



PHYSICAL ACTIVITY
AS AN EFFICIENT MEANS
OF NON-PHARMACOLOGICAL
CARE IN ONCOLOGY

KATEŘINA KAPOUNKOVÁ
AND COLLECTIVE OF AUTHORS

MASARYK
UNIVERSITY
PRESS

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Masaryk University Press

Brno 2024

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Podpořeno z programového projektu Ministerstva zdravotnictví ČR s reg. č. NU21-09-00558. Veškerá práva podle předpisů na ochranu duševního vlastnictví jsou vyhrazena.

Supported by Ministry of Health of the Czech Republic, grant nr. NU21-09-00558. All rights reserved.

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ISBN 978-80-280-0541-2 (online ; pdf)

ISBN 978-80-280-0540-5 (paperback)

ISBN 978-80-210-9787-2 (Czech ed. ; online ; pdf)

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FOREWORD

Significance of physical exercise for human health had been known to doctors since the Ancient Times. Proof of the link between physical activity and prevention of malignity occurrence first appeared more than 100 years ago and first physical activity recommendations were created in the year of 1950 short after the American College of Sports Medicine (ACSM) came into being. Despite the long history, the term of physical activity as prevention or therapy of tumours was known only to a small circle of scientists, which remained that way to the beginning of the 21st century. Nowadays, the theme of using physical activity as non-pharmacological means is becoming topical again and it has been reacted to by many professional medical societies (e.g. American College of Sports Medicine, 2017, World Cancer Research Fund/American Institute for Cancer Research, 2010).

It is becoming clear that regular physical activity relates to significant benefits for human health and that physical intervention could become one of the pillars of non-pharmacological treatment of tumorous diseases.

This material has been created due to the absence of similar material in the local market. Currently, there is no similar complex text in Czech language.

The theoretical part of the monography speaks about the subject matter of the occurrence of oncology diseases, biological effects of both tumours as well as therapy upon the organism. A significant part is dedicated to the existing research in the possible influence of directed physical activity upon human organism as well as the description of physical interventions.

The second part of the monography deals with the previous research, which is the area that has been the focus of the authors for many years.

1 Theoretical part

1.1 Oncological diseases epidemiology

Iva Hrnčířiková

The chances of survival in oncology patients has increased significantly thanks to early detection of oncological diseases, highly specialised and targeted treatment, and operation of comprehensive oncology centres. Even though occurrence of oncological diseases is on the rise (in the Czech Republic in 2011 +32 % in males, +22.8 % in females when compared with 2001), oncological diseases mortality has been increasing (in the Czech Republic in 2011 –4.7 % in males and –5.6 % in females when compared with 2001).

Oncological treatment carries various health consequences and reduces the quality of life of survivors. Therefore, it is essential to focus on follow-up care for oncology patients to improve their quality of life.

On average 87,000 malignant tumours are diagnosed every year in the Czech Republic (in 2017 there were 86,819 patients). Approximately 27,000 patients die of malignant tumour annually (in 2017 there were 27,320 patients). In total there are about 600,000 people in the Czech Republic with a malignant neoplasm or a history of the disease. (<https://www.linkos.cz/narodni-onkologicky-program/co-musite-vedet/ceska-republika-a-rakovina-v-cislech/>)

The incidence of malignant neoplasms in the Czech Republic has been increasing in the long-term. The most frequent newly diagnosed malignant disease in 2017 were **skin tumours excluding melanoma**, i.e., bazaliomas and squamous cell carcinomas. Thanks to the prognostically relatively favourable nature of the disease and their frequent early diagnosis, the mortality rate for this type of malignant tumours is consistently very low.

The incidence rate is higher in men than in women. The prevention of this disease is primarily limiting UV exposure and screening for skin changes.

Other most frequent diagnoses include **colorectal and rectal carcinoma, prostate malignant tumours in men, breast carcinoma in women and tumours of trachea bronchus and lungs** (<https://www.linkos.cz/narodni-onkologicky-program/co-musite-vedet/ceska-republika-a-rakovina-v-cislech/>).

The increasing number of reported cases is probably related to the increasing average age of the population (life expectancy at birth). Age is the major risk factor for malignancies, partly due to the cumulative effect of risk factors.

Other possible influences on the increasing absolute incidence are the higher incidence of both physical and chemical carcinogens. Paradoxically, it is the improved malignant neoplasm diagnostics and the overall quality of medical care that contribute to the increased number. Mammography screening (breast cancer in women) was officially launched in the Czech Republic in 2002, cervical screening (cervical cancer in 2008 and colorectal carcinoma screening in January 2009 (<https://www.linkos.cz/narodni-onkologicky-program/co-musite-vedet/ceska-republika-a-rakovina-v-cislech/>)).

