made within multidisciplinary tumour board (that include all healthcare professionals possibly involved in the treatment plan).

Peritoneal carcinomatosis

Peritoneal carcinomatosis refers to multiple metastatic involvement of the peritoneum. It is a sign of advanced cancer, which has usually spread to another organs as well (most commonly breast cancer, colorectal carcinoma), or it might be the only site of dissemination (particularly in ovarian cancer). Peritoneal carcinomatosis might also be associated with primary peritoneal tumours like malignant mesothelioma. The basis of treatment is peritoneal **resection** (so-called cytoreduction), in certain cases, surgical procedure might be followed by **intraperitoneal administration of chemotherapy** (either intraoperatively or early after the operation). In select patients, intraoperative intraperitoneal chemotherapy (most commonly mitomycin, oxaliplatin, cisplatin, doxorubicin, docetaxel or paclitaxel) may be combined with hyperthermia (known as **HIPEC** - **hypertermal intraoperative chemotherapy)**.

Peritoneal carcinomatosis is often accompanied by ascites refractory to diuretic therapy, which is best managed by paracentesis or peritoneal drainage. Placement of drainage catheter and paracentesis should be performed under ultrasound control due to the risk of haemorrhagic complications in case of inadvertent puncture of a peritoneal tumour mass. Symptomatic treatment includes pain management (mostly with opioids and spasmolytics) and administration of antiemetics and corticosteroids. Peritoneal carcinomatosis can sometimes lead to multifocal **malignant bowel obstruction**. In such cases, an important role of palliative care is to **provide nutritional support** to the patient (enteral tube feeding or long-term parenteral nutrition might be necessary in some patients).

Pulmonary and pleural metastases

Malignancies most likely to spread to lungs are bronchogenic carcinoma, breast and kidney cancer, malignant melanoma and digestive tract tumours. (Figure 5, Figure 6).

Fig. 5. Massive metastatic involvement of lungs (chest X-ray)

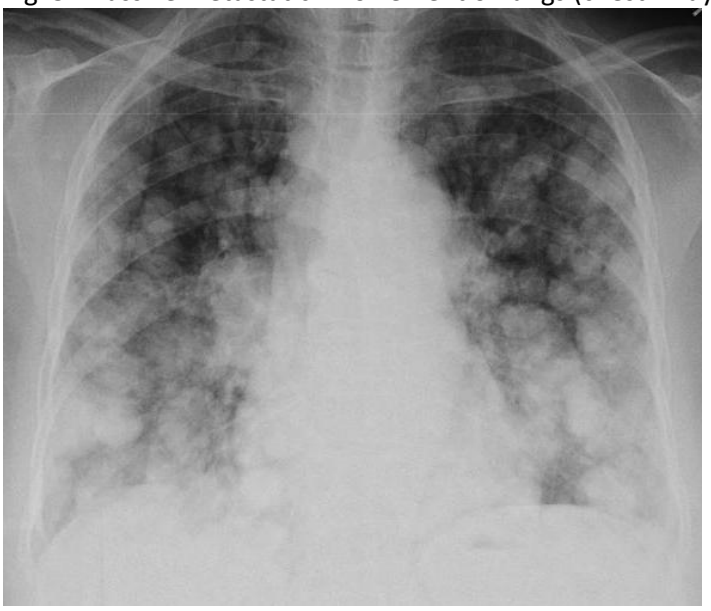
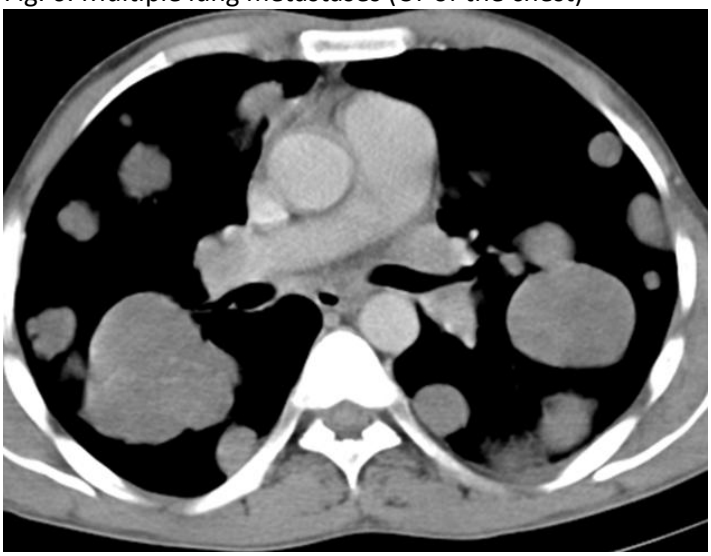


Fig. 6. Multiple lung metastases (CT of the chest)



Metastatic lung disease may manifest with dyspnoea, cough, chest pain or haemoptysis. The treatment method of choice is **systemic therapy**, only few indicated cases (solitary metastasis or a limited number of lesions confined to one pulmonary lobe) might be considered for **surgical resection** or **stereotactic radiotherapy**. Besides causal treatment, symptomatic therapy of the associated symptoms is of crucial importance. Patients with airway symptoms may be treated with endobronchial brachytherapy. Other bronchoscopic techniques include endobronchial laser, electrocautery, endobronchial stenting or cryotherapy. These methods are effective in restoring airway patency and reducing dyspnoea. In patients with laryngeal infiltration not amenable to ablative techniques, it might be necessary to perform tracheostomy. Metastatic lung disease may sometimes manifest in the form of **lymphangitic carcinomatosis,** characterised by diffuse infiltration of pulmonary parenchyma with a typical CT or X-ray image. The administration of corticosteroids

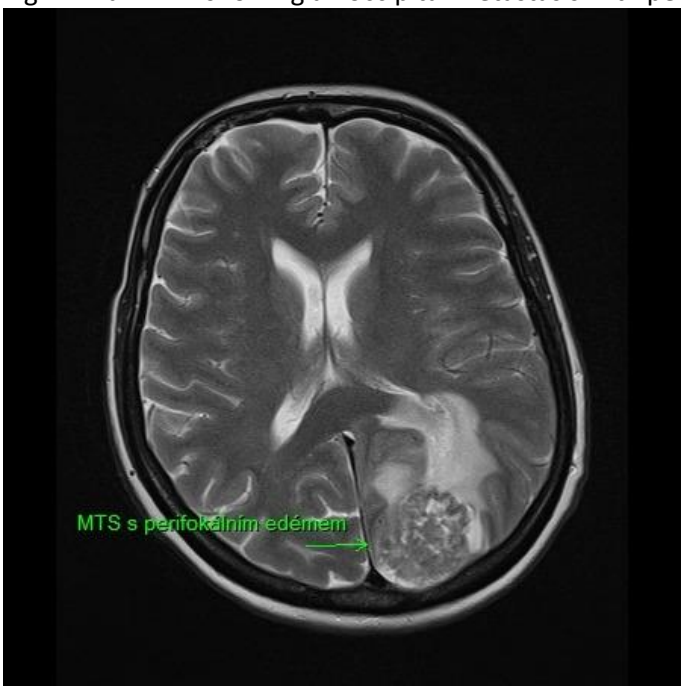
might help to relieve dyspnoea associated with this condition. Another common complication of pleural or lung metastases is the development of pleural effusion. If causal treatment of the underlying malignancy fails to resolve associated symptoms like dyspnoea, cough or chest pain, **thoracentesis** or a placement of indwelling **chest drain** may be considered. An alternative procedure used to prevent recurrent pleural effusion is **pleurodesis**. The instillation of a chemical substance (talc or bleomycin) leads to adhesions of the visceral and parietal pleura resulting in pleural space obliteration. However, patients with refractory effusions and insufficient lung expansion after primary pleural drainage are unlikely to benefit from pleurodesis and should be managed with pleuro-peritoneal shunt.

CNS metastases

Brain metastases are about 10 times more frequent than primary brain tumours (Fig. 7). Primary tumours prone to brain dissemination are bronchogenic carcinoma, breast and kidney cancer or malignant melanoma. Specific **neurological symptoms** (paresis, dysphasia, vertigo, cognitive impairment, etc.) may be indicative of tumour location. Non-specific symptoms include headache, blurred vision, altered level of consciousness, epilepsy, or **nausea** and **vomiting** associated with **intracranial hypertension**. Approximately one third of patients afflicted by brain metastases are asymptomatic. Definitive diagnosis is based on CT or MRI findings. MRI has a superior sensitivity for detection of meningeal disease. Solitary metastatic lesions should be considered for **neurosurgical treatment** or **stereotactic radiotherapy. External beam radiotherapy** is indicated in patients with multiple brain metastases. Most patients also require **anti-oedema therapy** with **glucocorticoids** and **mannitol** – an osmotic diuretic that leads to rapid but short-lived reduction of intracranial pressure. Its effect wears off after 7-10 days and the therapy should be discontinued. It is necessary to monitor fluid balance and maintain adequate hydration during the administration of mannitol. Brain metastases often induce **secondary epilepsy**. We usually use benzodiazepines (most commonly diazepam or clonazepam) for acute management of seizures. Anticonvulsants, such as valproate or levetiracetam are indicated in the case of refractory seizures and are prescribed by a neurologist.

A specific case of metastatic involvement of multiple areas of craniospinal axis is referred to as **leptomeningeal carcinomatosis**. Primary tumours with predilection to meningeal spread are mainly breast and lung carcinoma, melanoma or haematological malignancies. The imaging method of choice is MRI, histopathological diagnosis may be obtained from cerebrospinal fluid cytology. External beam radiotherapy is often used to relieve neurological symptomatology. Additionally, intrathecal chemotherapy (e.g. methotrexate, cytarabine or thiotepa) can be administered via lumbar puncture or intraventricular Omaya reservoir.

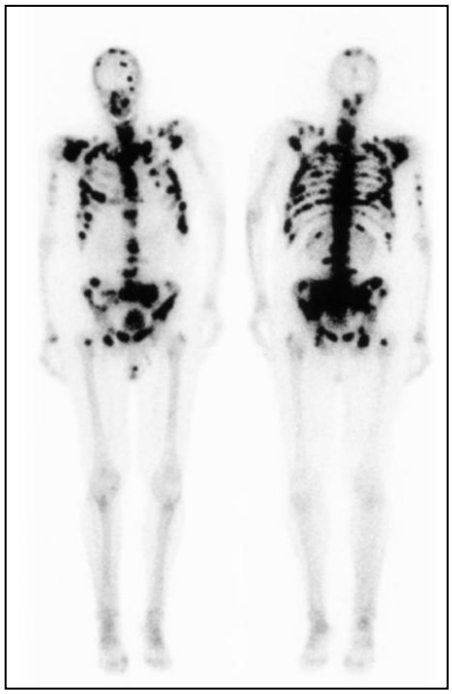
Fig. 7. Brain MRI showing an occipital metastasis with peripheral oedema



Bone metastases

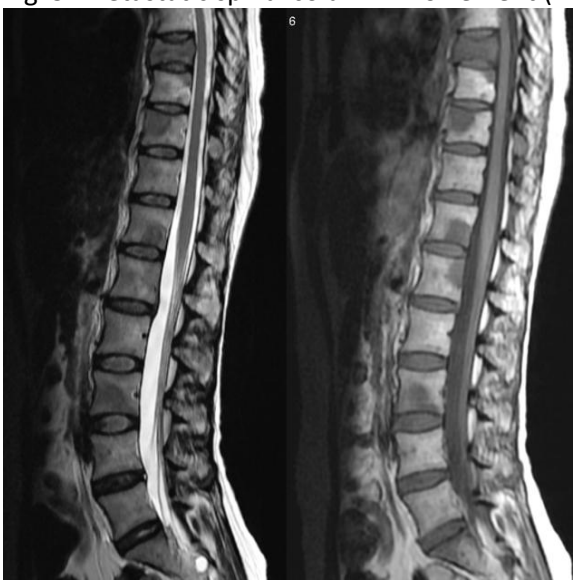
The skeleton belongs to the most common sites of solid tumour dissemination. Skeletal metastases are predominantly associated with breast, prostate and lung carcinoma. The presence of bone metastases is indicative of advanced incurable disease. The most common presenting symptoms are back pain or pathological fracture. Depending on their morphology, **osteolytic, osteoplastic** and **mixed types** of bone metastases are distinguished. **Osteolytic lesions** with prevailing bone resorption are typically associated with thyroid gland, kidney, adrenal gland and digestive tract tumours. **Osteoblastic** metastases characterized by defective bone deposition are typical for prostate cancer (Fig. 8); occasionally they occur with carcinoid, bladder and stomach cancer. Most of patients present with **mixed type** of metastases, especially in lung and breast cancer, melanoma and gynaecological tumours (Fig. 9). Multiple myeloma is another tumour with typical skeletal involvement pattern.

Fig. 8. Bone scintigraphy showing multiple metastatic skeletal involvement in prostate cancer



Causal treatment of the underlying primary tumour plays a crucial role in the management of bone metastases. In addition to analgesic treatment, we use **palliative radiotherapy** in the form of external beam irradiation or **radionuclides** (radium-223, strontium-153, samarium-89) for pain management. Bone remodelling process can be influenced by ***bisphosphonates*** *or* ***RANKL inhibitors*** *(denosumab)*, which are also effective in the treatment of hypercalcaemia caused by excessive bone resorption. Since bone metastases negatively influence bone architecture and resistance and thereby increase the risk of fractures, a preventive use of **prosthetic devices** (e.g. fixation collars, Jewett brace, lumbar belts) is often indicated. Impending pathological fractures, especially if located in the axial skeleton, can be managed with radiotherapy or an orthopaedic surgeon might be consulted for preventative intervention. If a pathologic fracture occurs, it often presents with sudden decompensation of bone pain or deformity. First aid involves external fixation and pain management. Treatment may pursue with surgical intervention (internal fixation) depending on the character and extent of the underlying disease, clinical condition of the patient and his life expectancy. Vertebral fractures can be treated conservatively or by vertebroplasty in the case of **spinal cord compression**.

Fig. 9. Metastatic spinal column involvement (MR spine)



Spinal cord compression might also develop as a complication of direct tumour spread. Thoracic spine is most commonly affected, followed by lumbosacral and cervical spine. It is considered an emergency that has to be managed within 24 hours after the onset of symptoms (see the chapter Emergencies in oncology).

Cutaneous metastases

Skin is relatively uncommon site of metastatic spread. Tumours prone to skin involvement are advanced **breast cancer**, **melanoma, kidney cancer, or tumours of the ENT area.** Treatment options include palliative surgical excision (as a preventive measure against malignant wounds), external beam radiotherapy or topical chemotherapy with 5-fluorouracil cream. Chronic exulcerated lesions usually require interdisciplinary treatment and specialized wound care within a high-volume oncology centres.

Retroperitoneal metastases

Retroperitoneum is a predilection site for **testicular, kidney and digestive tract** metastases. Patients often present with lower back pain, which may also be the initial manifestation of a malignancy. It is therefore necessary to include retroperitoneal lymphadenopathy in the differential diagnosis of low back pain. Retroperitoneal or pelvic metastases are also associated with signs of **hydronephrosis** due to mechanical urinary tract obstruction. The initial work-up should include basic blood chemistry and ultrasound examination to assess extent of renal pelvis dilation. Depending on the severity of hydronephrosis and the underlying cause, either external drainage in the form of nephrostomy or internal drainage by ureteral stenting may be considered.

To summarize, the diagnostic approach to a metastatic disease should be guided by the primary tumour histology and location of metastases. Preferentially, it should be aimed at the identification of patients with curable disease. Prior to any diagnostic procedure, its potential risk-benefit ratio with regard to each patient's overall health condition should be considered. Treatment decisions must be made with respect to tumour histology, the extent of the disease, patient's age and performance status. The intent of treatment in metastatic disease is often palliative, however, an appropriate treatment strategy can provide significant survival benefit or even high chances of cure in particular cases. Every patient with metastatic disease should be referred to oncology or preferably, he should be consulted within a multidisciplinary tumour board in order to ensure optimal patient-tailored treatment plan.

Hereditary Cancer Diseases

L. Foretová

Epidemiology

Each type of cancer can be either sporadic or inherited. About 5-10% of all cancers are a part of a hereditary cancer syndrome. Most of these conditions are caused by pathogenic mutation in a single gene (monogenic hereditary disease), particularly in a tumour suppressor gene, DNA repair gene, or less frequently, in an oncogene. Such mutations are present in all cells of the affected individual and in the case of autosomal-dominant inheritance pattern, they are transmitted with 50% probability, regardless of gender. On the other hand, penetrance, i.e. the clinical manifestation of a mutation, usually varies depending on gender and other genetic or non-genetic factors. Less often, syndromes can be inherited in autosomal recessive fashion. They occur primarily in siblings and are usually absent in preceding generations. The most common syndromes include hereditary forms of breast, ovarian, colorectal and uterine cancer. To date, more than 200 hereditary cancer syndromes have been reported, however, there is still a number of tumours, in which high risk genes are yet to be identified.

Diagnostics

Genetic testing is relevant only in the case of high-risk genes, while screening of low and moderate-risk genes is of limited clinical significance. Patient with an increased personal and familial risk of cancer should be referred to a genetic specialist for further assessment. Based on thorough risk evaluation, the geneticist determines susceptible genetic changes and decides on family members who are to be tested. He interprets the results and suggests further investigations or preventative measures. Patient informed consent is always required prior to genetic testing. DNA testing is performed by accredited molecular genetic laboratories. Specific mutations are identified by Sanger sequencing or next-generation sequencing (NGS) and every positive result has to be confirmed by another independent genomic DNA testing.