In 2016, a total of 96,500 cases of malignant neoplasms and neoplasms in situ (dg. (diagnosis number) C00–C97 and D00–D09 according to MKN-10), were newly reported to the National Cancer Registry of the Czech Republic (NCR) out of which 49,302 cases were in men and 47,198 cases were in women.

Positive trends of stagnation or even a slight decline in some major diagnoses (lung cancer in men, colorectal cancer) are offset by an increase in breast cancer in women and by an increase in skin cancer in both sexes. Mortality from cancer has shown a relatively clear decline since 2003.

Since 1979 in situ neoplasms (pre-invasive tumours) have been monitored in the National Cancer Registry. This is the initial state of malignancy, i.e., the pre-malignant state, when the cells that make up the lesion show certain atypia (failure of differentiation, mitotic figures) but are still localized intraepithelially and do not penetrate deep into the surrounding tissue. This is crucial for the patient as an individual with the tumour in situ should not have any metastases (Novotvary, 2016).

1.1.1 Malignant neoplasm of the colon and rectum

one of the most common oncological diagnoses in the Czech Republic is malignant neoplasm of **the colon and rectum (dg. C18–C20)**. Globally, the Czech Republic has the sixth highest incidence of this disease. In 2016, 7,610 colorectal malignities were reported (i.e., a slight absolute decrease compared to the previous year). Of these, there were 4,582 cases in men (i.e., 88.2 cases per 100,000 men) and 3,028 cases in women (i.e., 56.4 cases per 100,000 women). In both sexes, colorectal cancer is the second most common cancer diagnosis after prostate cancer in men and breast cancer in women, after exclusion of “other malignant neoplasm of the skin“ (dg. C44). In 57 % of cases in men and 67 % in

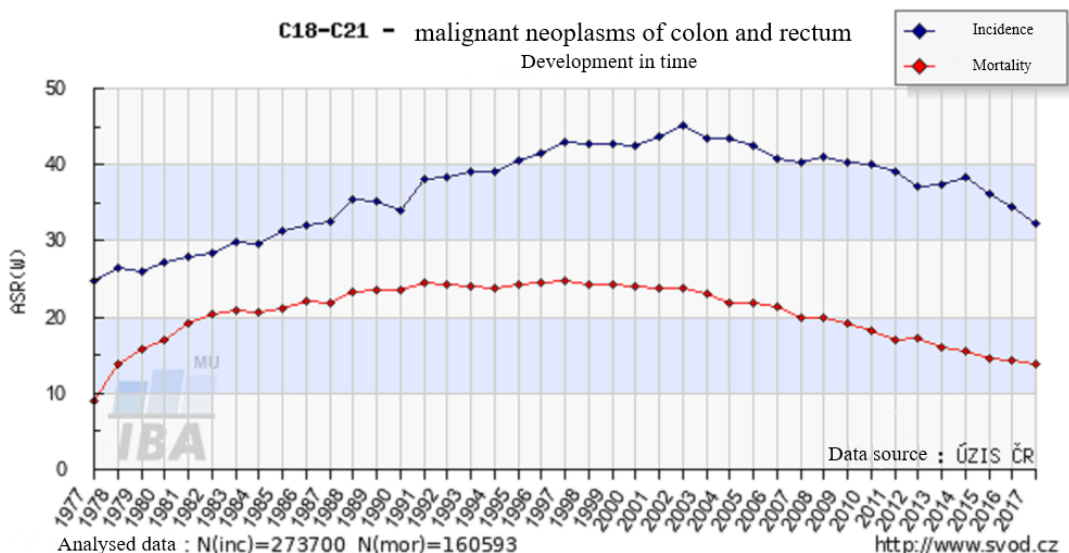


Fig 1 Incidence and mortality of malignant neoplasms of colon and rectum (Dušek et al., 2018)

women, the neoplasm is located in the colon (dg. C18). Compared to 2015 the standardised incidence rates for both men and women have decreased slightly (Neoplasms 2016).

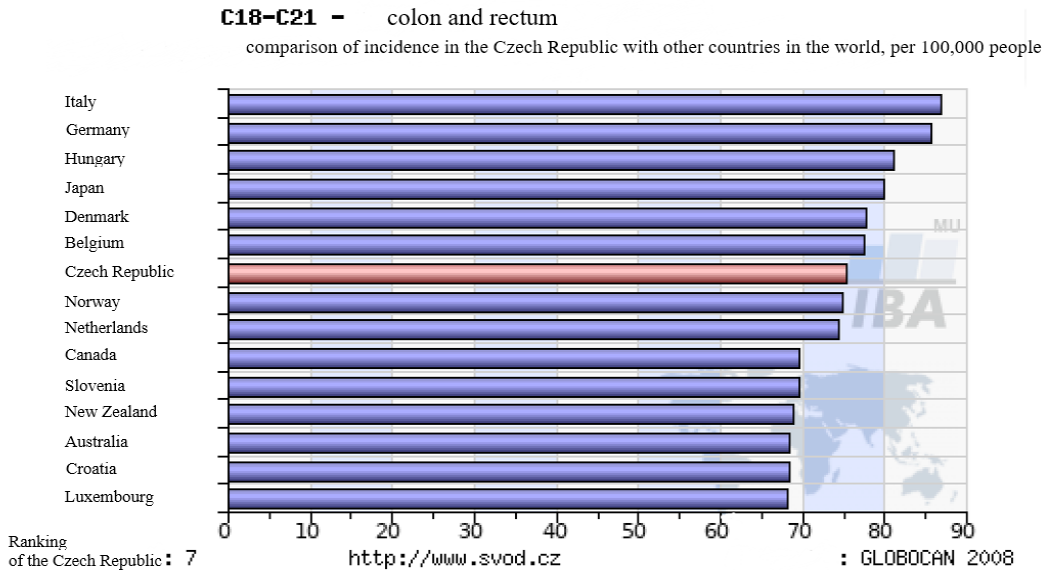


Fig 2 Comparison of the incidence of malignant neoplasms of colon and rectum globally and in the Czech Republic ČR (Dušek et al., 2018)

In terms of age distribution, more than four fifth (82 %) of colorectal malignities are reported in people over 60 years of age. The mean age at diagnosis is higher in women than in men (70 vs. 69 years of age). Most cases were reported in men and women aged 70–74 years of age.

1.1.2 Malignant neoplasm of the lungs

Malignant neoplasms of the trachea, bronchus, and lungs (dg. C33–C34) is the second most commonly occurring malignity. In 2016 a total of 6,782 cases of tumours of this localisation were reported in the Czech Republic (3 % more than in 2015). The prevalence of this type of cancer is higher in men (4,478 cases, i.e., 86.2 cases per 100,000 men) in comparison with the occurrence in women (2,304 cases, i.e., 42.9 cases per 100,000 women). Most cases are detected at an advanced stage. It is the most common cause of death in cancer patients (Neoplasms 2016).

1.1.3 Malignant neoplasm of the breast

Malignant neoplasm of the breast (dg. C50) was the most common cancer in women (except for dg. C44) in 2016. The 7,220 new cases detected (134.4 cases per 100,000 women) represented almost 18.0 % of all reported malignities in women (dg. C00–C97).

Probably in connection with the screening programme, the number of detected in situ breast (dg. D05) has also increased in recent years, in 2016, as in the previous year, 649 cases were registered (i.e., an increase of 41.1 % compared to 2011).

Although the treatment of breast cancer is very successful, especially in the early stages (relative 5-year survival of treated patients is almost 100 % in clinical stage I, and almost 90 % II), breast cancer remains one of the most common causes of cancer deaths in women (second most common after trachea, bronchus, and lung cancer). In 2016 1,685 women died of breast cancer, i.e., 76 more than in the previous year (Neoplasms 2016).

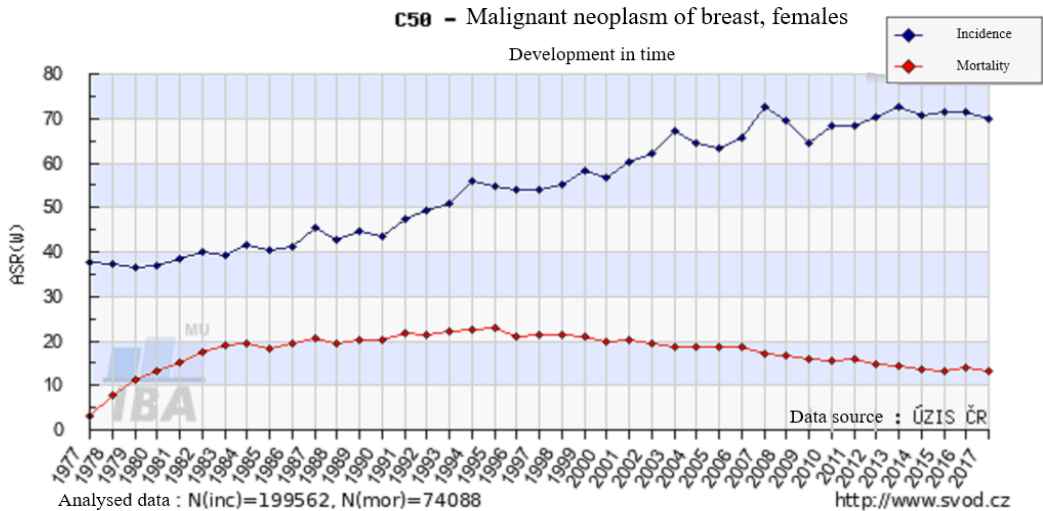


Fig. 3 Incidence and mortality of the malignant neoplasm of the breast (Dušek et al., 2018)