Table 1. Outline of the most common hereditary cancer syndromes

The name of the syndrome	**Mutated gene**	**Major malignancies**
Cowden syndrome	*PTEN*	multiple hamartomas, breast and colorectal cancer, follicular thyroid cancer
familial adenomatous polyposis	*APC*	colorectal cancer, papillary thyroid cancer, CNS tumours, sarcomas,

		pancreatic, gastric, intestinal cancer
Juvenile polyposis	*SMAD4 / BMPR1A*	bowel and gastric hamartomas, digestive tract and pancreatic cancer
Familiar melanoma	*CDKN2A / p16 / p14*	melanoma, pancreatic and breast cancer
Hereditary diffuse gastric cancer	*CDH1*	gastric and breast tumours
Gorlin syndrome	*PTCH*	basaliomas, skeletal abnormalities and malformations
Familial papillary renal carcinoma	*MET*	Type 1 papillary renal cancer
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	Breast, ovarian, colorectal, gastric, prostate and pancreatic cancers, melanoma, cholangiocarcinoma
Hereditary non-polyposis colorectal carcinoma (Lynch syndrome)	*MLH1, MSH2, MSH6, PMS2*	colorectal, endometrial, ovarian, intestinal, gastric, urinary tract, hepatobiliary cancers, melanoma, lymphoma, tumours of CNS and breast cancer
Li-Fraumeni syndrome	*TP53*	sarcomas, adrenocortical carcinoma, breast cancer, leukaemia, brain tumours
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	tumours of the pituitary and parathyroid gland, pancreatic cancer
Multiple endocrine neoplasia type 2 (MEN2)	*LIP*	Medullary thyroid cancer, pheochromocytoma
neurofibromatosis type 1 and 2	*NF1, NF2*	neurofibromas, schwannomas, meningeomas
Peutz-Jeghers syndrome	*STK11*	multiple polyps in the gastrointestinal tract, ovary, cervix, testes, mucocutaneous pigmentation
Retinoblastoma	*RB1*	retinoblastoma
Tuberous sclerosis	*TSC1, TSC2*	Hamartomas
Von Hippel-Lindau syndrome	*VHL*	renal cancer, hemangioblastoma, pheochromocytoma
Wilms tumour	*WT1, WT2, WT3*	Wilms tumour
BAP1 syndrome	*BAP1*	malignant mesothelioma, uveal melanoma, Spitzoid type of skin cancer, renal, breast, ovarian cancers

Hereditary pheochromocytomas and paragangliomas	*SDHA, SDHB, SDHC, SDHD, SDHAF2*	feochromocytoma, paraganglioma
Hereditary leiomyomatosis and renal carcinoma (HLRCC)	*FH*	cutaneous and uterine leiomyomas, renal cancer (papillary, oncocytic, tubulopapillary, etc.)
Birt-Hogg-Dub syndrome (BHDS)	*FLCN*	renal tumours (mainly oncocytic and chromophobic), mucocutaneous fibrofoliculomas, spontaneous pneumothoraxes

Indications for genetic counselling

Every patient with suspected hereditary cancer syndrome should be referred for genetic testing. Most common clinical presentations indicative of a genetic predisposition include:

- Ovarian cancer (regardless of age) or recurrent breast carcinoma in the family history, bilateral breast cancer, multiple breast cancer or breast tumour in a patient before the age of 45, breast cancer in men.
- Increased incidence of colorectal / uterine cancers in a family, multiple tumours, metachronous cancers, colorectal or uterine tumours in patients under the age of 40.
- Increased incidence of any tumour among family members, with suspected hereditary cause (melanomas, multiple basal cell carcinomas, diffuse gastric cancer, kidney tumours and syndromes), rare types of tumours, multiple malignancies, early-onset tumours
- precancerous conditions, such as colorectal and gastric polyps, even in children
- Genetic testing is performed primarily in a patient with the highest probability of hereditary cancer syndrome. After a specific mutation is identified, predictive genetic testing might be offered to other at-risk relatives. Testing can also be performed in the closest relatives of patients who have already succumbed to the cancer.

Prevention and screening of cancer syndromes

Each cancer syndrome is characterised by a well-known spectrum of clinical manifestations and associated cancer risk. Patient-tailored preventative strategies are designed in accordance with general recommendations and specific personal and family history. Patients with hereditary cancer syndromes should be regularly monitored within comprehensive oncological centres with access to advanced diagnostic methods.

In the case of family planning, in vitro fertilisation including pre-implantation genetic testing might be recommended to germline mutation carriers, who wish to prevent the transmission of a genetic disorder to their offspring.

The most common hereditary cancer syndromes

Hereditary syndrome of breast and ovarian cancer

This syndrome is an autosomal dominant disorder caused by germline mutations of **BRCA1** (locus 17q21-q24, 24 exons) and **BRCA2** (locus 13q12-q13, 27 exons) genes. It is estimated that approximately one in 300-800 people carry either mutation.

BRCA (breast cancer susceptibility genes) are **tumour suppressor genes** involved in the regulation of cell cycle and apoptosis, homologous recombination (HR) and associated DNA reparative mechanisms. The BRCA2 gene is essential for transporting the RAD51 protein into cellular nucleus. It is a part of Fanconi anaemia pathway, which is involved in the reparation of DNA interstrand cross-links.

There are also other gene mutations associated with breast cancer susceptibility (CHEK2, ATM, PALB2, NBN, BRIP1). Higher risk of breast cancer is associated with Li-Fraumeni syndrome, neurofibromatosis type 1, Peutz-Jeghers syndrome, and diffuse gastric cancer syndrome.

Basic criteria for BRCA genetic testing are:

Sporadic occurrence:

- bilateral breast cancer, first before the age of 50 years, or both before 60 years of age
- unilateral breast cancer before 45 years (or before 50 years if family history is not known)
- all patients with epithelial ovarian carcinomas, fallopian tube carcinomas and peritoneal carcinomas irrespective of age
- breast and ovarian cancer duplicity at any age
- breast tumour in a male
- medullar carcinoma before 60 years
- triple-negative breast cancer before 60 years of age
- breast and pancreatic cancer duplicity at any age

Familiar occurrence:

- at least 3 relatives with breast cancer, no age limitation
- 2 relatives with breast cancer, at least one of them diagnosed before 50 years of age; or both before 60
- proband with breast cancer under the age of 50 whose direct relative has a history of tumour associated with hereditary breast and ovarian cancer syndrome (prostate, pancreas)

Lifetime risks of certain BRCA-associated diseases:

The *BRCA1* gene mutation		**Carrier mutation of *BRCA2* gene**	
Breast cancer before the age of 70 years	RR = 10	Breast cancer	RR = 10
Metachronous breast cancer	up to 60%	Metachronous breast cancer	up to 55%
Ovarian carcinoma	RR = 30	Ovarian carcinoma	RR = 10
Colorectal carcinoma	RR = 4.11	Pancreatic carcinoma	RR = 3.51
Prostate cancer	RR = 3.33	Hepatobiliary cancer	RR = 4.97
Breast cancer in males	RR = 50	Prostate cancer	RR = 4.65
		Gastric cancer	RR = 2.59
		Breast cancer in males	RR = 100
		Malignant melanoma	RR = 2.58

Prevention and genetic surveillance

In BRCA1/2 mutation carriers, screening starts at the age of 20-25 years, depending on the family history of the earliest cancer occurrence. It includes:

- oncology checks with comprehensive physical examination every 6 months
- breast examination twice a year by ultrasonography alternating with MRI (up to 60 years), mammography at the age of 25 to detect calcifications, from the age of 35 years all the examinations on an annual basis
- gynaecological surveillance including vaginal ultrasound and measurement of CA125 tumour marker twice a year
- annual haemoccult test from the age of 40
- colonoscopy every 3-5 years from the age of 40 (including gastroscopy in BRCA2 mutation carriers)
- annual abdominal ultrasound
- annual dermatological and ophthalmological examination (especially for BRCA2)

Surveillance is of particular importance in pregnant and lactating women, as the occurrence of aggressive, rapidly growing breast tumours in this period is quite common. These women should be preferably examined by breast ultrasound.

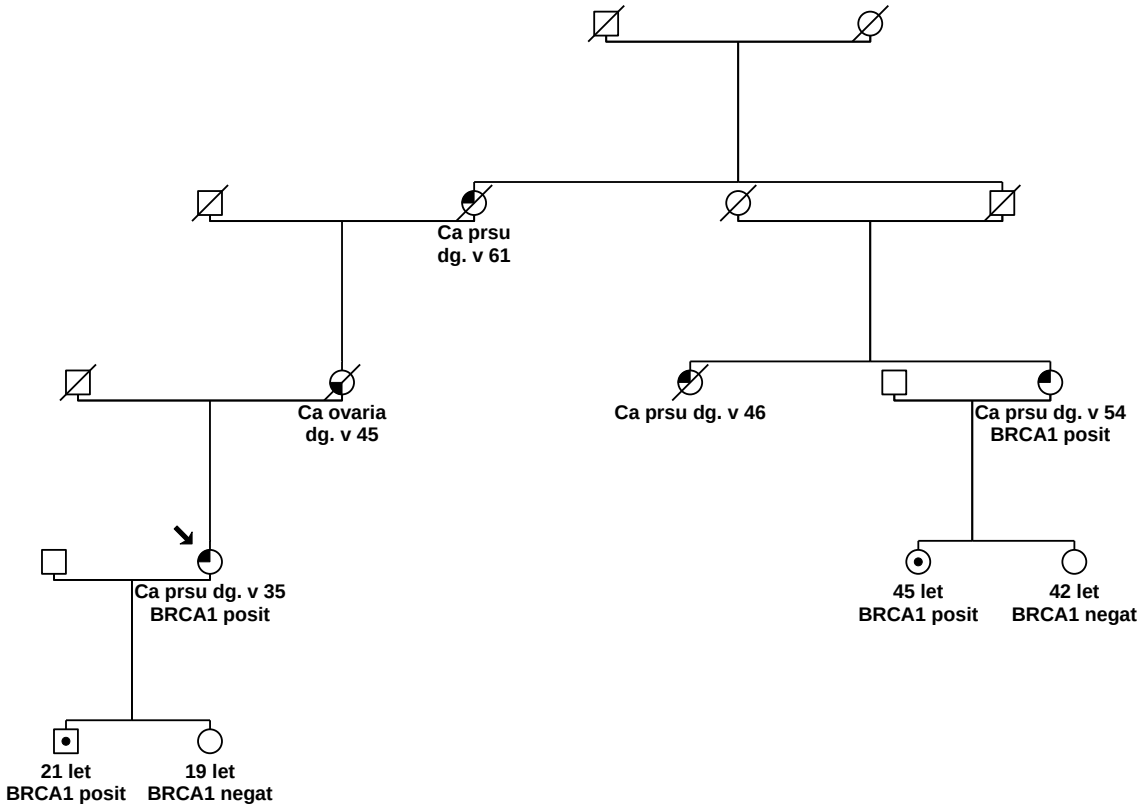
In male BRCA1 / 2 mutation carriers, screening starts at 30 years of age and includes:

- oncology checks with thorough physical examination every 6 months
- annual clinical breast examination and breast ultrasound

- annual abdominal ultrasound
- haemoccult test every year from the age of 40
- colonoscopy every 3-5 years from the age of 45 (gastroscopy in BRCA2),
- annual urological follow-up including PSA measurements from the age of 45
- annual dermatological and ophthalmological examination (especially for BRCA2)

In addition to secondary prevention, a **risk-reducing mastectomy** and **prophylactic hysterectomy with oophorectomy** might be discussed with high-risk patients, usually upon completion of childbearing (the procedure reduces lifetime risk of breast cancer from 85% to 1-5%, and the risk of ovarian cancer from 20-60% to 1-5%).

Fig. 1. A family with hereditary breast and ovarian cancer syndrome



Hereditary non-polyposis colorectal carcinoma (Lynch syndrome)

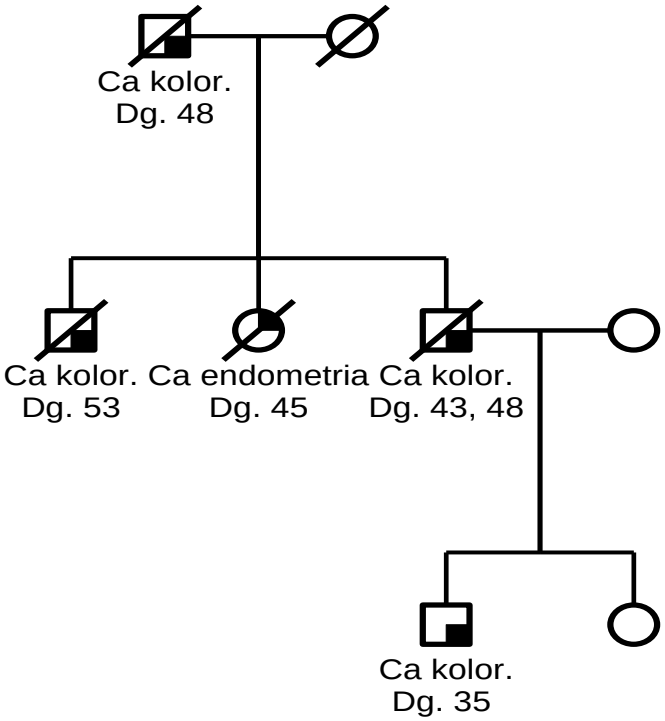
Approximately **5-10 % of colorectal tumours** can be attributed to genetic predisposition syndromes. Similarly to population screening for colorectal cancer, early identification of individuals with genetic susceptibility to colorectal cancer may have a crucial impact on patient prognosis. Patients with Lynch syndrome (LS) have a ten-fold higher risk of developing a colorectal cancer. Other cancers that occur with increased frequency are uterine, ovarian, gastric, small intestine, biliary tract, urinary system and pancreatic cancer, melanoma, and other less common tumours. The prevalence of LS is

approximately 1: 2000. LS can be caused by a germline mutation in one of four mismatch-repair genes (**MLH1, MSH2, MSH6, and PMS2).** Rarely, mutations in MLH3, EXO1 and EPCAM genes might be detected in LS. Genetic testing is recommended in patients with sporadic colorectal or uterine tumours before the age of 40, with synchronous colorectal and uterine cancer (or other LS-related cancer), family history of colorectal / uterine cancer in at least two successive generations with at least one of them diagnosed <50 years. Immunohistochemistry testing for deleterious MLH1, MSH2, MSH6 and PMS2 proteins from tumour blocks can be used as an initial screening method in order to determine a specific type of LS-associated mutation in newly diagnosed patients. A more detailed molecular work-up and subsequent MSI and germline testing is usually indicated based on the results.

Preventive measures

If LS is confirmed, annual colonoscopy screening is recommended from the age of 20 years. Women may be offered prophylactic oophorectomy and hysterectomy. Surveillance for other cancers (gastric, urinary system, prostate etc.) might be recommended with respect to a specific family history.

Fig. 2. A family with hereditary non-polyposis colorectal carcinoma



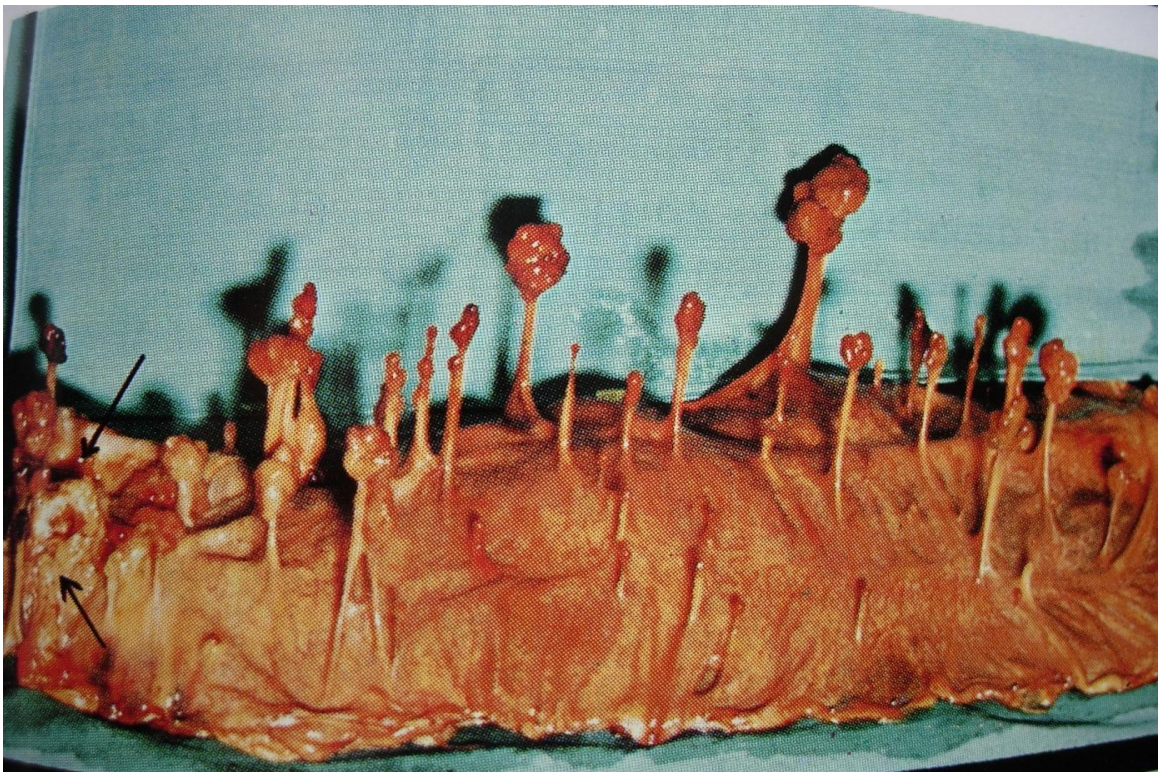
Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant hereditary disease with an incidence of about 1: 8000 and penetrance up to 100%. It accounts for less than 1% of all colorectal cancer cases, occurring predominantly at a very young age. FAP is characterised by a germline mutation in the **APC gene** (locus 5q21-22) that results in the development of **multiple adenomatous colonic polyps (hundreds to thousands).** They occur most commonly in the rectum and sigmoid and carry a high risk of malignant transformation. A large proportion of patients with FAP present with "de novo" APC germline mutation without any family history of the disease.

The phenotypic expression and associated risks may vary depending on the site of APC gene mutation. Mutations between codons 1- 163 and 1860-1987 or exon 9 usually result in an attenuated form of FAP with later onset of the disease and fewer (up to 100) polyps. A very severe form of FAP occurs with mutations in codons 486-499 and 1249-1464 or in codon 233. Congenital hypertrophy of retinal pigment epithelium is related to mutations in codons 463-1387. High risk of desmoids is associated with mutations in codons 1445-1578. Mutations in codons 457-1307 may cause paediatric hepatoblastoma that occurs most often before 5 years of age. Other FAP-related disorders include osteomas, dental anomalies, polyps and tumours of the upper gastrointestinal tract, pancreatic cancer, brain and thyroid tumours.

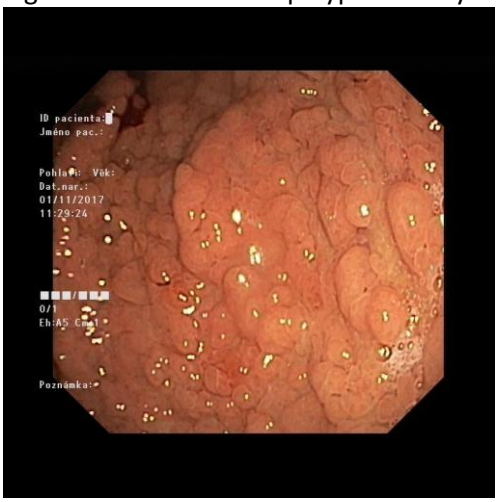
Given the early occurrence of hepatoblastoma, predictive testing of at-risk relatives should be performed in already in early childhood age. Preventive measures comprise regular colonoscopy examination, sigmoidoscopy in children and endoscopic management of polyps, abdominal ultrasound, gastroduodenoscopy, urological follow-up from the age of 40, regular ophthalmological, neurological and dental checks.