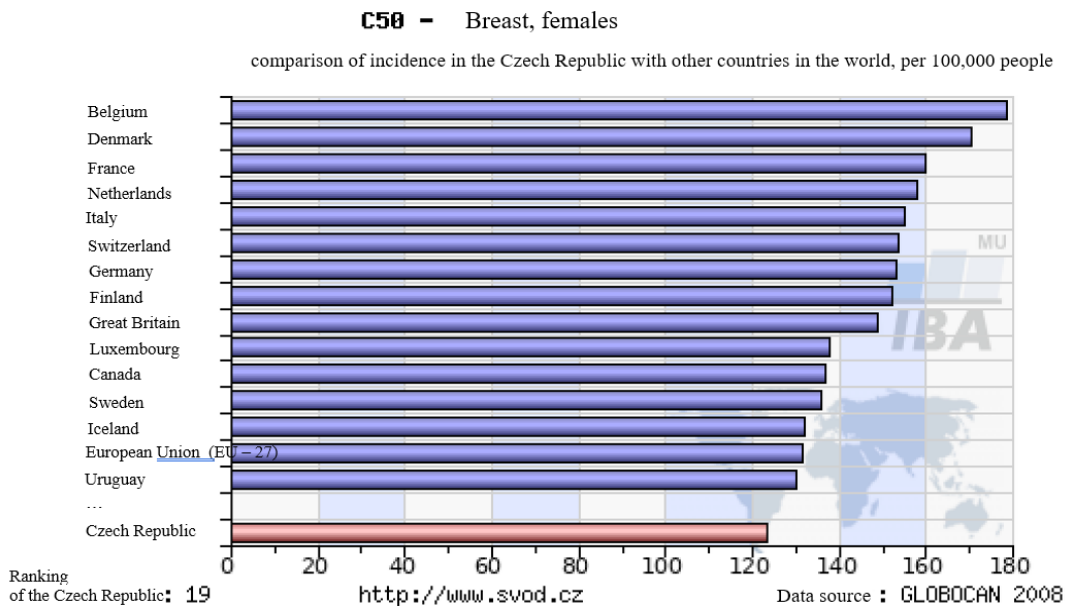


Fig. 4 Comparing the incidence of the malignant neoplasm of the breast in the world and in the Czech Republic (Dušek et al., 2018)

1.1.4 The malignant neoplasm of the prostate

The most frequent malignant tumour in men (except for the diagnosis C44) has been since 2005 the malignant neoplasm of the prostate (dg. C61). In 2016 there were 7,305 cases of the malignant neoplasm of the prostate (i.e., an increase in cases of approximately 3 % when compared with the year of 2015), per capita it was 140.7 cases in 100,000 men. A rapid increase of the malignant neoplasm of the prostate has been monitored since the early 1990s. Currently, it is stabilised. The standardised prostate cancer mortality rate has been declining since 2004, in recent years is stabilised. In 2016, 1,421 men died of the diagnosis C61 in the Czech Republic (27.4 per 100,000 men).

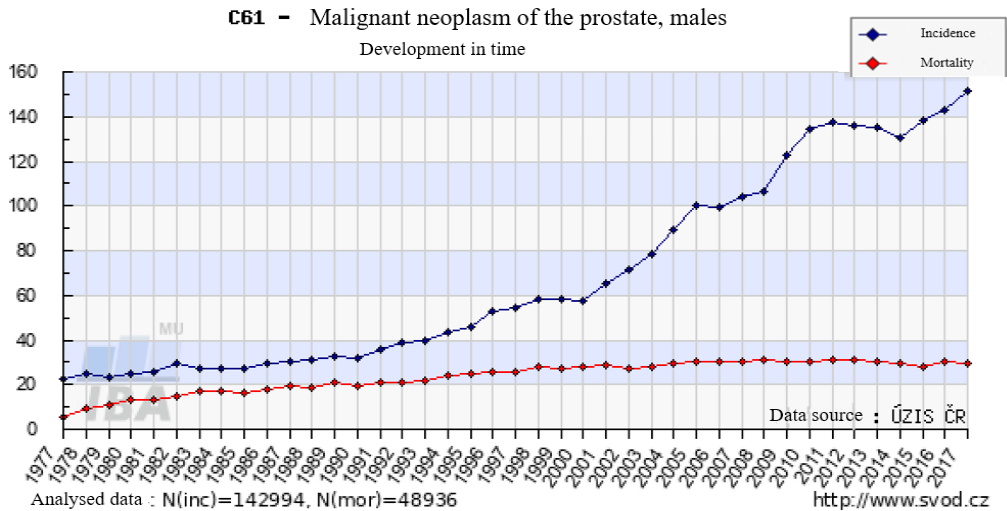


Fig. 5 Incidence and mortality of the malignant neoplasm of the prostate (Dušek et al., 2018)

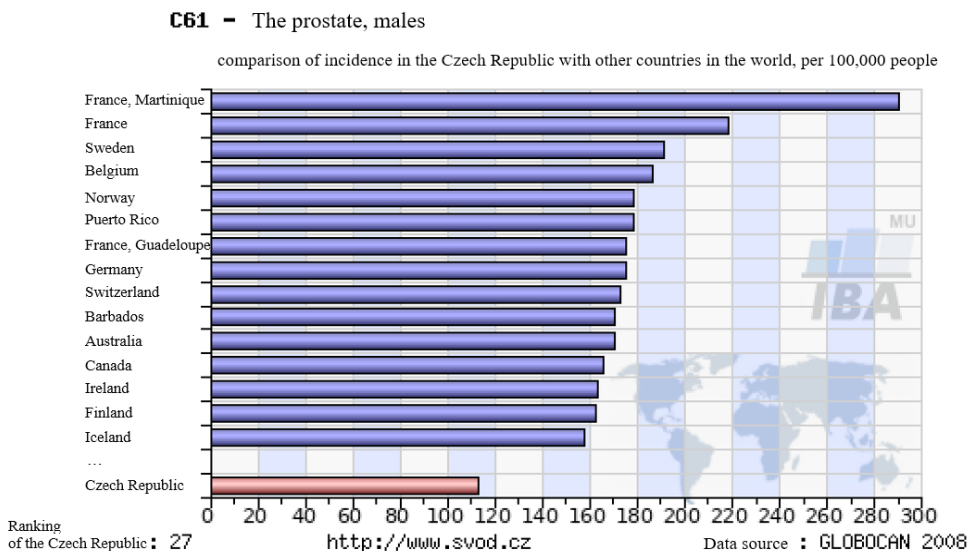


Fig. 6 Comparing the incidence of the malignant neoplasm of the prostate in the world and in the Czech Republic (Dušek et al., 2005)

1.1.5 Other common tumours

Other common malignancies in men in 2016 included renal cancer (dg. C64) with 2,000 cases, bladder cancer (dg. C67) with 1,559 cases, cutaneous melanoma (dg. C43) with 1,404 cases, oral cavity, and pharynx cancer (dg. C00–C14) with 1,167 cases and pancreatic cancer (dg. C25) with 1,165 newly reported cases.

In women, the most common cancers, apart from breast, colorectal and lung cancer, were uterine cancer (dg. C54 and C55) with 2,012 cases, cutaneous melanoma (dg. C43) with 1,205 cases, kidney cancer (dg. C64) with 1,202 cases, pancreatic cancer (dg. C25) with 1,078 cases and ovarian cancer (dg. C56) with 998 newly reported cases.

1.2 Consequences and late complications of oncology treatment

Jana Halámková

Anticancer treatment is a series of therapeutic modalities that can be combined with each other. It is divided into local treatment: surgical treatment, radiotherapy, local ablation methods (e.g. chemoembolization methods, radiofrequency ablation, etc.) and systemic treatment: chemotherapy, targeted therapy, immunotherapy, hormonal therapy. The majority of side effects stem from systemic therapy. The most common adverse effects include cardiotoxicity, haematological toxicity, nausea and vomiting, neurotoxicity, pulmonary toxicity, hepatotoxicity, nephrotoxicity, skin toxicity secondary tumour formation, fatigue, weakness, bones density.

1.2.1 Cardiotoxicity

Cytostatics from the anthracycline group (doxorubicin, epirubicin, daunomycin) are most frequently cardiotoxic, less frequently antracenoids (mitoxantron). Alkylating agents are cardiotoxic especially in higher doses (cyklofosamid, ifosamid). Rarely, this side effects are also encountered after administration of 5-fluorouracil, mitomycin C, cisplatin, vinkristin, bleomycin and paklitaxel. Recently, cardiotoxicity has also been described in targeted anticancer therapies, especially anti-HER2 agents (trastuzumab, pertuzumab, trastuzumab emtansin, lapatinib).