Fig. 3: FAP, multiple colonic polyposis, after colectomy. A carcinoma is indicated by arrows.



GAPPS ("gastric adenocarcinoma and proximal polyposis of the stomach") is a ***variant of FAP*** caused by a mutation in APC gene promoter 1B, i.e. in the regulatory region of the APC gene. The phenotype is marked by polyposis restricted to ***gastric fundus and body*** (without antral and duodenal involvement) and high risk of gastric adenocarcinoma. The onset of symptoms is variable; however, prophylactic gastrectomy is usually necessary at an early age.

Fig.4: Massive stomach polyposis in a young patient with GAPPS, preventive gastrectomy



Endocrine tumour syndromes

Multiple endocrine neoplasia type 1 (MEN1)

The incidence of MEN1 is about 1:50 000 with penetrance of 95%. This autosomal dominant hereditary syndrome is caused by mutations in the **MEN1** gene (locus 11q13). The main presenting symptom is **hypercalcaemia**, which often manifests by renal colic caused by kidney stones. Other symptoms are often related to a specific type of MEN-associated tumour and corresponding hormonal secretion. Besides **parathyroid adenomas** causing **hyperparathyroidism**, MEN1 predisposes mutation carriers to **entero-pancreatic endocrine tumours** (e.g., insulinomas, gastrinomas, VIPomas), **pituitary adenomas** (e.g., prolactinomas, somatotrophinomas), adrenal cortex tumours and carcinoids (of the thymus, bronchi, stomach).

Multiple endocrine neoplasia type 2 (MEN2)

MEN2 is an autosomal dominant hereditary syndrome resulting from a mutation in the **RET** proto-oncogene (locus 10q11). Phenotypic expression depends on a specific subtype of mutation associated with the syndrome. Incidence is reported to range from 1:25,000 to 1:50,000, penetrance is approximately 80%.

- MEN2A is the most common subtype, resulting in primary hyperparathyroidism and the development of pheochromocytomas and medullary thyroid carcinomas.
- MEN2B syndrome is manifested by marfanoid habitus, ocular anomalies, pheochromocytomas, schwannomas, mucosal and digestive neurofibromatosis and medullary thyroid carcinoma.
- Familial medullary thyroid carcinoma is a specific subtype, which is not associated with any other disorder.

Activation mutations of the RET proto-oncogene result in constitutive stimulation of signalling pathways independent on growth factors. Predictive testing should be performed in early childhood. A prophylactic thyroidectomy is usually recommended due to high risk of aggressive medullary thyroid carcinoma.

Li-Fraumeni syndrome

This autosomal dominant hereditary syndrome is associated with increased risk of **sarcoma, breast and brain tumours, leukaemia, lymphoma** and **adrenocortical carcinoma,** however, it may predispose to any type of tumour. **Multiple malignancies** are not uncommon in individuals with this type of genetic disorder. Li-Fraumeni syndrome can be caused by **mutations in the TP53 gene** (17p13.1) that often arise "de novo". As many as 50% of mutation carriers will develop malignancy before the age of 50. The mutation is responsible for up to 1% of early breast tumours. Thus, testing

of the TP53 gene should be performed in all patients with breast carcinoma before 35 years of age. Childhood predictive testing for Li-Fraumeni is strongly encouraged, as the possibilities of ensuing preventive care have greatly broadened in the last few years. Genetic surveillance of afflicted individuals comprises regular physical examinations, usually provided by an oncologist. Height, weight and blood pressure measurements, laboratory tests (CBC, LDH, adrenal hormones, urinalysis), abdominal and breast ultrasound, brain and whole-body MRI, colonoscopy and gastroscopy are routinely performed.

Molecular diagnostic testing of hereditary cancer syndromes

Comprehensive genetic assessment includes:

- genetic counselling and recognition of individuals who could benefit from genetic testing
- molecular genetic testing provided by a specialized accredited laboratory
- biological interpretation of the results and laboratory report
- genetic consultation and communication of the outputs to the counselee

Only an accurate assessment of genetic risks by a specialist physician can yield an optimal prevention and screening strategy. Nowadays, genetic counselling and testing is a routine part of oncology practice. It contributes to a patient-tailored preventive approach to at-risk population and offers guidance for surgical and oncological treatment planning. There is a multitude of hereditary cancer syndromes that require genetic surveillance and their complete description goes beyond the scope of this publication. For detailed information, refer to the following literature:

1. Supplement of the Journal of Clinical Oncology 2006 - Hereditary Cancer Diseases at http://www.linkos.cz/casopis-klinicka-onkologie/archiv/detail/cislo/2006-04-30-supplement/
2. Supplement of the Journal of Clinical Oncology 2009 (Volume 22) - Dispensarization of Inherited Cancer Syndromes at http://www.linkos.cz/casopis-klinicka-onkologie/archiv/detail/cislo/2009-06-10-supplement-1/
3. Supplement of the Journal of Clinical Oncology 2012 (Volume 25) - Hereditary Cancer Diseases III http://www.linkos.cz/casopis-klinicka-onkologie/archiv/detail/cislo/2012-08-15-supplement-1/
4. Supplement of the Journal of Clinical Oncology 2016 (Year 29) - Hereditary Cancer Diseases IV http://www.linkos.cz/casopis-klinicka-onkologie/archiv/detail/cislo/2016-01-15-supplementum-1/
5. Oncology - minimum for practice. Tomášek J. a kolektiv. Asclepius 2015. ISBN 978-80-88046-01-1. Foretová L. Inherited Cancer Diseases pp. 44-63
6. Molecular genetics in oncology. Foretová, L. et al. Publishing house Mladá fronta as 2014. ISBN: 978-80-204-3236-0

The most common childhood cancers

V. Bajčiová, J. Štěrba

Paediatric oncology deals with solid tumours and haematological malignancies in children from 0 to 15 years of age and in teenagers aged 15 to 19. The emergence of paediatric oncology as an independent medical discipline reflects the fact that tumours in children and adults are fundamentally different from each other. Childhood tumours are specific in terms of:

- unique characteristics of a paediatric patient
- specific tumour properties

The paediatric patient

A child is not a "miniature adult". During childhood, the organism is evolving and individual organs undergo a steady functional development. Maturing organs (such as the brain) often limit the choice of treatment options. Moreover, anticancer therapy imposes a significant risk of serious late side effects and complications on cancer survivors. On the other hand, childhood is characterized by faster healing, higher rate of adaptation, good organ function, and better compensation mechanisms. Children usually do not have any serious co-morbidities and tolerate anticancer treatment better than adults.

Generally, age plays an important role in oncology. The incidence of tumours is often age-specific, tumour biology and clinical behaviour also varies across different age groups. For many childhood tumours, the age itself is a prognostic and predictive factor. In addition, host's biology changes with age – a variety of metabolic changes occur and the number of co-morbidities increases. In addition, epigenetic changes and mutations underlying cardiovascular, metabolic, neurodegenerative diseases and tumours accumulate as a result of lifestyle factors. At cellular level, these processes induce DNA damage, mitochondrial and proteasome dysfunction, telomerase reactivation, and disorders of mechanisms involved in cell death regulation.

Tumour properties

Childhood tumours typically comprise:

- tumours originating from undifferentiated tissues, referred to as **embryonal type of tumours** (neuroblastoma, Wilms tumour, retinoblastoma, hepatoblastoma, medulloblastoma, etc.)
- tumours that arise from connective tissue, so-called **mesenchymal type of tumours** (sarcomas)

Epithelial tumours (carcinomas) typical for adulthood are extremely rare in children and account for less than 2% of all malignancies in children up to 15 years of age and around 12 % of all tumours in adolescents.

Principal differences between tumours in children and adults:

a) Epidemiology: Childhood cancers belong to rare diseases that represent less than 1% of all malignancies diagnosed in the population. Statistically, one of every 600 children under the age of 15 will develop cancer. Boys are more likely to be affected by cancer than girls are. The incidence is highest among children younger than 5 years in both genders. The second peak occurs in puberty and adolescence.

The incidence of malignancies in children aged 0-19 years in the Czech Republic shows a significant steady upward trend with an increase of about 0.5% of new cases per year. The world age-standardized incidence rates reported in 2016 were 184 cases per million children.

Fig. 1: The incidence of tumours in children and adolescents by diagnosis (according to international classification of childhood cancer) in the Czech Republic, 1994 - 2016

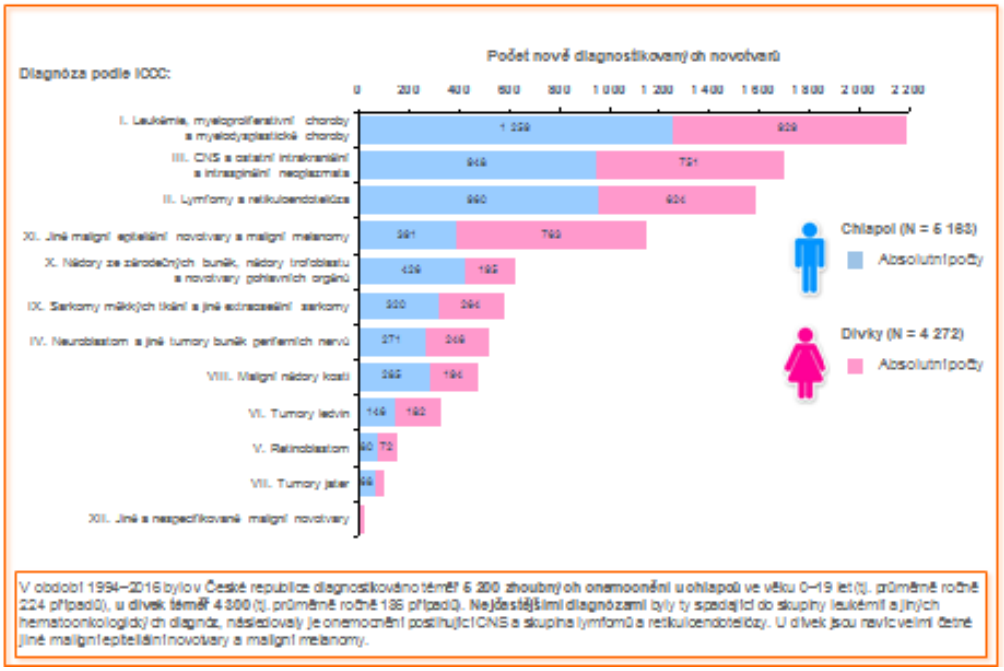
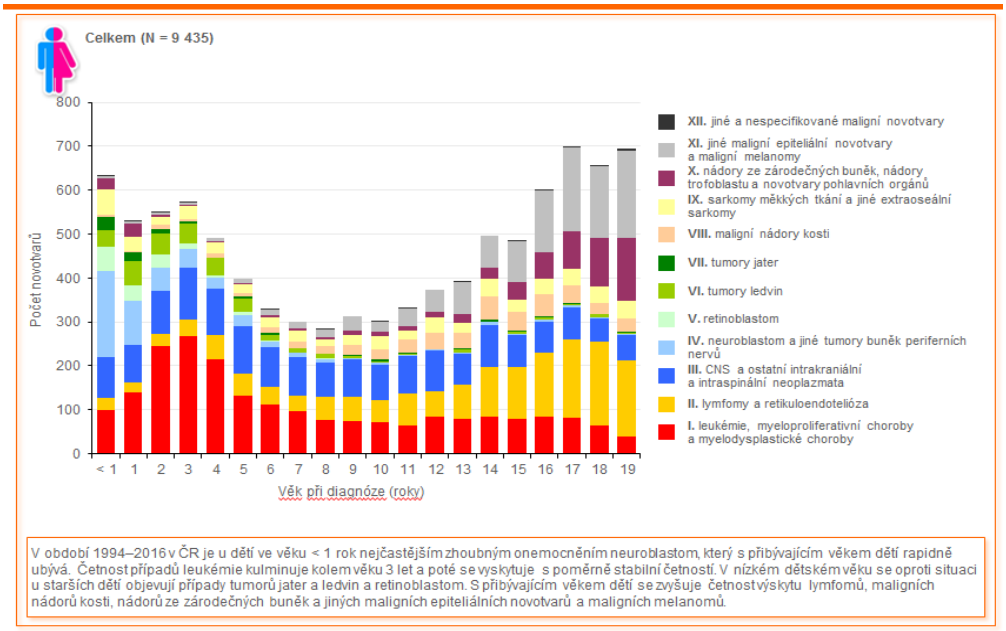


Fig. 2: Age distribution of tumours in the Czech Republic between 1994 - 2016



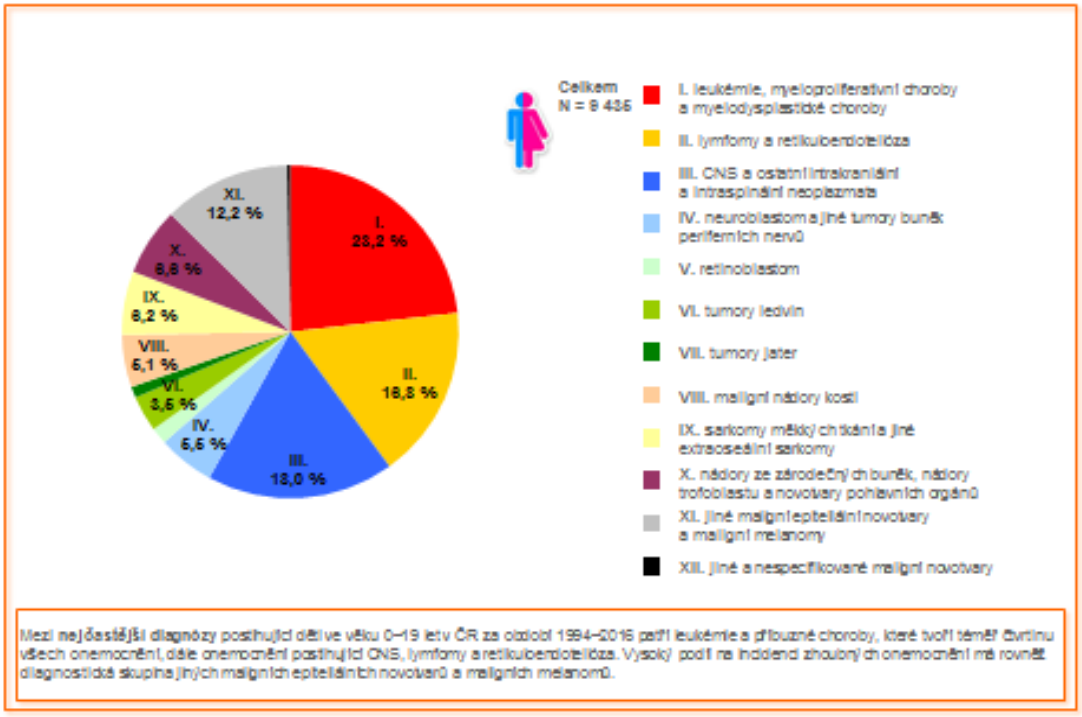
b) Aetiology and pathogenesis: Most childhood tumours (80-90%) are sporadic and their underlying cause remains unknown. The impact of environmental factors is only marginal and often indirect, conferred by parental exposure. In 5 to 10% of patients, the occurrence of tumour is associated with hereditary factors or genetic predisposition syndromes (e.g. Wioedemann-Beckwith syndrome, WAGR syndrome, type I neurofibromatosis, etc.). Besides, immune disorders may also predispose to tumour development. The process of carcinogenesis is believed to be driven by epigenetic changes that emerge as a result of gene-environment interactions. While the impact of external and lifestyle risk factors on the development of adulthood tumours through epigenetic changes is well described (smoking, obesity, alcohol, stress, toxic agents, etc.), their role in the etiopathogenesis of childhood tumours is far less important. More likely, the burden of lifestyle-induced epigenetic changes would transpose to next generations. In fact, cell differentiation during the early embryogenesis comprises many specific epigenetic modifications, however, this process is accomplished before the child is born, usually in the **first trimester of pregnancy**. In this period, foetus is very sensitive to environmental exposures, such as diet and lifestyle of the mother or the way of conception (natural vs. assisted fertilization). Several studies have confirmed the effect of maternal smoking on epigenetic changes in their children. Prenatal exposure to tobacco affects methylation of DNA in foetal haematopoietic cells. Similarly, alcohol consumption in pregnant women was associated with alteration of DNA methylation in neonates. Significant influence on epigenetic changes is also attributed to paternal life-style factors (smoking, alcohol, drugs, medication, stress, higher age, etc.). Although it is not possible to influence genetic predisposition and genome, healthy lifestyle of child's parents can significantly reduce epigenetic changes and thus decrease the risk of malignancy.

Given the prevailing sporadic occurrence of childhood cancers, there have not been any specific risk factors identified and thus, routine cancer screening is not provided in paediatric oncology.

c) Histologic types of childhood tumours are age-specific and differ from the spectrum of tumours in adults (see Figure 3)

d) Biological behaviour of the tumour: childhood cancers are highly malignant, rapidly growing and prone to early metastatic spread by both haematogenous and lymphatic route. Proliferation activity is high with doubling time in the order of hours or a few days. Precanceroses (tumours in situ) are uncommon in childhood tumours.

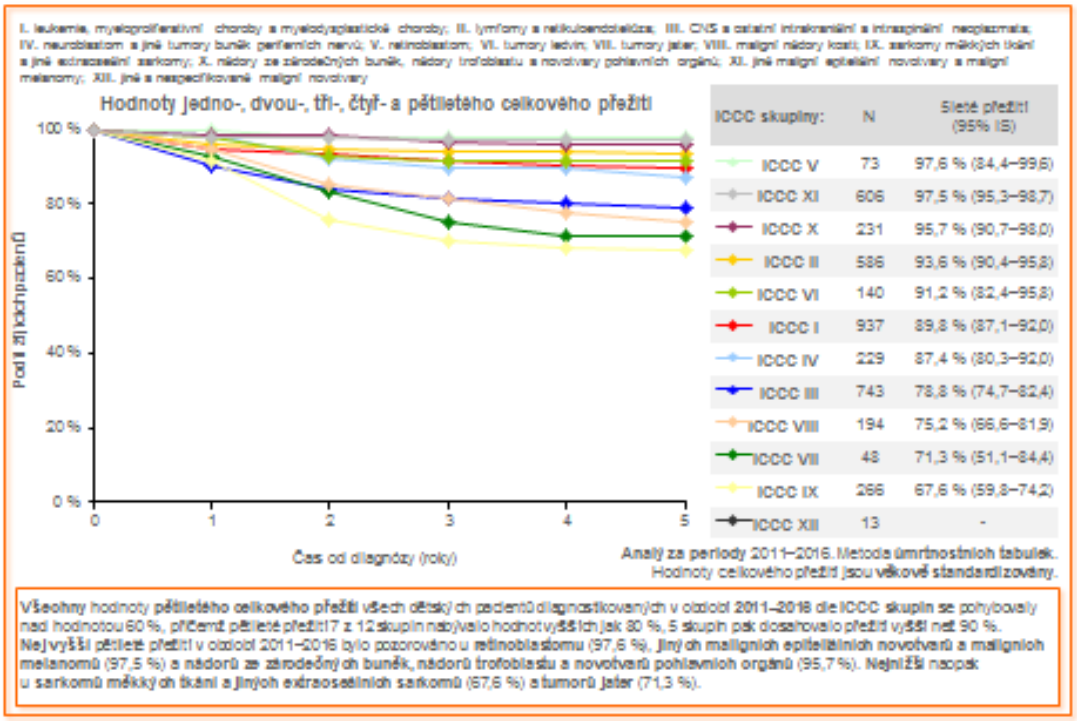
Fig. 3: Most common childhood cancer types in the Czech Republic between 1994 and 2016.



e) Clinical presentation: symptoms of childhood tumours are non-specific and depend on the age of the child, type of tumour, its location, size and the extent of the disease. Symptoms may be local or systemic (weight loss, temperature, sweating, weakness, etc.). Paraneoplastic symptoms are significantly less common in children than in adults.

f) Treatment outcomes are significantly better in paediatric patients than in adults. This is mainly due to high chemosensitivity and radiosensitivity of childhood tumours. Currently, survival rates of childhood cancer exceed 85%.

Fig. 4: Mortality and overall survival trends in paediatric oncology in the Czech Republic by diagnoses between 2011 and 2016



g) Classification of childhood tumours is different from tumours in adults. Whereas adulthood tumours are classified according to ICD-O (International classification of diseased for oncology) system based on tumour location, childhood tumours are assessed according to ICCC (International Classification of Childhood Cancer), on the basis of tumour morphology.

h) Organization of care in paediatric oncology: Diagnosis and treatment is managed within high-volume paediatric oncology centres. Ideally, a one centre should cover 5-7 million inhabitants.

Childhood leukaemias

Leukaemias are the most common type of cancer in children, comprising approximately 30% of all malignancies. Among all types of leukaemia, **acute lymphoblastic leukaemia** (ALL) is the prevailing diagnosis, accounting for **75-80% of all leukaemias**. Approximately 10-15% of cases are attributed to acute myeloid leukaemia (AML), whereas chronic myelogenous leukaemia (CML) is rare among children, representing less than 5-10% of all haemoblastoses.

Epidemiology

Every year, 80-100 children are diagnosed with ALL in the Czech Republic, while 20-30 children are afflicted by AML. The cancer is more common in boys with a peak incidence in the pre-school age.

Risk factors

ALL is caused by repeated DNA damage in lymphoid precursors that leads to impaired cellular differentiation and apoptosis and results in their uncontrolled proliferation. Intrinsic risk factors include genetic predisposition syndromes associated with increased chromosomal instability and defects in DNA repair mechanisms (Fanconi syndrome, Bloom syndrome, Down syndrome, Kostman syndrome, etc.). Environmental factors increasing the risk of ALL are repeated exposure to radiation and certain chemical carcinogens (pesticides, cytostatics) in pregnancy.

Clinical presentation

Clinical symptoms are mostly insidious and non-specific. A classical **triad** of **leukemic symptoms** includes **bleeding disorders, lymph node enlargement** and **hepatosplenomegaly**. Other common manifestations are fever, fatigue, dyspnoea, loss of appetite, skeletal pain due to bone marrow expansion, particularly in long bones and associated gait disturbances. Symptoms related to mediastinal compression, leukostasis or hyperluekocytosis may occur. The duration of symptoms ranges from 2 to 6 weeks. Sometimes, ALL may manifest as a life-threatening emergency (multiple organ dysfunction, tumour lysis syndrome, superior vena cava syndrome or hyperviscosity syndrome).

Diagnosis and staging

The mainstay of diagnosis is laboratory examination of CBC with differential and bone marrow aspiration for immunophenotyping, morphological, cytogenetic and molecular testing. The evidence of **more than 25% and 20% of bone marrow lymphoblasts** is diagnostic of ALL and AML, respectively.

The phenotype of leukaemia is classified based on morphological features of leukemic blasts determined by light microscopy and immunohistochemical detection of their surface antigens by flow cytometry. Cytogenetic detection of fusion genes has not only a diagnostic, but also predictive and prognostic significance (e.g., t (9; 22) or the BCR-ABL gene in Ph1-positive leukaemia). Routine imaging methods include chest x-ray, ultrasound of the abdomen and lymph nodes. In boys, a physical and ultrasound examination of testicles should be performed due to high risk of testicular involvement. Brain MRI and analysis of cerebrospinal fluid from lumbar puncture is recommended to rule out CNS involvement.

Basic principles of treatment

Acute leukaemia is considered a chemosensitive disease. In most ALL, systemic chemotherapy leads to durable haematological remission. The advances in cytogenetics and findings on molecular

mechanisms underlying leukaemia gave rise to risk-stratified treatment protocols based on distinct clinical, biological and genetic alterations in patients with ALL.

The whole treatment takes about 2 years and has several components - an **induction** phase of treatment (aimed at achieving clinical and haematological remission), **consolidation, reinduction** and **maintenance** chemotherapy. Commonly used regimens include corticosteroids, vincristine, anthracyclines, L-asparaginase, methotrexate and nucleotide analogues. For the prophylaxis or therapy of CNS involvement, chemotherapy is administered intrathecally. In high-risk patients and in some patients with relapse of the disease, myeloablative chemotherapy followed by allogeneic bone marrow transplantation is recommended.

Radiotherapy is used as a part of preparative regimen prior to allogeneic bone marrow transplantation (total body irradiation). Brain irradiation for CNS prophylaxis is indicated primarily in T-ALL. Its negative impact on cognitive functions is a major and limiting side effect.

Treatment of AML differs from ALL therapy. It takes less than a year and the chemotherapy is administered in several intensive blocks.

Prognosis

Acute leukaemia is a chemosensitive and highly curable disease. Five-year survival is more than 90% in children with ALL and more than 85% in the case of AML. The prognosis of leukaemia is determined by a number of clinical, molecular and biological factors. Adverse prognostic factors are age (<1 year or > 10 years), high leukocyte count at the time of diagnosis (> 50 x 10/9 / l), male gender, and T-cell immunophenotype. Chemosensitivity and response to treatment is another important prognostic factor. Bone marrow examination at day 15 and day 33 of induction therapy has both predictive and prognostic value and provides a guidance for subsequent treatment strategy and risk reassessment.

The most important prognostic factor in tumours harbouring a fusion gene is the monitoring of so-called Minimal Residual Disease (MRD) by flow cytometry or PCR, which enables detection of the disease below the limit of morphologic examination.

Hodgkin lymphoma

Hodgkin's lymphoma is a malignant lymphoma characterized by the presence of Reed-Sternberg cells or Hodgkin's cells on the background of reactive inflammatory cells like lymphocytes, plasma cells, histiocytes, etc. Hodgkin cells are derived from lymph-node germinal centre B cells that acquired resistance to apoptosis.

Epidemiology

Hodgkin lymphoma (HL) constitutes 5-6% of all malignancies in children under 15 years of age. The incidence peaks in adolescence (the 2nd most common tumour in this age and the most common tumour in adolescent girls). HL is rare in children younger than 5 years and occurs more often in boys.

Risk factors

Only a few risk factors associated with HL have been convincingly identified, the incidence is predominantly sporadic. A higher incidence was reported in families with small number of children or with higher socio-economic status. The association of HL with viral or bacterial infections has not been unequivocally confirmed. There is an evidence that patients with immune deficiency and patients on long-term immunosuppressive therapy (e.g. after organ transplantation) are at higher risk of developing Hodgkin lymphoma. HL may also occur as a secondary malignancy in childhood cancer survivors.

Clinical presentation

Patients often present with non-specific symptoms and mainly with a painless progressive lymphadenopathy typically localized in the neck and supraclavicular region (though other nodal involvement is also possible).

Approximately 25% of children develop so-called **B-symptoms** (intermittent fever > 38°C not responding to antibiotic therapy, night sweats, weight loss > 10% of body weight within 6 months, pruritus), general weakness and fatigue. Sometimes a skin rash may be present.

Mediastinal lymphoma may manifest with dry cough or dyspnoea in the case of massive mediastinal involvement. Superior vena cava syndrome is rare in Hodgkin lymphoma. Infa-diaphragmatic disease is less frequent and rarely symptomatic.

Diagnosis and staging

Special attention during physical examination should be paid to lymph node palpation, liver and spleen examination and evaluation of Waldeyer's tonsillar ring in order to rule out asymmetric enlargement. Affected lymph nodes are non-tender, matted together, fixed to the surrounding and with rubbery consistency.

Imaging studies (ultrasound, **CT** of the lungs and abdomen) are used to determine the extent of lymphadenopathy or extranodal disease. **PET** scan is currently the method of choice in the diagnosis of HL as well as in early tumour response evaluation (already after the first block of chemotherapy). PET findings are crucial for further treatment decisions.

Clinical staging of HL reflects the extent of the disease by imaging methods. Four stages are distinguished according to **Ann Arbor classification. I**n addition, A or B designations denote the presence (B) or absence (A) of B symptoms.

Histologic confirmation is always required for a definitive diagnosis of HL. Based on tumour histopathology, HL is grouped into two major subtypes according to WHO classification from 2008:

1. **Classic Hodgkin lymphoma**, which includes 4 subtypes:
    a) lymphocyte-rich HL (with lymphocyte predominance)
    b) nodular sclerosis HL (most common in children and adolescents)
    c) mixed cellularity HL (typical for prepubertal age)
    d) lymphocyte-depleted HL (rare in children)
2. **Nodular lymphocyte-predominant HL** (NLHL)

Basic principles of treatment

Surgery is only a diagnostic method (for tissue sampling) and its role in HL therapy is marginal. An exception is clinical stage I NHLH, in which surgical resection is a curative treatment method.

The basic therapeutic modality in childhood Hodgkin's lymphoma is **systemic chemotherapy**. Treatment strategy is based on clinical stage, risk classification and the early response outcomes. A standard regimen used in the treatment of Hodgkin's lymphoma in paediatric oncology is DBVE (doxorubicin, bleomycin, vinblastine and etoposide) with the addition of cyclophosphamide and prednisone (DBVE-PC) in an advanced disease. There is a general tendency to minimize the use of radiotherapy in paediatric patients and the treatment of HL includes only low-dose involved field irradiation (standard dose is 21Gy). The indication of radiotherapy depends on clinical stage and response to chemotherapy at the early assessment.

The main goal and important aspect of HL treatment is to prevent or minimize the risk of late adverse effects in cancer survivors, especially the development of secondary malignancies (thyroid carcinoma, breast cancer, etc.).

Prognosis

Factors that influence prognosis include the stage of the disease, presence of B symptoms, bulky disease and extranodal involvement, histological subtype, and early response to induction chemotherapy assessed by PET scan. Treatment outcomes are generally worse in adolescent boys. Five-year overall survival in Hodgkin lymphoma is more than 95%.

Non-Hodgkin lymphoma (NHL)

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of malignancies derived from lymphatic tissues and organs (lymph nodes, thymus, spleen, bone marrow, appendix, and Peyer's patches in the intestinal wall). The most common types of NHL in children and adolescents are **lymphoblastic lymphoma** (usually T-cell), **Burkitt lymphoma** and **large cell lymphoma**. Paediatric NHL is different from NHL in adult age in terms of epidemiology, histological subtypes, biological behaviour of the tumour, treatment and therapeutic outcomes. A vast majority of NHLs in children have a **high degree of malignancy.** Low-grade lymphomas (follicular lymphoma, MALT, primary CNS or skin lymphoma) are extremely rare in children.

Epidemiology

The NHL is the fifth most common malignancy and represents approximately 7% of all malignancies in children under 15 years of age. The peak incidence is in adolescents with male predominance.

Risk factors

In most patients with NHL, the underlying cause remains unknown. Patients with primary immunodeficiency syndrome (e.g. Wiskott-Aldrich syndrome) and secondary immunodeficiencies (after organ transplantation, with AIDS) or patients with genetic predispositions (ataxia teleangiectatica, Nijmegen-breakage syndrome, germinal mismatch repair defects) are at higher risk of developing NHL. Environmental factors associated with NHL include infectious diseases (co-infection with Epstein-Barr virus and malaria are implicated in the development of endemic Burkitt's lymphoma, HTLV-1 virus, hepatitis C virus). Chemical agents (pesticides, herbicides) are of minor importance in paediatric NHL, except for prior treatment with chemotherapy.

Clinical presentation

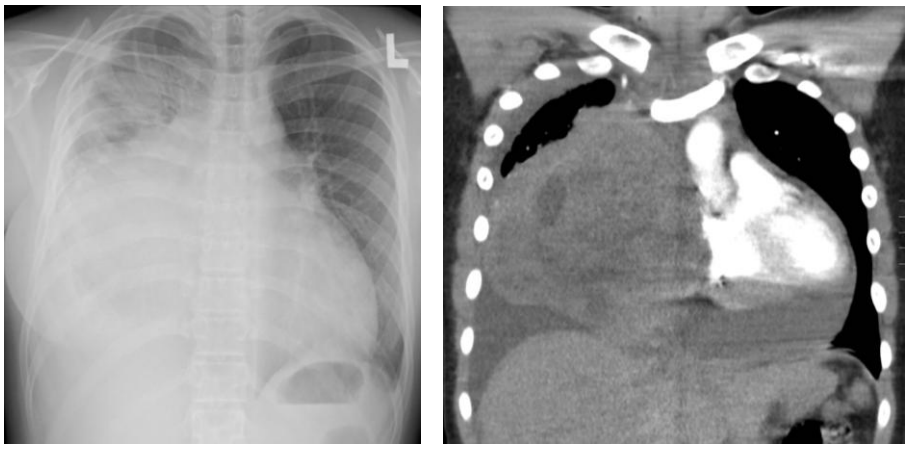
Clinical manifestation is dominated by symptoms related to NHL location, mainly in the form of rapidly progressing lymphadenopathy. In the case of mediastinal involvement (typical for T-NHL, DLBCL), presenting symptoms include dry, non-productive cough, dyspnoea and superior vena cava syndrome. The involvement of infradiaphragmatic lymph nodes and organs is typical for B-NHL and usually manifests with nonspecific abdominal pain, dyspepsia or a palpable mass. Abdominal NHL may be often associated with medical emergencies like bowel invagination or obstruction. Approximately 20 - 30% of children present with constitutional symptoms (fever > 38°C, night sweats, weight loss) that progress very fast – in the order of days. Patients with high-grade NHL with high proliferation rates are at risk of tumour lysis syndrome and ensuing renal failure.

Diagnosis and staging

Physical examination findings may include peripheral lymphadenopathy, hepatomegaly and splenomegaly, abdominal or testicular mass in boys. There are no specific laboratory tests specific for NHL, however, secondary disease-related abnormalities may be observed. Elevation of serum LDH levels is indicative of extensive tumour mass. Cytogenetic and molecular genetic studies are essential for accurate classification of NHL. Each NHL subtype is characterized by one or more molecular mutations and chromosomal translocations. This examination is also important for the evaluation of minimal residual disease.

Imaging methods (ultrasound, CT / MRI) are used for baseline clinical staging. PET scan is important for the evaluation of metabolic activity, especially in tumour response assessment and in the post-treatment setting.

Fig. No. 5: X-ray and CT images of mediastinal T-NHL with pleural and pericardial effusion



The establishment of NHL diagnosis requires histopathological examination (morphological and immunohistochemical), immunophenotyping by flow cytometry and cytogenetic analysis (by FISH and PCR) of a lymph node, bone marrow, peripheral blood and cerebro-spinal fluid or effusion (if present).

In clinical practice, paediatric NHL are classified into four major groups:

- **Burkitt lymphoma**: represents 40-50% of all children's NHL. The tumour cells are mature B-lymphocytes. It is one of the most aggressive tumours, which is extremely chemosensitive. It is typically located in the abdomen.
- **Lymphoblastic NHL**: accounts for 30-35% of all NHL in children. 50-70% of lymphoblastic NHL is localized in the mediastinum and neck.
- **Large cell lymphoma**: comprises 15-20% of NHL in children. It is a heterogeneous group of tumours and is more frequent in adolescents.
- **Low grade lymphoma**: are typical for adult age and very rare in the paediatric population.

Bilateral bone marrow aspirate and trephine biopsy are a standard part of initial work-up necessary for the assessment of bone marrow infiltration. The presence of more than **25% of blasts** in the bone marrow is an arbitrary limit for the diagnosis of **acute lymphoblastic leukaemia**. An involvement of **less than 25%** of bone marrow is considered a **lymphoma infiltration** that is classified as **clinical stage IV** disease. Similarly, the presence of blasts in cerebro-spinal fluid is another criterion for clinical stage IV NHL.

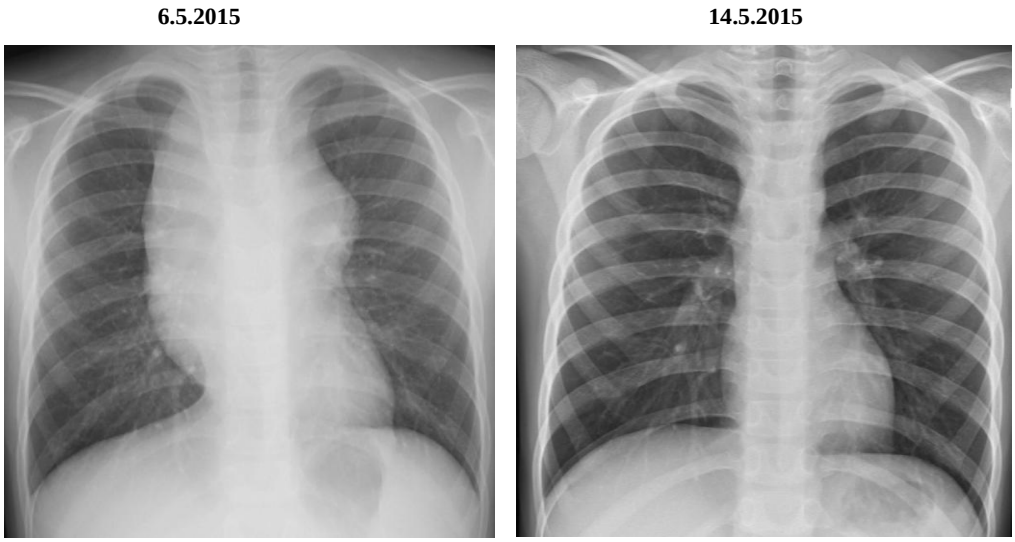
Basic principles of treatment

Given the aggressive character of paediatric NHL and the risk of acute life-threatening complications (tumour lysis syndrome, superior vena cava syndrome, acute renal failure, acute abdomen), every child with suspected diagnosis of NHL should be immediately referred to a specialized paediatric oncology centre.