We consider cardiotoxicity to be an echocardiographic finding:

- a) a decrease in ejection fraction (LVEF) of 10 % or more; or
- b) a decrease in LVEF below 50 % (Zamorano et al., 2016).

The main risk factors of cardiotoxicity include: cardiac disease, reduced left ventricular ejection fraction below 50 %, previous treatment with anthracyclines with a high cumulative dose, uncontrolled or poorly controlled arterial hypertension, ischaemic heart disease, significant valvular defect, certain arrhythmias and higher BMI (Ewer et al., 2005).

A group of endothelial growth hormone (VEGF) inhibitors can lead to exacerbation of left ventricular dysfunction, coronary artery disease and hypertension. In case of clinical symptomatology examination by a cardiologist is necessary.

The treatment of heart failure resulting from the administration of cardiotoxic drugs is no different from the treatment of heart failure due to other causes. Can be observed with several targeted agents (e.g. sorafenib, cabozantinib, sunitinib, pazopanib, dabrafenib, vemurafenib, ribociclib, etc.), which result in prolongation of the normalized QT interval (QTc interval). Finally, myocarditis or pericardial damage related to immunotherapy (e.g. ipilimumab, nivolumab, etc.) should be mentioned. Side effects may occur during treatment (*acute toxicity*), immediately with cessation of the treatment (*subacute toxicity*), months after cessation of the treatment (*chronic toxicity*) or as late effects many years after the cessation of the treatment (*late toxicity*) (Halámková, Novotný, and Vydrošová, 2016).

1.2.2 Haematological toxicity

Haematological toxicity is one of the most common side effects of systemic cancer therapy. It is encountered with practically most cytostatics. It is most frequently observed after alkylating cytostatics.

Neutropenia (neutrophil decline) can be asymptomatic, caught incidentally, when the patient is without any clinical symptoms, or febrile, when neutrophil decline is complicated by increased temperature and infectious state. The treatment of febrile neutropenia is urgent, given the risk of septic complications that may result in septic shock.

A common side effect of systemic treatment is anaemia, which leads to decline in performance, fatigue and has a significant impact on quality of life.

Thrombocytopenia, a platelet deficiency, results in increased bleeding, which is manifested by the formation of hematomas, suffusions, petechiae and can lead to severe bleeding. In the case of thrombocytopenia, the patient must take increased caution against possible injury.

As the number of cycles of chemotherapy increases, the haematopoietic reserve of the bone marrow is gradually depleted, and the percentage of serious side effects increases.

1.2.3 Nausea and vomiting after anticancer treatment

Nausea and vomiting are among the most common side effects of cytostatics and radiation. Even if these are frequently short-term problems, they can significantly reduce quality of life. There are now several preparations, which in combination are sufficiently effective in preventing nausea and vomiting.

Acute vomiting (within 24 hours) occurs as early as a few hours starting cytostatic treatment or later, within 9–18 hours.

Delayed vomiting usually occurs on days 2 to 5 after the start of chemotherapy, but in many cases it is a continuing acute vomiting rather than a newly arising problem.

Anticipatory nausea and vomiting are a learned response to cytostatic treatment, and these symptoms occur in subsequent cycles of chemotherapy before the actual administration of the cytostatic, for example, at the patient's arrival to the hospital. The occurrence is conditioned by the previous experience, i.e. previous vomiting after cytostatics.

This type of vomiting is very difficult to influence by pharmacological therapy (Tomášek et al., 2011).

Patients who do not experience acute vomiting after chemotherapy usually have lower incidence of delayed vomiting. Therefore, vigorous prophylaxis of acute vomiting is an effective prevention of delayed vomiting. Treatment of delayed vomiting that has already occurred is very difficult. That is why prophylaxis of delayed vomiting should be instituted in all patients with emetogenic chemotherapy from the second day after the initiation of cytostatic therapy.

1.2.4 Mucositis

Systemic chemotherapy is mainly targeted upon rapidly proliferating tumour cells. However, it has also the side effect of affecting rapidly proliferating cells of the body itself, such as mucosal epithelial cells. These effects most often accompany treatment with 5-fluorouracil or capecitabine, which may be followed by diarrhoea, frequently bloody, leading to dehydration and the need for parenteral infusion therapy during hospitalisation. Oral mucositis in the form of small or large mucosal defects is also common and may lead to difficulty in chewing or swallowing food. It is important to note that defects visible on the oral mucosa can be present throughout the digestive tract and can form large wound areas that, without adequate therapy, can be fatal to the patient.