The role of surgery in the management of NHL is limited to diagnostic biopsy or lymph node extirpation. Primary surgical intervention is performed only in the case of acute abdomen caused by infra-diaphragmatic spread of NHL. Radical resection of lymphoma is not necessary. Second-look surgery is indicated in patients with residual tumour mass at the end of systemic therapy.

The preferred treatment modality in children with NHL is **systemic chemotherapy**. Due to aggressive biological behaviour and high proliferation rate of NHL (doubling time only 24-48 hours), treatment response is usually excellent and prompt. The character and dose intensity of chemotherapy regimen depends on the type of NHL, its clinical stage and specific risk. To date, two monoclonal antibodies are available in the treatment of NHL in children and adolescents - **rituximab** (anti-CD20) for children with CD20 positive B-NHL and **brentuximab vedotin** (anti-CD30) for patients with ALCL. Radiotherapy has only a limited role in the treatment of paediatric NHL. It may be used in palliative setting (e.g. treatment of T-NHL with CNS involvement) or as a symptomatic treatment (e.g. in pain management).

Fig. 6: Rapid response of mediastinal T-NHL to chemotherapy



Prognosis

The prognosis of paediatric NHL has improved significantly within the past decades and most paediatric NHLs are today curable. The prognosis depends on several factors: tumour stage, tumour bulk, presence of the residual disease after the initial treatment, NHL subtype and patient age (age > 10 years is an adverse prognostic factor). Five-year overall survival for NHL is more than 85%.

Central nervous system tumours in children

Primary central nervous system (CNS) tumours are the most common paediatric solid tumours and the second most common malignancy after leukaemias. It is a heterogeneous group comprising a wide range of histologic subtypes with distinct biological and clinical behaviours, ranging from benign tumours to highly malignant cancers. The most common paediatric CNS tumours are **gliomas (astrocytomas)** and **so-called embryonic CNS tumours (medulloblastomas)**. In contrast to tumours of adult age, paediatric CNS tumours are characterised by predominant infra-tentorial location (75%) in the posterior fossa and midline location. The spinal cord is affected in about 10% of patients.

Epidemiology

The incidence of CNS tumours is 2.5 - 3.5 cases per 100,000 children < 15 years of age, with moderate predominance among boys. The peak incidence is in pre-school children < 5 years of age.

Risk factors

The vast majority of paediatric CNS tumours are sporadic, without any detectable underlying cause. Exposure to ionizing radiation is the only established external risk factor (secondary CNS tumours may be induced by prior radiotherapy). Internal factors include hereditary predisposition syndromes

(e.g. neurofibromatosis type I and II, von Hippel-Lindau syndrome, tuberous sclerosis, Gorlin syndrome, germinal mismatch repair defects, etc.).

Screening and prevention

Screening for CNS tumours in children is not performed. Nevertheless, routine monitoring of children with genetic predispositions at oncology is necessary. It consists of regular clinical, neurological and imaging examinations.

Clinical presentation

Clinical symptoms depend primarily on child's age, tumour location, size, and proliferation rate. In general, clinical manifestations of tumours are related to direct damage to brain structures caused by invasive tumour growth and indirectly, by compression of surrounding tissues. These changes often induce **brain oedema.** The onset of symptoms is determined by the type of tumour and its location. Infants and toddlers often present with nonspecific symptoms (failure to thrive, lethargy, apathy, or increased irritability, psychomotor retardation). In the later course of the disease, enlargement of head perimeter (macrocephaly) and arching of the large fontanel may occur.

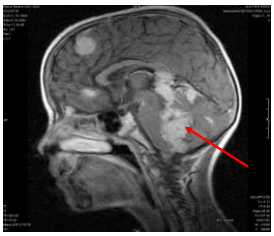
Generally, CNS tumours are often associated with symptoms of **increased intracranial pressure (headache, emesis)**. Behavioural changes, fatigue, apathy, cognitive deterioration and growth disturbances are reported mainly in older children.

Local symptoms depend on tumour location – corticospinal tract disorders manifest with hemiparesis, cerebellar disorders may result in impaired coordination or ataxia, cranial nerve disorders may include visual disturbances in optic nerve gliomas, etc. Tumours located in the midline are often associated with endocrine disorders (panhypopituitarism, pubertas praecox, diabetes insipidus). Supratentorial tumours may present with seizures, behavioural and cognitive impairment.

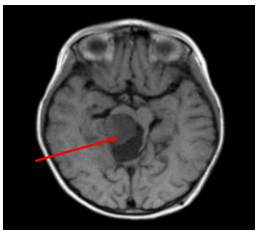
Diagnosis and staging

The initial evaluation is based on detailed neurological assessment and dilated pupil eye exam. CT and MRI of the brain and spinal cord are essential for the diagnosis and evaluation of CNS lesions. The majority of CNS tumours are detectable by contrast-enhanced CT, however, it might be false negative, especially in brain stem tumours. MRI examination provides a more accurate view of brain structures including the brainstem and medulla oblongata. MRI is therefore the essential imaging method used in the diagnosis and tumour response evaluation in paediatric CNS tumours. The initial assessment also includes the spinal cord MRI and examination of cerebrospinal fluid from lumbar puncture due to the high risk of spread along the liquor pathway.

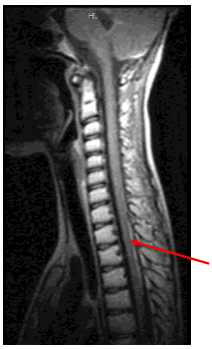
Fig. 7: Typical images of brain tumours on imaging examinations.



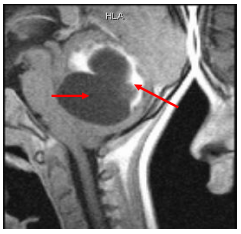
metastatický medulloblastom



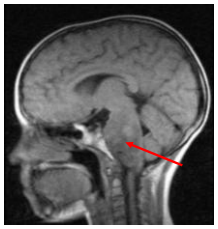
ependymom postranné komory



polevové metastázy



astrocytom zadní jámy



gliom mozkového kmene

For all types of brain tumour, histopathological verification and exact classification according to the current WHO scheme from 2016 is required. This also includes molecular genetic analysis of frozen tissue specimens. Molecular profiling is used to refine the histopathological diagnosis. For example, four subgroups of medulloblastoma are distinguished based on specific genetic signature, with distinct clinical and biological behaviour, treatment approach and prognosis.

Basic principles of treatment

Treatment of CNS tumours in children and adolescents should be provided within a high-volume centre with adequate expertise, experience and with the access to modern diagnostic and therapeutic methods. The treatment strategy is linked to the tumour type, its location, feasibility and extent of resection, child's age and biological features of the tumour.

Surgical resection is the primary treatment modality and the radicality of resection is an important prognostic and predictive factor determining the character of subsequent treatment.

Radiotherapy is irreplaceable in some types of CNS tumours (medulloblastoma, malignant glial tumours, ependymomas), but it is contraindicated in children under 1 year of age because of its serious late side effects including developmental disorders like severe psychomotor retardation, neurocognitive disorders, growth arrest, endocrinopathy, etc. Therefore, children under the age of 3 years are initially treated with **chemotherapy** in order to defer necessary radiotherapy. Patients with high-risk CNS tumours (medulloblastoma) are treated with high-dose sub-myeloablative chemotherapy regimens followed by autologous transplantation of peripheral haematopoietic stem cells.

The impact of chemotherapy on CNS tumours is limited by the presence of the blood-brain barrier that is restrictive to a wide range of cytostatics. Therefore, chemotherapy regimens used in CNS

tumours comprise mostly lipophilic agents (cisplatin, carboplatin, carmustine, lomustine, etc.). Intrathecal administration of cytostatics (via lumbar puncture or Omaya reservoir) may be used to bypass the blood-brain barrier.

In the past few years, several targeted agents have become available in the therapy of brain stem gliomas. Hyper-mutated forms of brain tumours may be treated with immunotherapy (**anti-PD-L1** monoclonal antibodies).

Prognosis

The dominant prognostic factors in CNS tumours are histologic type and molecular characteristics of the tumour, its location, radicality of resection, extent of the tumour (clinical stage), presence of metastases and patient age.

Five-year survival rate for intermediate-risk and high-risk medulloblastoma is 70-85% and less than 40%, respectively. For grade 3 ependymoma, the five-year survival rate ranges from 50 to 64%.

Low-grade astrocytomas have an excellent prognosis, from 95 to 100% of children will survive for five years and more. For anaplastic astrocytomas, the prognosis is significantly worse. Gliomas of the brain stem carry the worst prognosis among all paediatric tumours, as they are often inoperable. Median time to progression is only a few months (6 to 8 months), less than 10% of children survive more than 2 years after the diagnosis.

Nefroblastoma (Wilms tumour)

Renal tumours represent about 4-8% of all malignancies in children under 15 years of age. Majority of renal tumours in childhood are malignant, benign lesions account for less than 4% of tumours. Nefroblastoma (Wilms tumour) is the most common renal malignancy in children. It is a typical embryonal tumour that originates from primitive metanephrogenic blastoma.

Epidemiology

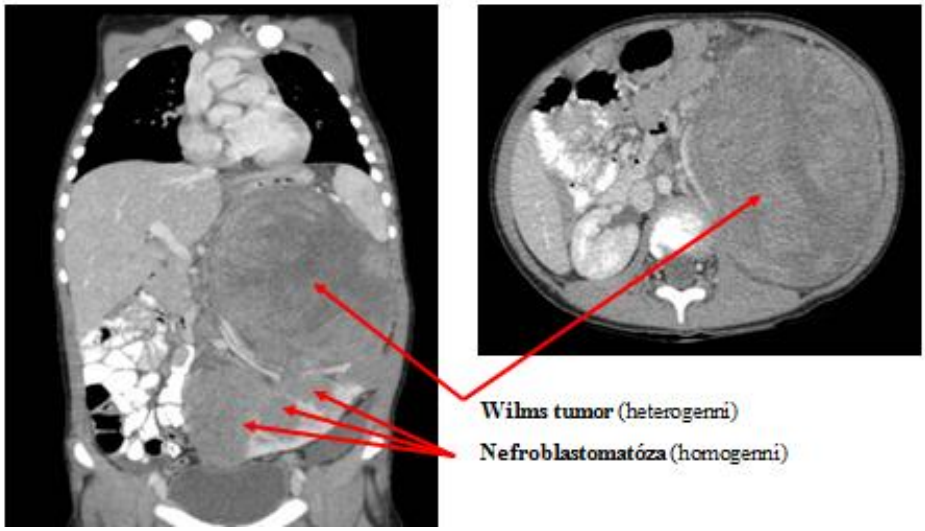
Wilms tumour comprises approximately 87 % of all kidney tumours in children, the incidence is 1/10 000. The peak in incidence rate is in children before 5 years of age, the median age at diagnosis is 3.5 years. The tumour is rare after the age of 10 years. In the 15-19-year-old age group, renal cell carcinoma is more common. Most Wilms tumours are unilateral, only 5 - 10% of them are bilateral.

Risk factors

Wilms tumour is a sporadic disease without any specific precipitating factor. Approximately 10% of cases occur as a part of congenital malformation syndromes (Wioedemann-Beckwith, WAGR, Frasier, Denys-Drash syndrome, hemihyperplasia, etc.) Over 30% of Wilms tumours (often bilateral) develop

in the setting of nephroblastomatosis (i.e. presence of foetal nephrogenic rests in the normal renal tissue).

Fig. No. 8: Wilms' tumour in the setting of perilobar nefroblastomatosis



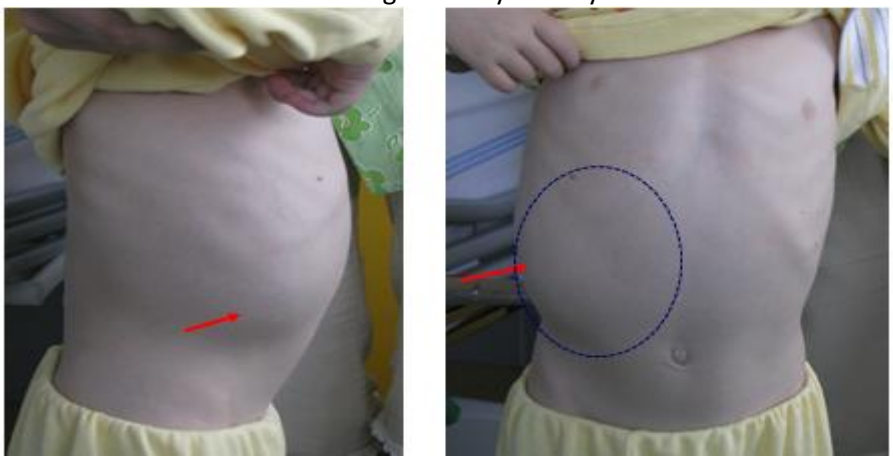
Screening and prevention

Screening of kidney tumours is not routinely performed. Children with hereditary predisposition syndromes are monitored at paediatric oncology by abdominal ultrasound examination every 6 months up to 7 years of age.

Clinical presentation

Wilms tumour is often clinically silent and presents as an incidental finding. The most common initial manifestation is an asymptomatic palpable (and often visible) abdominal mass. The overall health status of the child is very good, without any significant alteration. Constitutional symptoms (fever, fatigue, pallor) or local symptoms (constipation, abdominal pain) occur in less than 1/3 of patients. Approximately 10 to 30% of patients may present with micro/macroscopic haematuria (due to renal pelvis infiltration). Renovascular hypertension has been reported in 25% of patients.

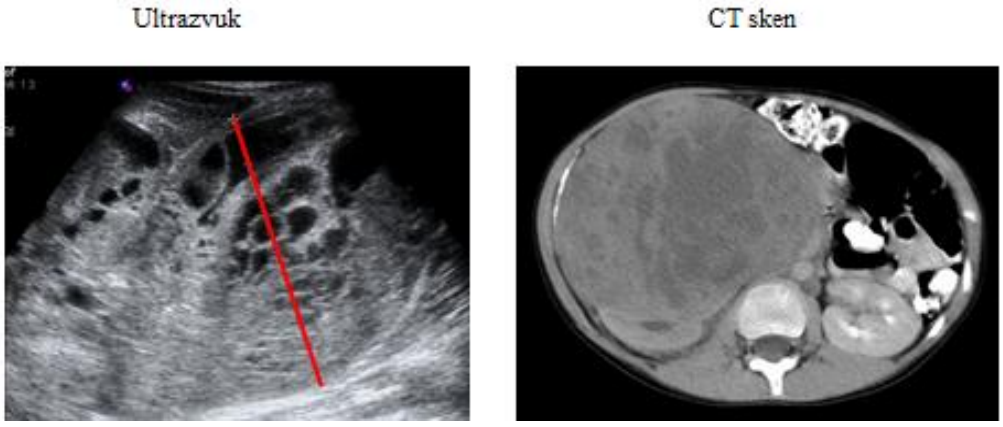
Fig. 9: Visible Wilms tumour of the right kidney in a 3-year-old child



Diagnosis and staging

Diagnostic work-up begins with thorough medical and family history focused on congenital anomalies or genetic predispositions. Physical examination may reveal an abdominal mass, however, palpation should be careful due to high risk of tumour rupture into the peritoneal cavity. Imaging studies (abdominal ultrasound, CT / MRI abdomen, CT lungs) are used to assess the extent of the disease. Brain CT and bone scintigraphy are indicated only in certain histologic subtypes, 18 FDG PET scan is not routinely recommended. It is always necessary to examine renal functions and determine the patency of inferior vena cava. Wilms tumour does not produce any specific tumour markers, though, LDH may be used as a non-specific marker of tumour extent. The histopathological confirmation of the tumour accompanied by cytogenetic and molecular genetic studies is essential for tumour risk stratification and further management.

Fig. 9: Typical appearance of Wilms tumour on different imaging examinations



Basic principles of treatment

Treatment is characterized by a combined-modality approach including surgical treatment and chemotherapy with or without postoperative radiotherapy depending on tumour stage and risk group.

In Europe, the standard treatment consists of neoadjuvant chemotherapy followed by so-called delayed surgery (transabdominal nephrectomy). In contrast, US practice favours primary surgery followed by adjuvant chemotherapy depending on risk group. Heminefrectomy (nephron sparing surgery) is indicated only in specific cases such as solitary kidney, or bilateral tumour. Nephrectomy through lumbotomy is a non-lege artis procedure in oncology patients.

Given the risk of late toxicities of radiotherapy, its indications have been significantly narrowed. Adjuvant radiotherapy is used only in the case of intraoperative tumour rupture, abdominal lymph node involvement and for residual pulmonary metastases at the end of chemotherapy.

In bilateral renal tumours, the primary goal of multimodal treatment is to preserve functional renal parenchyma to the largest extent possible.

Prognosis

Wilms tumour belongs to highly **curable diseases.** Tumour histology, response to neoadjuvant chemotherapy and the extent of the disease are the most important prognostic factors. Patients with localized disease have a 90% 5-year-survival rate. Over 80 % of children with metastatic Wilms tumour survive 5 years and more.

Hepatoblastoma and liver tumours in children

Epidemiology

Liver tumours are rare in children and adolescents, representing only 1% of all paediatric cancers. Up to 2/3 of the liver tumours in children are malignant. Liver tumours are age-specific; the most

common type of malignant liver cancer is **hepatoblastoma**, an embryonal tumour with a peak incidence before the age of 5 years, and **hepatocellular carcinoma,** which typically affects older children and adolescents. The incidence of primary liver cancer is comparatively low compared to secondary hepatic tumours. Sarcomas, neuroblastoma or germ cell tumours are most likely to spread to the liver. Most common benign liver tumours are hemangioma or haemangioendothelioma.

Risk factors

Most hepatoblastomas are sporadic, only a small part is associated with genetic predisposition syndromes such as Gardner's syndrome, Wiedemenn-Beckwit syndrome or familial adenomatous polyposis. Extremely low birth weight (<1000gr) and congenital anomalies (hemihypertrophy) are also linked to an increased risk of hepatoblastoma.

Hepatocellular carcinoma in children and adolescents usually develops in otherwise healthy liver parenchyma, without any underlying cirrhosis. Risk factors include congenital metabolic disorders (tyrosinemia, glycogen storage disease, alpha 1 antitrypsin deficiency), chronic hepatitis C and B, long-term use of anabolic steroids or exposure to aflatoxins. In most cases, however, the aetiology remains unknown.

Screening and prevention

Routine screening is not performed. Only children with congenital genetic predispositions are monitored by ultrasound every 6 months.

Clinical presentation

Clinical symptoms of hepatoblastoma or hepatocellular carcinoma are usually a feature of an advanced disease. The initial presenting symptom is often a palpable mass or apparent disfiguration of the abdomen. A marked alteration of overall health status is rare. Deterioration of liver function is uncommon even in large tumours, thus, jaundice, ascites or coagulopathy are very rare at the time of diagnosis. Approximately 20% of patients present with symptoms related to metastases.

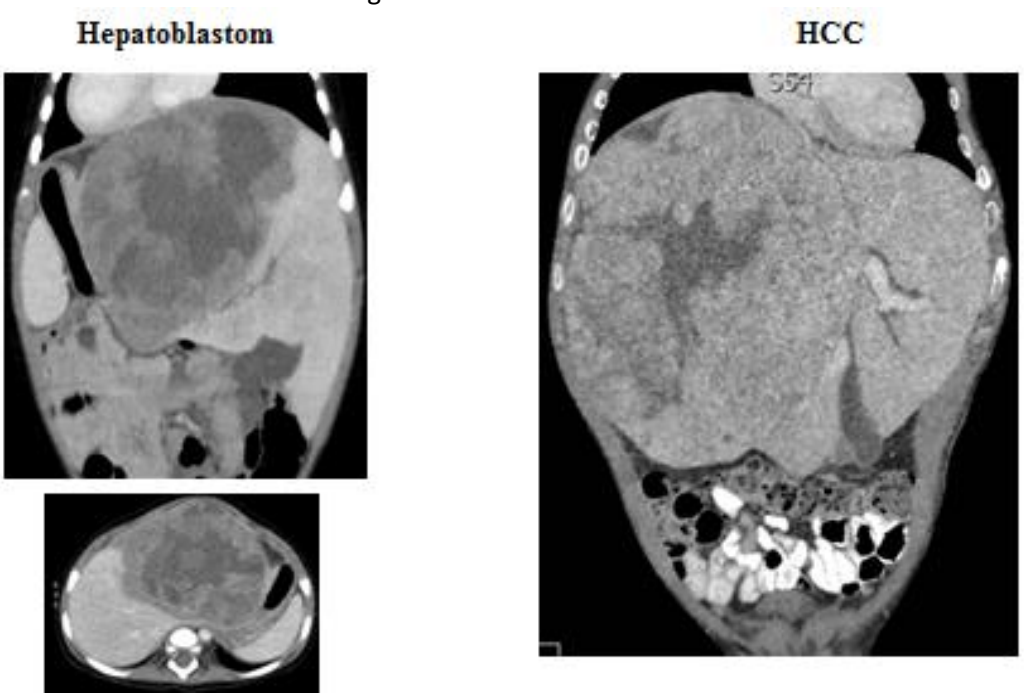
Diagnosis and staging

The diagnostic approach is the same for all childhood liver tumours and does not significantly differ from the evaluation in adult oncology. Medical history should include information on birth weight, congenital abnormalities, hereditary syndromes and metabolic disorders, vaccination or stay in endemic risk areas.

Complete blood count, basic chemistry profile, hepatitis serology and tumour markers (primarily AFP) should be obtained. Imaging studies (ultrasound, CT / MRI) are important for determining the

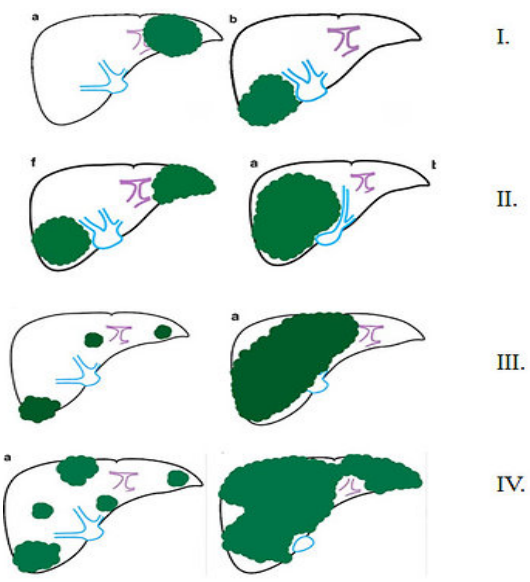
exact location and extent of the tumour, its relation to perihillar structures, bile ducts and hepatic vascular supply.

Fig. no. 10: Abdominal CT scan showing different liver tumours



Preoperative evaluation of the tumour extent (PRETEXT) classification system is used for liver tumour staging and risk stratification that are necessary for treatment decision making.

Fig. No. 11: PRETEXT system for childhood liver tumour classification



PRETEXT = pretreatment extension:

PRETEXT number	Definition
I	One section is involved and three adjoining sections are free
II	One or two sections are involved, but two adjoining sections are free
III	Two or three sections are involved, and no two adjoining sections are free
IV	All four sections are involved

+

V hepatic veins involvement
P vena portae involvement
E extraliver disease
R rupture of the tumor
F multifocal disease

Basic principles of treatment

Radical surgical resection is the cornerstone of hepatic tumour treatment and offers a chance of long-term cure. Inoperable hepatic tumours can be managed by locoregional therapy (thermoablation, chemoembolization). Patients with multifocal tumours confined to liver may be considered for liver transplantation.

The implementation of systemic chemotherapy in hepatoblastoma therapy has significantly improved treatment outcomes and patient survival. In contrast, hepatocellular carcinoma is resistant to conventional chemotherapy and non-resectable tumours convey a very poor prognosis. Promising results have been shown with the use of targeted agents (sorafenib, regorafenib, cabozantinib) and immunotherapy (anti-PD-L1 monoclonal antibodies) in the management of advanced hepatocellular carcinoma.

Prognosis

Hepatoblastoma belongs to highly curable types of tumours, with more than 75% of patients alive at five years. Overall survival for patients with hepatocellular carcinoma is significantly worse, only about 25% of patients live 5 years or more.

Neuroblastoma

Neuroblastoma is an embryonal type of tumour that originates from primitive sympathetic ganglion cells (the precursor cell is a foetal neuroblast from the neural crest). Neuroblastoma is a markedly heterogeneous disease in terms of tumour location, histopathology, and, above all, biological behaviour (ranging from spontaneous regression to maturation to benign ganglioneurinoma, or highly aggressive and often fatal neuroblastoma).

Epidemiology

Neuroblastoma is the most common solid extra-cranial tumour in children. Up to 90% of cases are diagnosed before 5 years of age, with the median age at diagnosis being 2 years. Approximately 25-30 of new neuroblastoma cases are diagnosed in the Czech Republic every year. Despite the advances in treatment options, neuroblastoma significantly contributes to the number of all paediatric cancer fatalities.

Risk factors

As with other paediatric malignancies, most neuroblastomas are sporadic and their cause is unknown. Approximately 1-2% of neuroblastomas are hereditary, mostly with autosomal dominant pattern of inheritance with incomplete penetration. Familial neuroblastomas usually occur at younger age (median of 17 months) and are often multifocal.

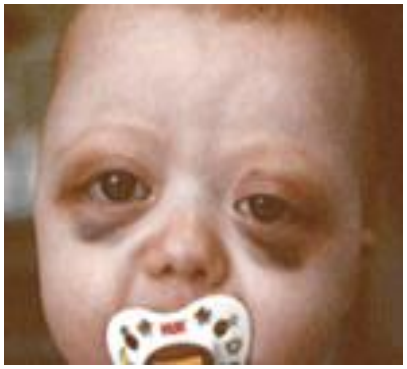
Screening and prevention

Neuroblastoma screening is not performed.

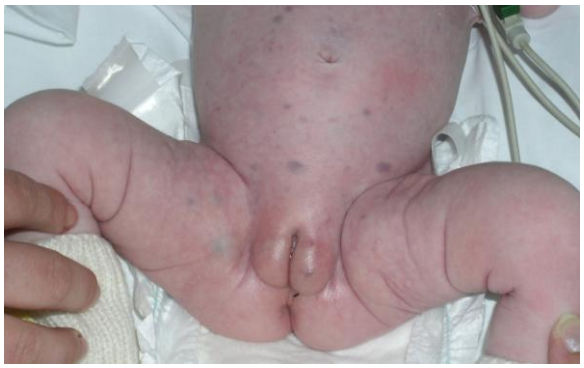
Clinical presentation

Neuroblastoma can arise in any site with sympathetic innervation (adrenal gland, retroperitoneum, posterior mediastinum, neck, pelvic sympathetic ganglia, etc.). More than a half of neuroblastomas (65%) develop in the **retroperitoneum**. In about 1% of neuroblastomas, the primary site remains unknown. Symptoms related to metastases are often the initial presenting symptoms (neuroblastoma most commonly spreads to regional lymph nodes, cortical bone and bone marrow, orbit, liver and skin). Pulmonary metastases are uncommon. Patients with localized disease are often asymptomatic, whereas patients with advanced disease present with serious systemic symptoms. Clinical signs of neuroblastoma include palpable/visible tumour mass, abdominal pain, constipation, exophthalmos, periobital ecchymoses ("raccoon eyes") caused by retroorbital metastases, Horner syndrome, overall weakness, hypertension, bone pain, gait disturbances. Paravertebral tumours may spread to the spinal canal and result in spinal cord compression (so-called dumbbell tumours).

Fig. 12: Clinical manifestations of neuroblastoma



„racoon eye“, mývalí oči



„blueberry muffin baby“ – kožní metastázy NBL

Neuroblastoma is one of a few paediatric tumours that may present with paraneoplastic symptoms (hypertension, skin flushing, opsoclonus-myoclonus-ataxia syndrome, autonomic tumour secretion of the vasoactive intestinal peptide that causes secretory diarrhoea).

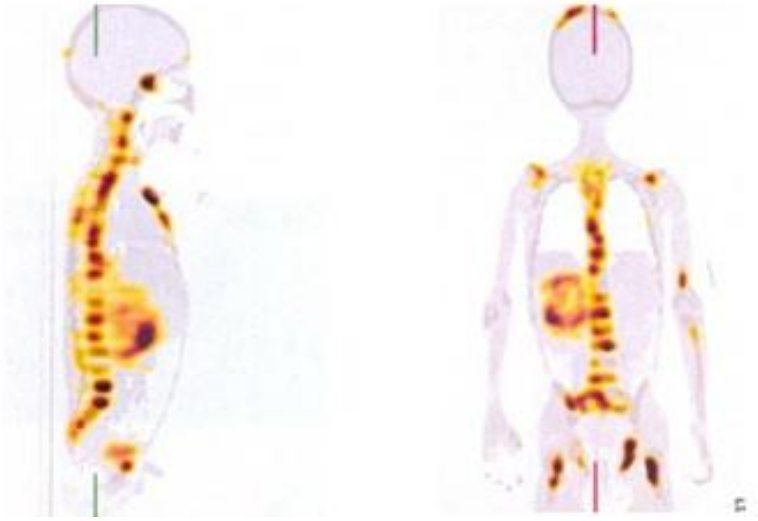
Diagnosis and staging

The initial evaluation begins with medical history and physical examinations. Specific laboratory investigations include the detection of serum and urinary catecholamine metabolites (vanillylmandelic and homovanillic acid, VMA and HVA), preferably from a 24-hour urine sample. Catecholamine levels are increased in more than 90% of patients with neuroblastoma. Neuroblastoma-associated tumour markers are NSE (neuron-specific enolase), ferritin and lactate

dehydrogenase (LDH). However, their prognostic value has been surpassed by molecular biomarkers (genetic and chromosomal abnormalities such as NMYC amplification, deletion 1p, 11q LOH, 17q gain, ploidy). These markers (particularly NMYC amplification) also play an important role in tumour risk-stratification and tumour response prediction.

The initial staging should also include bone marrow examination and whole-body MIBG scan (scintigraphy method with an iodine-123-radiolabeled molecule similar to noradrenaline used to detect adrenergic tissue). The sensitivity of the examination is around 90%. Other routine imaging studies involve CT / MRI of the abdomen and small pelvis and chest CT in the case of positive or inconclusive chest X-ray. MRI of the brain is indicated only in patients presenting with neurological symptoms or proptosis.

Fig. 13: MIBG scan showing disseminated neuroblastoma with multiple bone metastases



Tumour extent is classified according to the International Neuroblastoma Staging System (INSS). Definitive diagnosis and risk-stratification is based on histopathological and molecular genetic testing.

Basic principles of treatment

The management of neuroblastoma is dictated by risk-stratified treatment approach. Low, intermediate and high-risk groups are distinguished based on age, tumour stage, histology and molecular and genetic biomarkers.

Low-risk patients with favourable histology are treated with surgery alone and do not require any further oncology treatment. These patients have an excellent prognosis. Watchful-waiting strategy

might be adopted in infants who present with so-called perinatal neuroblastoma, since most of them may experience spontaneous tumour regression.

Patients with intermediate-risk neuroblastoma are treated with radical surgery (if possible) followed by adjuvant chemotherapy. Radiotherapy could be considered in tumours inappropriate for surgery.

Patients with high-risk neuroblastoma older than 18 months with advanced disease and adverse prognostic biomarkers require intensive multimodal therapy (surgery, high-dose chemotherapy with autologous hematopoietic stem cell transplantation, radiotherapy, therapeutic I122 MIBG and 13-cis-retinoic acid administration).

A novel treatment options for high-risk neuroblastomas include targeted therapy with monoclonal antibody against the cell surface antigen disialoganglioside 2 (anti GD2). Despite the advances in treatment, the prognosis of these tumours remains very poor.

Prognosis

Patients with low-risk neuroblastoma have an excellent prognosis; almost 100% of patients are alive 5 years after the diagnosis. Five-year overall survival for intermediate-risk neuroblastoma is 75-85%. In the high-risk group, less than 40% of children survive for 5 years or more.

Retinoblastoma

Retinoblastoma is a rare malignant tumour that originates from primitive foetal retina cells, prior to their final differentiation. It is the most common primary intraocular malignancy in children. Retinoblastoma is remarkably chemosensitive and radiosensitive, however, it also may be fatal if it remains untreated. It is responsible for 5% of childhood blindness and 1% of paediatric mortality. Retinoblastoma occurs in a sporadic or congenital form. Patients with congenital retinoblastoma have a high risk of developing a secondary malignancy.

Epidemiology

Retinoblastoma is a rare tumour, representing about 2-4% of all childhood malignancies. The peak incidence is around 18 months of age, with a modest predominance in boys. Up to 90% of retinoblastomas are diagnosed before the age of 5 years.

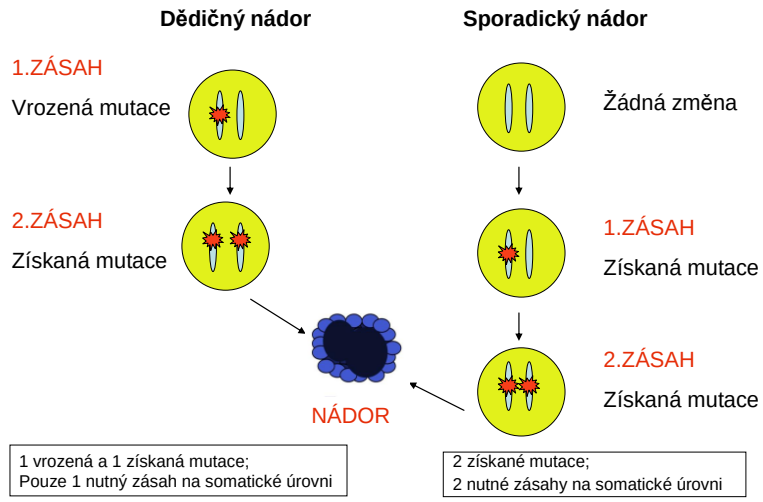
Risk factors

Two types of retinoblastoma can be distinguished - hereditary and non-hereditary form. Both of them are associated with a mutation in the RB1 tumour suppressor gene.

Non-hereditary (sporadic) retinoblastoma comprises 2/3 of all retinoblastomas. It results from somatic mutations of RB1 gene in retinal cells. It is usually unilateral and unifocal, diagnosed at a median age of about 24 months.

Hereditary retinoblastoma constitutes 1/3 of all retinoblastomas. It is caused by germline mutations of RB1 gene that are present within every cell of the affected individual. This form of retinoblastoma is inherited in autosomal dominant pattern (Knudson's two-hit theory).

Fig. No. 14: The Knudson Theory of Double Action



Screening and prevention

Patients with positive family history of retinoblastoma are recommended to undergo genetic testing and prenatal screening of the RB1 mutation.

Clinical presentation

The most common clinical symptoms of retinoblastoma are leukocoria (white pupillary reflex or cat's eye reflex), strabismus (mostly convergent), glaucoma, cataract, proptosis, visual loss, different colour of iris, orbital swelling, or pain.

Fig. 15: Clinical presentations of retinoblastoma

Diagnosis and staging

CT provides an optimal method for the initial evaluation of the extent of intraocular involvement, locoregional tumour extension (into orbit, optic nerve) and the presence of distant spread (CNS, lungs, regional nodes, liver, bone, bone marrow). An essential part of baseline investigations in all patients with retinoblastoma is genetic testing.

Basic principles of treatment

The primary goal of treatment is not only to treat the tumour itself, but also to preserve as much vision as possible („eye-free survival“) and minimize late complications of treatment including secondary malignancies (especially in the hereditary form of retinoblastoma).

Radical surgical management in terms of enucleation or orbital exenteration are reserved only for patients with extensive tumours or unfavourable cases.

Fig. No. 16: Enucleation for large intraocular retinoblastoma

Small tumours can be managed by local intraocular treatment methods such as cryotherapy, laser, photocoagulation, or by the use of radioactive isotope plaques. Due to significant morbidity and late complications associated with the used of radiotherapy (secondary osteosarcomas, orbital hypoplasia, etc.) this method is being superseded by other treatment modalities, such as chemotherapy reducing the tumour bulk possibly followed by local ablative techniques. Chemotherapy can also be administered locally by intra-arterial application via ophthalmic artery or by subtenon injections.