1.2.5 Neurotoxic manifestations

Peripheral nervous system damage is one of the most common side effects of taxanes, platinum derivatives, bortezomib or vinkaalkaloids.

Peripheral neuropathy causes paraesthesia and numbness initially in the fingers and toes and can later affect motor fibres. Autonomic nerve neuropathy is much more severe and can result in paralytic ileus (Tomášek et al., 2011). Some preparations, such as cisplatin, can lead to hearing impairment, while others result in visual impairment or increased tearing.

Impairment of the central nervous system is rare and currently occurs more in the context of immunotherapy with check-point inhibitors or ipilimumab.

1.2.6 Pulmonary toxicity

Medicaments that have toxic effects on the lung parenchyma usually cause an interstitial type of damage. The degree of lung damage is usually related to the cumulative dose of these medicaments and is potentiated when the lung is damaged by other agents, e.g., radiotherapy.

The earliest sign of lung damage is usually an irritant cough. Monitoring of lung function is recommended when administering medicaments with the potential for cumulative pulmonary toxicity, especially diffusion, which in the case of the interstitial type of damage worsens already in the case of subclinical damage (Tomášek et al., 2011).

Pulmonary toxicity occurs with e.g. bleomycin, busulfan or immunotherapy.

1.2.7 Hepatotoxicity

Hepatotoxic effects of common chemotherapy are rare, although the liver is the organ where cytostatics are most frequently metabolized.

Hepatotoxicity is usually reversible and liver function is restored after treatment (Tomášek et al., 2011). It is manifested by an increase in the activity of the liver enzymes and bilirubin concentration, pain in the right ileac region or icterus (yellowing).

1.2.8 Nephrotoxicity

Nephrotoxicity is predominantly manifested by damage to tubular cells and their functions. The best-known medicament with proven nephrotoxicity is cisplatin. The degree of nephrotoxicity depends on the amount of administered cisplatin. Some cytostatics, such as e.g. ifosfamid, damage predominantly the urothelium of the bladder. Adequate prophylaxis of renal damage is consistent hydration, and in the case of the prophylaxis of urothelium damage uro-protective agents (e.g. mesna) administered.

1.2.9 Skin toxicity

The most common and well-known undesirable side effect of cytostatics is hair loss (alopecia). The occurrence of alopecia depends on the dose and type of cytostatic. Hair growth usually resumes quickly after the end of chemotherapy. However, skin pigmentation may occur.

A typical side-effect of 5-fluorouracil and capecitabine is acute painful erythema (*hand-foot syndrome*) (Tomášek et al., 2011), when the sensitivity of the palms of the hands and feet is accentuated, with subsequent blistering and peeling of the limbs; sufficient skin hydration through oily creams is a preventive measure. In the case of capecitabine even a temporary loss of fingerprints has been described.

1.2.10 Secondary tumours

The mutagenic and potentially carcinogenic effects of cytostatics increase the likelihood of secondary malignancies. Chemotherapy has the potential to induce mainly malignant transformation of haematopoiesis.

1.3 Biological and physiological changes in the body during tumorous disease and their long-term impact

Iva Hrnčířiková, Zora Svobodová, Iva Burešová, Pavlína Bazalová

Up to 50 % of cancer patients experience significant atrophy of adipose tissue and muscle mass. This condition is called cachexia. It is manifested by loss of overall weight, loss of skeletal muscle, reduced quality of life and consequently reduced survival time.

Diagnostic criteria for cachexia are weight loss greater than 5 % in the last 6 months (in the absence of simple starvation) or a BMI less than 20 and continued weight loss of more

than 2 % or sarcopenia (men <7.26 kg/m²; women <5.45 kg/m²) accompanied by any degree of weight loss greater than 2 % (Fearon et al., 2011).

It is estimated that cachexia is the cause of death in up to 30 % of patients. Depending on the type of tumour, cachexia occurs in 30–80 % of patients, of whom severe cachexia (weight loss of more than 10 % of the original weight) occurs in 15 % of patients.

Patients with pancreatic or gastric cancer have the highest weight loss, while patients with non-Hodgkin lymphoma, breast cancer, acute nonlymphocytic leukaemia and sarcomas have the lowest weight loss.

Cachexia is manifested by an increased metabolic turnover, increased energy expenditure, not only in large but also in small tumours, therefore the idea that cachexia is caused by the energy requirements of the tumour is excluded. It is caused by neurohumoral changes, of which the secretion of pro-inflammatory cytokines (interleukins Il-1, Il-6, TNF- α), changes in hormone levels (cortisol and glucagon) and the effects of substances produced by tumour cells are considered to be the most important. Increased production of prostaglandin PGE 2, which is secreted from the hypothalamus, causes increased thermogenesis, and thus increased metabolic turnover. Muscle tissue loss occurs due to inhibited protein synthesis and in combination with increased proteolysis (Holeček, 2016).