Prognosis

Retinoblastoma has a high cure rate with five-year overall survival ranging from 86 to 95%. Prognosis depends on the presence of genetic burden (mortality is higher in patients with hereditary

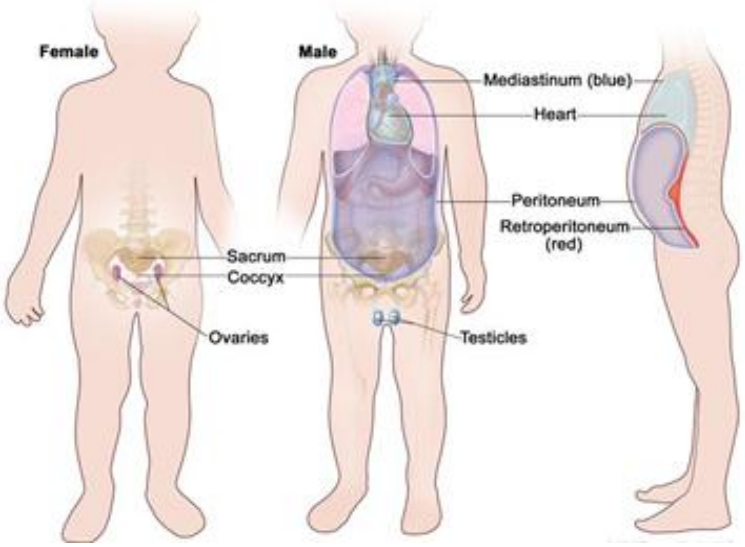
retinoblastoma), tumour size and the extent of local or distant spread. An early diagnosis usually warrants favourable treatment outcomes, whereas children with advanced disease or optic nerve involvement have five-year survival rates lower than 6%. Patients with trilateral retinoblastoma (hereditary retinoblastoma associated with intracranial neuroblastic tumour) have a poor prognosis with a median survival of about 8 months.

Extracranial germinal tumours

Germ cell tumours (GCT) constitute a heterogeneous group of malignancies varying in terms of location, histopathologic appearance and biologic characteristics. GCTs arise from primordial pluripotent germinal cells and often contain tissues not corresponding to their site of origin.

The distribution of GCTs with regard to tumour location and histology is age-specific. Primary tumours may be detected in gonads (ovarian, testicular), extragonadal primaries typically involve midline locations (neck, mediastinum, retroperitoneum, sacro-coccygeal region). Clinical and biological behaviour depends on child's age at the time of diagnosis, tumour location and histologic type.

Fig. No. 17: Localization of extracranial germinal tumours



Based on the production of tumour markers (AFP, β-HCG), GCTs can be classified as secretory and non-secretory types.

Epidemiology

GCTs are rare among children under 15 years of age, accounting for 3-5 % of all tumours in this age group. Incidence increases in adolescents, in whom GCT represent up to 14 % of all tumours, with testicular GCT being the most common tumour in adolescent boys. The incidence has a bimodal age distribution - the first peak is in children under 3 years of age with prevalence of extragonadal

location, the second peak is in adolescents with gonadal GCTs. Infants and young children are most often affected by intracranial GCTs and sacro-coccygeal teratomas.

Risk factors

Most GCTs are sporadic. Established risk factors associated with GCT are congenital malformations of the urogenital system (cryptorchism, hydrocele, hypospadia) or genetic syndromes with sex chromosome aberrations (Klinefelter's syndrome, gonadal dysgenesis syndrome, Turner syndrome). There have not been reported any environmental risk factors involved in development GCT.

Screening and prevention

There is not any routine screening for GCT performed.

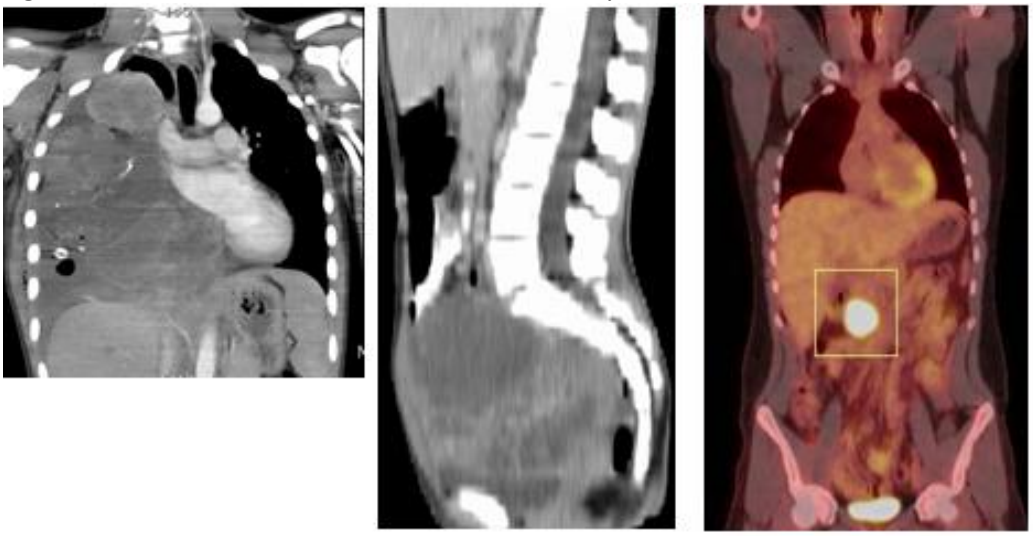
Clinical presentation

Clinical symptoms are related to the location and histological type of the tumour and patient age. Often, the tumour is asymptomatic and the initial presenting symptom is a palpable / visible tumour mass. Local symptoms usually result from malignant compression of the surrounding structures, such as urinary tract obstruction, constipation, cough, dyspnoea or pain. Constitutional symptoms (fever, weight loss, fatigue, sweating, etc.) are rare in GCT. Sometimes, GCT may manifest with endocrine abnormalities and paraneoplastic symptoms (e.g. gynecomastia in testicular GCT).

Diagnosis and staging

Medical history focused on the course of puberty, menarche and menstrual cycle irregularities in girls is essential in the initial diagnostic evaluation. Detailed physical examination should also involve assessment of pubertal development. The primary imaging method used to assess tumour size and character (cystic, solid, presence of calcification, etc.) and its relationship to surrounding structures is usually the ultrasound. 18-FDG PET scan may be helpful to detect tumour dissemination and it is irreplaceable in the evaluation of residual disease after systemic chemotherapy, because of its potential to differentiate vital malignant disease from fibrotic and normal tissues.

Fig. 18: different locations of GCT demonstrated by CT and PET/CT



mediastinální GCT ovariální GCT metastáza do retroperiton LU

Certain types of germinal tumours are characterized by secretion of tumour markers - α-fetoprotein (AFP) and β-subunit of chorionic gonadotropin (HCG). Their initial levels and monitoring during the course of treatment have significant prognostic value. Another important but non-specific marker is serum LDH (lactate dehydrogenase), which correlates with the volume of tumour mass.

Genetic testing including karyotyping and SRY (sex-determining gene in the Y chromosome) testing is indicated if a sex differentiation disorder or gonadal dysgenesis is suspected.

Basic principles of treatment

Primary surgical treatment is recommended in non-metastatic tumours that do not spread beyond the affected organ. In mature teratomas, a standalone surgical resection is the curative method of choice. A fertility-preserving approach (unilateral salpingo-oophorectomy or inguinal unilateral orchiectomy) is the standard of treatment in gonadal GCT.

Patients with metastatic or invasive tumours are treated with preoperative chemotherapy followed by delayed tumour resection. Radical treatment of sacro-coccygeal tumours includes resection of the whole coccyx. In testicular tumours, high inguinal orchiectomy is the mainstay of treatment. Dissection of retroperitoneal lymph nodes is not performed even if they are affected. Most of patients with GCTs receive postoperative multiagent chemotherapy. The intensity of treatment depends on tumour stage and radicality of resection.

There is no role for irradiation in the first or second line treatment due to serious late adverse effects, however, it can be used in a palliative setting.

Prognosis

Germ cell tumours belong to the most curable paediatric malignancies. Their prognosis has dramatically improved after the introduction of cisplatin-based chemotherapy regimen. Five-year survival rate for localized GCT exceeds 95%. Similarly, advanced and metastatic disease convey a favourable prognosis with 5-year overall survival of 85-90%.

Soft tissue sarcomas

Soft tissue sarcomas (STS) constitute a heterogeneous group of tumours that arise from primitive mesenchymal tissue. They account for 7% of all childhood malignancies. STS are divided into two major groups based on their histological pattern:

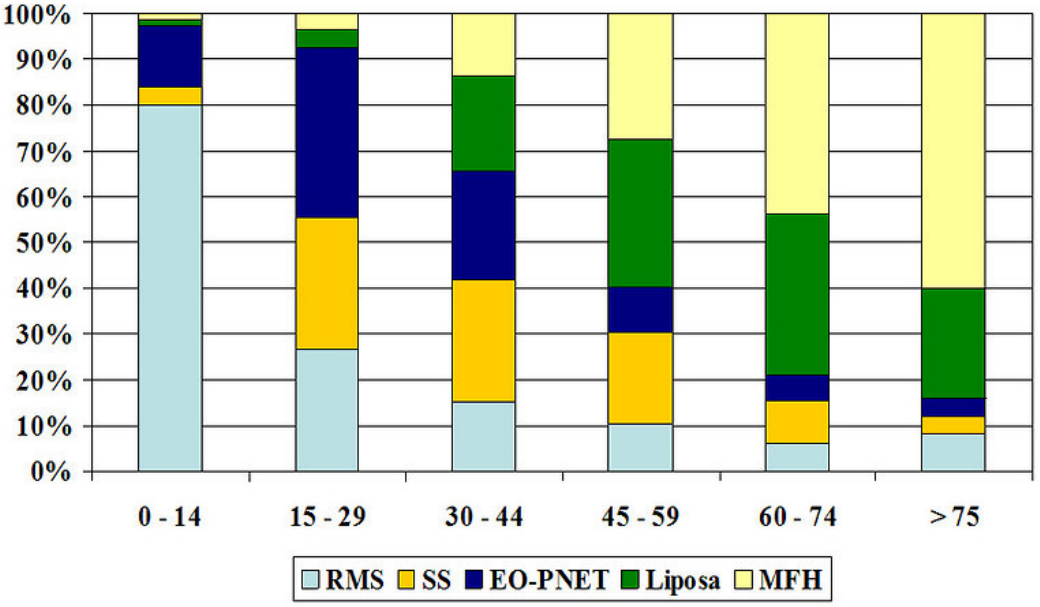
1. rhabdomyosarcoma
2. non-rhabdomyosarcomatous STS (NRSTS)

Morphologically, over 40 different types of STS have been identified. Tumours can develop anywhere in the body and they may occur at any age.

Epidemiology

The annual incidence of soft tissue sarcomas in children is around 0.8 per 100,000, with moderate predominance in boys. The most common and typical paediatric STS is **rhabdomyosarcoma**, representing 50-60 % of all sarcomas in children under the age of 15, with peak incidence between 2 and 6 years of age. NRSTSs account for only around 3 % of all sarcomas. The most common type of paediatric NRSTS is synovial sarcoma, fibrosarcoma or peripheral nerve sheath tumour. NRSTS occur predominantly in adolescents. Distribution of STS subtypes is age-specific.

Fig. No. 19: Age-specific distribution of soft tissue sarcomas



RMS: rhabdomyosarcoma, SS-synovial sarcoma, MFH-malignant fibrous histiocytoma
EO-PNET:extraosseal PNET, liposa – liposarcoma

Correspondingly, location of STS is also age-specific. Infants and toddlers most often present with STS located in the head and neck area (about 40 % of the STS) or urogenital tract (vagina, paratesticular tissues, prostate or bladder). In adolescents, STS are predominantly located in limbs (about 20 % STS), chest wall and retroperitoneum.

Risk factors

As with other paediatric malignancies, the occurrence of STS is sporadic and the etiopathogenesis is unknown. Genetic predisposition syndromes associated with increased risk of STS include Gorlin syndrome, Li Fraumeni syndrome, Beckwith-Wioedemann syndrome, type I neurofibromatosis, RB1 gene mutation, tuberous sclerosis and others.

Environmental factors, which may play a role in STS development through epigenetic changes are exposure to radiation and cytotoxic agents (arsenic, PVC), virus infections (HIV, EBV) or parental use of marijuana.

Screening and prevention

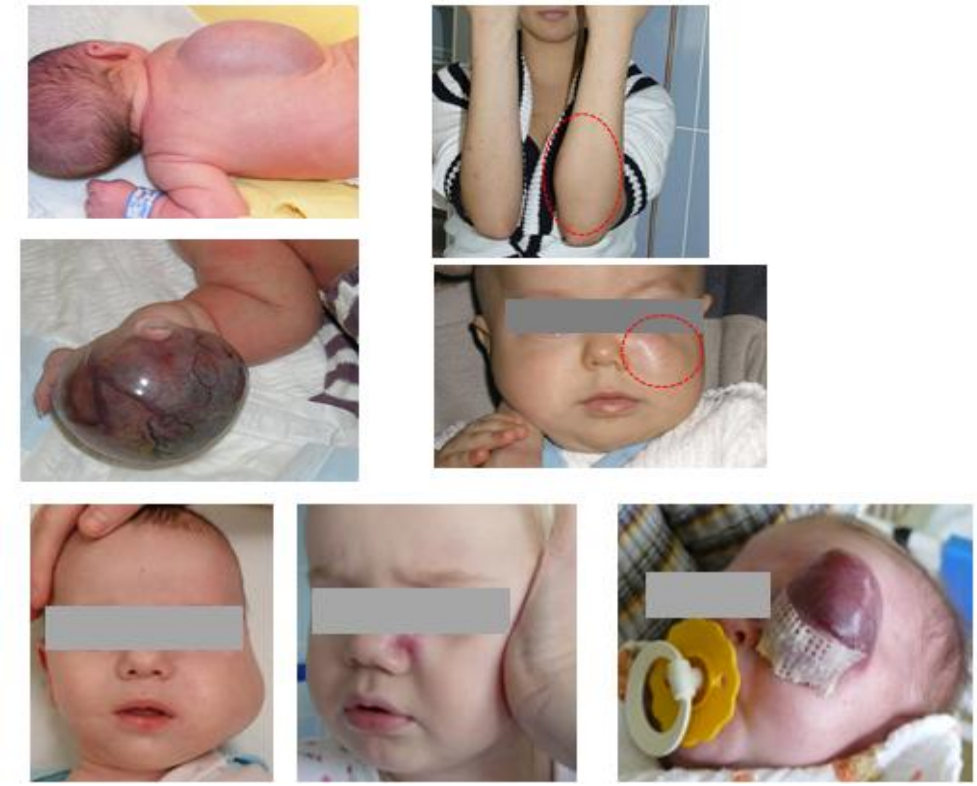
Screening of soft tissue sarcomas is not performed.

Clinical presentation

The diagnosis of STS is often delayed because of a long clinically silent period of tumour growth. Clinical presentation depends primarily on tumour localization, size and growth rate, as well as the child's age at the time of diagnosis. STSs usually manifest as an expanding and mostly painless mass.

Local symptoms, such as pain, erythema or functional impairment appear later in the course of the disease.

Fig. No. 20: Clinical images of soft tissue sarcomas with various locations



Constitutional symptoms (temperature, weight loss, fatigue, sweating) are uncommon. As many as 20% of patients present with symptoms related to metastatic disease (due to the infiltration of cortical bone, bone marrow, lungs or lymph nodes).

Diagnosis and staging

The diagnostic approach is the same for all histological types of STS. A patient with suspected STS should be immediately referred to a tertiary care centre that specializes in care of patients with STS.

Clinically, the primary tumour should be measured in at least two diameters. In addition, the assessment of regional lymph nodes is an essential part of physical examination. There is no specific tumour marker for STS, laboratory studies include CBC and basic blood chemistry, **LDH** might be used as a non-specific marker of tumour load. Aspiration and trephine biopsy of the bone marrow is a standard part of the initial work-up. CT scan should be obtained to assess intrathoracic, intraabdominal or retroperitoneal STS. MRI is preferred in orbital, paraspinal STS or STS localized in extremities. **PET** scan is useful adjunct method for baseline staging, as well as tumour response evaluation. Its sensitivity and specificity for rhabdomyosarcoma is up to 83% and 97%, respectively. Bone scintigraphy can help to verify metastatic bone spread.

Histopathological examination of tumour tissue and bone marrow (in terms of morphology, immunohistochemistry, proliferation rate) is necessary for accurate diagnosis and risk-stratification. To date, tumour microenvironment and PD-L1 expression is also evaluated in advanced tumours. Cytogenetic and molecular genetic testing is a routine part of the initial investigations. It is used to detect specific chromosomal translocations and fusion genes. These molecular characteristics are critical in tumour risk-stratification or in the monitoring of minimal residual disease.

Fig. 21: Specific translocations in soft tissue sarcomas by histological types

Typ sarkomu	Translokace	Chimer. produkt	Prevalence
Alveolární RMS	t(2;13) (q35;q14) t(1;13) (p36;q14) t(X;2) (q13;q35)	PAX3-FKHR PAX7-FKHR PAX3-AFX	60 – 80% 10 – 20% vzácně
Desmoplastický SRCT	t(11;22) (p13;q12)	EWS-WT1	>90%
PNET/ ES	t(11;22) (q24; q12) t(21;22) (q22; q12) t(7;22) (p22; q12)	EWS-FLI1 EWS-ERG EWS-ETV1	85 -95% 5 – 10% vzácně
Synoviální sarkom	t(X;18) (p11;q11)	SYT-SSX1 SYT-SSX2	65% 35%
Alveolar soft part sarkom	t(X;17)(p11;q25)	ASPL-TFE3	>90%
Clear cell sarkom	t(12;22)(q13;q12) t(2;22) (q32;q12)	EWS-ATF1 EWS-CREB1	> 90% vzácně
Infantilní fibrosarkom	t(12;15)	ETV6-NTRK3	80 -90%
Myxoidní liposarkom	t(12;16)(q13;q12) t(12;22)(q13;q12)	TLS-CHOP EWS-CHOP	95% vzácně

Basic principles of treatment

The treatment of STS is often multidisciplinary. Surgical resection is the curative method of choice in localized low-grade sarcomas. For high-grade malignant sarcomas (the vast majority of paediatric STSs), the primary goal of surgical treatment is a **radical resection** with at least 1-cm wide margin of healthy tissue, without unacceptable disfigurement or loss of function. Unresectable tumours are indicated for initial biopsy and second-look surgery after a period of neoadjuvant chemotherapy.

Basically all patients with rhabdomyosarcoma require **chemotherapy**, regimens and the duration of treatment vary depending on the stage and risk group. NRSTSs are less chemosensitive, however, chemotherapy has been shown to improve overall survival also in these patients and thus, it is currently a standard part of treatment.

Radiotherapy is crucial for local tumour control, especially in sarcomas with postoperative residual disease or in metastatic STS. The recommended dose in rhabdomyosarcoma is 50Gy and it should not be less than 40Gy.

Prognosis

Five-year overall survival in patients after complete resection (IRS Group I) is more than 85%. Patients with macroscopic residual tumour and metastatic disease have a 5-year survival rate of 50% and 20%, respectively. Factors that influence prognosis are patient age (>10 years is an adverse prognostic factor), histological type of sarcoma, its location and the extent of the disease (clinical stage).

Bone tumours

Bone tumours comprise a wide range of pathological lesions of both benign and malignant character. This chapter does not address non-malignant bone lesions (vascular, inflammatory or pseudo-inflammatory), though they have an important role in differential diagnosis of bone tumours.

The type of bone tumour, its location and character (osteolytic, osteosclerotic or mixed) is often age-dependent. Primary bone tumours represent the sixth most common paediatric malignancy, accounting for about 5% of all tumour types. In adolescents, they are the third most frequent tumour. Most common malignant bone tumours in children are osteosarcoma and Ewing sarcoma.

Besides primary bone tumours, skeleton is often the site of metastatic spread of other malignancies, primarily neuroblastoma, rhabdomyosarcoma or clear cell kidney sarcoma.

Osteosarcoma

Osteosarcoma is a malignant bone sarcoma derived from primitive mesenchymal bone-forming cell, characterized by production of osteoid and immature bone tissue. Osteosarcoma represents 5% of all malignant tumours in children under 15 years of age.

Up to 80% of osteosarcomas are located **in the long bones of the extremities**, near metaphyseal joint plates, with **52% of tumours in the distal femur**, 20% in the proximal tibia and 10% in the proximal humerus. Other less common locations include pelvis, shoulder or mandible, but the tumour can develop basically anywhere throughout the skeleton.

Epidemiology

Osteosarcoma is rarely diagnosed in children under 6 years of age. The highest incidence is in the adolescence, with significant male preponderance. In the age group between 12 and 20 years, osteosarcoma is the fourth most common tumour and accounts for up to 60% of all bone tumours.

Risk factors

Aetiology and pathogenesis of OSA remains largely unknown, the incidence is sporadic. Only a few risk factors have been identified in association with osteosarcoma - growth spurt in adolescents,

benign pre-existing bone diseases (hereditary multiple osteochondromas, fibrous dysplasia, enchondromas, etc.), or Paget disease in the elderly. Genetic factors increasing the risk of osteosarcoma are Li Fraumeni syndrome, Bloom syndrome and, above all, mutations of the RB1 gene. Exposure to ionizing radiation (> 20Gy) is an established environmental risk factor, the aetiopathogenetic contribution of virus infection or the history of trauma has not been convincingly proven.

Screening and prevention

Screening for osteosarcoma is not performed.

Clinical presentation

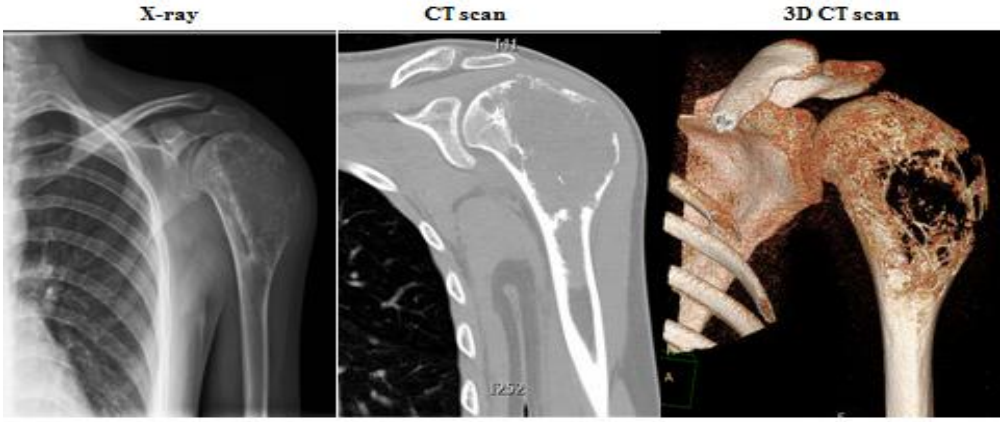
The first signs of osteosarcoma usually remain unrecognized or underestimated and a significant delay before the diagnosis is frequent in these tumours. Most common local symptoms include **pain at the site of the tumour.** Initially, it may be intermittent, more pronounced **at night**, later, the pain is usually associated with activity of the afflicted limb. Swelling can often develop after the initial complain of pain. If the tumour affects lower extremities, patients may present with gait disturbances. Rarely, the initial manifestation of the tumour is a pathological fracture. OSA spread mainly by haematogenous route, lymphadenopathy is rather uncommon. Lungs are the main site of metastasis, resulting in respiratory symptoms such as cough, tachypnoea, or dyspnoea. Constitutional symptoms are rare in osteosarcomas.

Diagnosis and staging

Physical examination usually reveals a palpable tender mass. If the tumour is located in extremities, a contralateral limb should always be thoroughly examined as a reference for assessment of function and shape.

Plain X-ray may delineate the extent of the tumour, the character of bone destruction (osteolytic vs. osteoblastic), reaction of the adjacent periosteum (characteristic Codman triangle) or joint involvement. For detailed evaluation of the primary lesion, further imaging studies should be obtained. MRI is the preferred method for the assessment of bone marrow and soft tissue involvement. It is also essential for subsequent surgery planning.

Fig. 22: Various imaging modalities showing an osteosarcoma of the left proximal humerus



CT scan and bone scintigraphy play an important role in tumour staging. Chest CT scan is the method of choice for the detection of lung metastases. Given the rare character and the large number of histologic subtypes of paediatric osteosarcomas, histopathological examination of the tumour should be performed by an experienced pathologist within an oncology centre specialized in the diagnosis and treatment of musculoskeletal tumours.

Osteosarcoma staging is based on the presence of metastases and histopathological character of the tumour. Three stages of OSA are recognized: localized low-grade OSA, localized high-grade OSA and metastatic OSA. The conventional TNM staging system is not used due to the absence of nodal spread.

Basic principles of treatment

The standard treatment approach consists of **neoadjuvant (preoperative) chemotherapy** followed by **surgery** and subsequent **adjuvant chemotherapy.**

The main goal of surgery is a safe and complete tumour resection with a minimal loss of function. Yet, radical resection of the tumour (R0 resection) is critical for achieving a long-term survival. The type of surgical procedure depends on the location and extent of the tumour. In certain tumours, amputation may be the treatment of choice, however, in almost 94% of patients with OSA, limb salvage surgery is the preferred option. Amputation is indicated only in about 6% of all paediatric patients with OSA, particularly in the case of tumour necrosis, the presence of a pathological fracture with vascular and nerve damage and as a palliative procedure in tumours with high risk of massive haemorrhage. Pelvic location of OSA is extremely unfavourable for a radical resection and hemipelvectomy may be required for appropriate tumour control.

Definitive tumour resection is usually followed by a reconstruction surgery. For optimal treatment outcomes, all surgical procedures should be conducted within a tertiary health care institution with sufficient expertise.

Multiagent chemotherapy is based on a combination of high-dose methotrexate, doxorubicin, cisplatin and ifosfamide. All current treatment protocols recommend the administration of neoadjuvant chemotherapy followed by delayed surgery after 10 weeks of systemic treatment. The histological response of the tumour to chemotherapy (good responder> 90% necrosis, poor responder <90% necrosis) is one of the most important prognostic factors in OSA.

Due to the high level of tumour resistance to radiotherapy, this modality has only a marginal role in the treatment strategy. It is indicated in cases where radical resection of the tumour is not possible or in the palliative setting for pain management and control of tumour bleeding.

Prognosis

The most common adverse prognostic factors are axial location of the tumour (pelvis, skull, spine), tumour size, the presence of pathological fracture, age over 10 years, male gender, soft tissue extension and metastatic disease (lung metastases> bone metastases). Tumour response to neoadjuvant chemotherapy (indicated by the amount of necrosis) is another important prognostic parameter.

The five-year survival rate for localized osteosarcoma is 65-70%, for OSA with resectable lung metastases it is approximately 55-65%. Disseminated osteosarcoma has a very poor prognosis with a 5-year survival rate of less than 10%.

Ewing sarcoma / PNET tumours

Ewing sarcoma family of tumours comprises several diagnoses that share particular genetic or biological features. These malignancies are considered to be of similar neuroectodermal origin and they may arise from bones or surrounding soft tissues.

Ewing sarcoma family of tumours or PNET tumours (primitive neuroectodermal tumours) include:

1. Ewing sarcoma (ES), which is the most common representative of the PNET group of tumours.
2. Extra-osseous Ewing sarcoma (EOS) that arises from soft tissues surrounding bones.
3. Peripheral primitive neuroectodermal tumours (pPNET) that may develop in both bones and soft tissues. If located in the chest wall, we speak of Askin tumour.

ES most commonly affects the **diaphysis of long bones** (in contrast to osteosarcoma, which is typically located in the epiphyseal region). **Pelvic** involvement is significantly more common compared to osteosarcoma (up to 25%), whereas 4% of PNETs are located in the head and neck area.

Epidemiology

Ewing sarcoma accounts for 10-15% of primary bone tumours and it is the second most common bone malignancy in adolescents. The annual incidence is around 1.5 – 3 per million children. Boys are afflicted more often than girls are. The age distribution of ES is bimodal with peaks around the age of 5 years and in the second decade of life.

Risk factors

Basically all Ewing sarcomas are sporadic without any clear underlying cause. The impact of environmental risk factors (irradiation, exposure to chemical elements, diet, etc.) on the pathogenesis of ES has not been confirmed, nor were any hereditary and genetic risk factors associated with a higher risk of ES. Familial occurrence is rare.

Screening and prevention

There is no available screening for Ewing sarcoma.

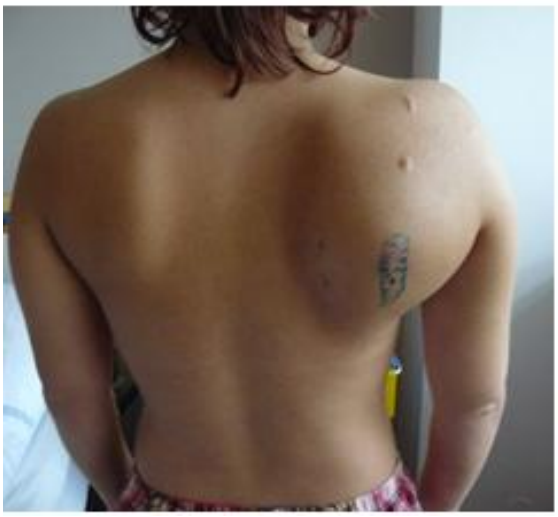
Clinical features

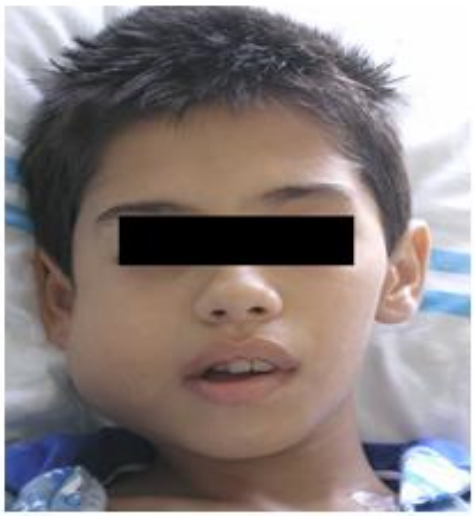
Local symptoms depend on the site and size of the tumour. The most common sign of ES is local **pain and swelling** due to mass effect. Night pain with an **"on – off"** character is typical. Other manifestations include palpable or visible tumour mass, gait disturbances or impairment of function. Pathological fracture is unusual. Pelvic tumours can present with symptoms related to mass compression of surrounding organs (intestine, urinary tract). The median duration of symptoms is usually 4 - 6 months.

In contrast to osteosarcoma, constitutional symptoms are comparatively common and include fever irresponsive to antibiotics, weight loss, night sweats, fatigue, loss of appetite, and overall weakness. Laboratory tests may reveal elevation of inflammatory parameters (FW, CRP) and LDH.

Up to 25% of patients are diagnosed with a metastatic disease (lungs, skeleton, bone marrow) and present with symptoms associated with a particular location of metastatic spread (cough, tachypnoea, thrombocytopenia, bone pain).

Fig. 23: Clinical appearance of Ewing sarcoma





Diagnosis and staging

The duration of symptoms (often in the order of months) might be important in the differential diagnosis of ES. Laboratory investigations usually reveal elevated ESR and markers of inflammation. Anaemia and / or thrombocytopenia are indicative of bone marrow infiltration. The baseline serum lactate dehydrogenase (LDH) levels have a prognostic value. In certain types of tumours, neuron-specific enolase (NSE) may be elevated.

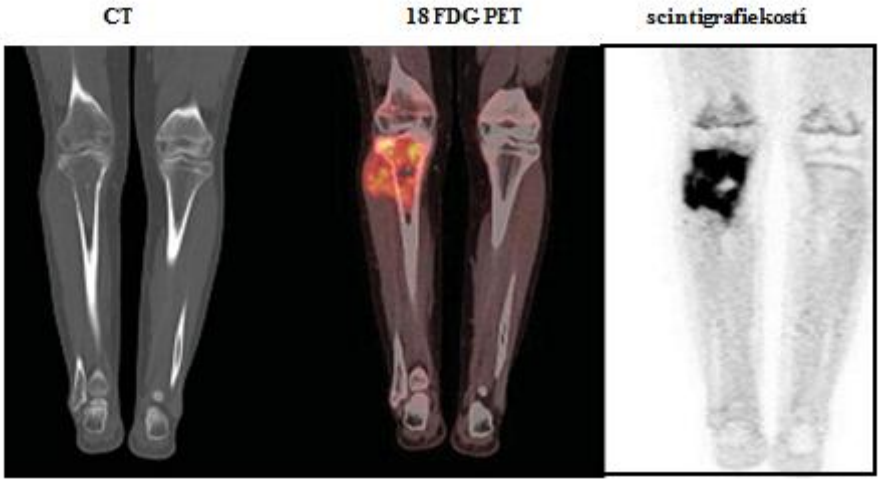
The initial evaluation should also include bone marrow aspiration and trephine biopsy.

Plain X-ray typically shows mixed diaphyseal lytic-sclerotic bone lesions and multilayer subperiosteal reactions (so-called onion skin appearance). It is always necessary to examine the entire bone and adjacent joint in order to rule out skip lesions or joint involvement. MRI is the best method for exact tumour delineation and evaluation of intramedullary disease, soft tissue involvement as well as the tumour relationship to an adjacent neurovascular bundle.

Currently, 18-FDG PET scan is the primary method for ES staging. Tumour activity on PET scan is considered to have an important predictive and prognostic value. Bone scintigraphy may be used to detect polyostotic bone lesions and bone metastases.

Based on findings of the staging procedures examinations, three major groups of Ewing's sarcoma are distinguished: localized disease, locally advanced disease and metastatic disease.

Fig. 24: Ewing sarcoma of proximal tibia on imaging examinations



Definitive diagnosis is confirmed by histopathological examination (including morphological, and immunohistochemical assessment).

Cytogenetic analyses may reveal a typical **Ewing sarcoma-specific translocation** (in 90-95% of patients) that involves **EWS gene (22q12) and FLI-1 (11q24)**. Bone marrow and peripheral blood samples are also tested for these translocations for the purpose of tumour response evaluation and monitoring of minimal residual disease after the treatment.

Basic principles of treatment

Tumour management requires a multidisciplinary approach and all patients with suspected Ewing sarcoma should therefore be referred to a health care institution specialized in the treatment of musculoskeletal tumours. The main therapeutic goal is to eliminate tumour mass, prevent recurrence of the disease and, if possible, preserve the function of the affected limb. The treatment strategy is dictated by the location and extent of the disease.

The role of **surgery** is both diagnostic (open tumour biopsy) and therapeutic - radical resection of the primary tumour. Local management of Ewing sarcoma is the main prerequisite for a favourable treatment outcome and patient prognosis. Radical resection, if possible, is preferred to local radiotherapy. If the tumour affects an extremity, a limb-salvage procedure is favoured. Otherwise, the indications for amputation are the same as in osteosarcoma, with the exception of pathological fracture, which is no longer indicated for primary amputation. Radical resection is usually preceded by six blocks of neoadjuvant chemotherapy.

The prognosis of Ewing sarcoma has considerably improved with the introduction of systemic **chemotherapy**. With the administration of neoadjuvant chemotherapy, a significant reduction of tumour mass as well as substantial eradication of potential micrometastases is achieved. The histological response to neoadjuvant chemotherapy is a key predictive and prognostic factor. The

intensity of postoperative chemotherapy depends on the histological response, the initial extent of the disease and the character of surgical treatment. Patients with metastatic disease and high-risk patients are indicated for high-dose adjuvant chemotherapy with autologous transplantation of peripheral stem cells.

Radiotherapy plays an important role in the local control of Ewing sarcoma. It can be used in combination with chemotherapy with curative intent or in palliative setting for pain management or irradiation of metastasis.

Prognosis

5-year survival rate for localized disease is 70 %, for metastatic disease ES with lung involvement it is 30%. Patients with extensive tumour dissemination (bone, bone marrow) have very poor prognosis, only less than 5% will survive for 5 years or more.

Recommended literature

For deeper insight into clinical oncology, the following publications are recommended:

Web Links:

1. Czech Best Practices (Blue Book of the Czech Cancer Society): http://www.linkos.cz/information-pro-praxi/modra-kniha/
2. American Recommended Treatment Procedures (NCCN Guidelines) www.nccn.org
3. European Recommended Therapeutic Procedures (ESMO Guidelines) http://www.esmo.org/Guidelines
4. Epidemiological Data on Cancer Diseases in the Czech Republic: www.svod.cz

Monographies:

1. Tomasek, J. et al. Oncology. Minimum for practice. Axonite, 2015, 445s.
2. Šlampa, P. et al. c. Third updated edition. MOÚ Brno, 2011, 312s.
3. DeVita V., Lawrence, ST., Rossenberg SA, Principles and Practice of Oncology, 10th Edition, Wolters Kluwer, 2014, 2280s.