Patients with cancer cachexia have an increased risk of side effects from cancer treatment and develop more complications. Cancer cachexia is manifested by poorer **performance status** and reduced quality of life. Czech sports medicine uses at the equivalent of the term performance status the term **physical fitness**.

Cachexia is a multifactorial syndrome in which there is a significant decrease in body weight, even weight loss, loss of skeletal muscle and other tissues. It is caused by an inability to take in food (anorexia) and changes in energy and nutrient metabolism. Cachexia is characterised by a negative nitrogen balance (Holeček, 2016; Lukešová & Kopecký, 2011; Tomáška, 2008).

Tab. 1 Pathogenesis of tumour cachexia (Holeček, 2016; Tomáška, 2008)

Carbohydrate metabolism	<ul style="list-style-type: none"> • predominance of anaerobic glucose breakdown to form lactate; • increased endogenous glucose production from lactate, amino acids, glycerol – gluconeogenesis; • increased glucose turnover – Cori cycle; • glucose intolerance, insulin resistance.
Lipid metabolism	<ul style="list-style-type: none"> • lipolysis in adipose tissue; • decreased lipoprotein lipase activity; • elevated lipid levels in plasma.
Protein metabolism	<ul style="list-style-type: none"> • protein catabolism; • reduced protein synthesis; • increased protein synthesis in the liver.

About 50 % of patients develop an acute phase reaction – with increased levels of C-reactive protein (CRP). Hypoalbuminemia is also seen. The acute phase reaction is induced by pro-inflammatory cytokines released by both the tumour cells and the surrounding cells. Induction of the cytokine cascade may promote the development of tumour cachexia and also creates an environment that promotes tumour growth (Lukešová & Kopecký, 2011; Wilhelm, 2001).

Cancer patients have lipid metabolism disorders (hyperlipidaemia with increased lipolytic activity), which are influenced by cytokines. The end products of increased oxidation of free fatty acids are the products for gluconeogenesis and for the formation of ketone bodies. Phospholipids in the biomembrane act not only as factors in membrane permeability but also as regulators of cellular functions. They are a source of arachidonic acid (n-6), which, when released from membrane binding by phospholipase A or C, becomes a precursor for the formation of prostaglandins, thromboxanes and leukotrienes. They are a source of arachidonic acid (n-6), which, once released from cancer cells, arachidonic acid metabolism is catalysed by cyclooxygenase or lipoxygenase depending on TNF- α levels. A high concentration of TNF- α stimulates the cyclooxygenase pathway with the formation of prostaglandin PGE₂, whereas a low concentration of TNF- α stimulates the lipoxygenase pathway. PGE₂ suppresses the immune response and induces increased protein catabolism in skeletal muscle. Consumption of fish oil is recommended in the treatment of inflammation - eicosanoid acid replaces arachidonic acid in the cell membrane and PGE₃ produced by the cyclooxygenase pathway has an immunostimulatory effect and does not induce increased protein catabolism (Wilhelm, 2001).

Tab. 2 Mediators of the cachectic process (Wilhelm, 2001)

Pro-inflammatory cytokines	TNF- α , Il-1, Il-6, IFN- γ	produced by host macrophages, negatively affect appetite
Neuroendocrine stress response	cortisol, myostatin	–

The interaction between the growing tumour and the body's immune system leads to an imbalance between orexigenic and anorexigenic processes. Peripheral signals announcing the energy deficit reach the hypothalamus, but cytokines cause the hypothalamus to become unresponsive, thus perpetuating the cachectic process. Cytokines can cross the blood-brain barrier where they activate anorexia-inducing cytokine systems. Interleukin Il-1 appears to mediate anorexia by stimulating serotonin release, inhibiting neuropeptide Y signalling, and inducing early satiety (Lukešová & Kopecký, 2011; Zadák 2016).

Other factors involved in the development of tumour cachexia include the age of the patient and the habitual level of physical activity. Sarcopenia occurs physiologically and with age. This process starts from the age of 30 in men, later in women. The progression of age-related sarcopenia cannot be stopped, but it can be slowed down with properly selected physical activity and targeted nutritional measures. Physical activity is an important stimulus for muscle protein production. In cancer, reduced activity may be

Vážení čtenáři, právě jste dočetli ukázkou z knihy ***Physical Activity as an Efficient Means of Non-pharmacological Care in Oncology.***

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