

ONCOLOGY

Renata Soumarová
et al.



Oncology

Renata Soumarová et al.

Reviewers:

doc. MUDr. Ing. Jakub Cvek, Ph.D., MBA

prof. MUDr. Jiří Petera, Ph.D.

Translated from the Czech original Renata Soumarová a kol., *Onkologie*,
Karolinum 2025, using DeepL Translator and edited by Gape Ragontse

Published by Charles University

Karolinum Press

Prague 2026

Edited by Jana Jindrová

Typeset by Karolinum Press

Printed by PBTisk, a. s., Příbram

First edition

On the cover: Malignant tumor, AI-generated image created with Adobe Photoshop, 2026.

© Charles University, 2026

© Renata Soumarová et al., 2026

Translation © Gape Ragontse, 2026

ISBN 978-80-246-6301-2

ISBN 978-80-246-6302-9 (pdf)



Charles University
Karolinum Press

www.karolinum.cz
ebooks@karolinum.cz

CONTENTS

PREFACE	7
GENERAL SECTION	9
1 Prevention and Screening in Oncology	11
2 Biology of Cancer	17
3 Assessment of Disease Extent and Response to Treatment	24
4 Predictive and Prognostic Markers – Molecular Testing	27
5 Systemic Therapy for Solid Tumors	32
6 Fundamentals of Radiation Oncology	56
7 Pain Management	76
8 Nutrition for Cancer Patients	86
9 Systemic and Paraneoplastic Manifestations of Malignant Diseases	90
10 Acute Conditions in Oncology	93
11 Venous Thromboembolic Disease in Cancer Patients	100
SPECIAL SECTION	109
12 Malignant Tumors of the Head and Neck	111
13 Breast Tumors	126
14 Tumors of the Lungs and Pleura	142
15 Esophageal Cancer	154
16 Stomach Cancer	159

17 Hepatocellular Carcinoma, and Biliary Tract Cancers	165
18 Pancreatic Cancer	172
19 Colorectal Cancer	177
20 Anal Cancer	184
21 Renal Cancer	188
22 Testicular Cancer	196
23 Prostate Cancer	202
24 Cancer of the Urinary Bladder	210
25 Primary Tumors of the Central Nervous System	214
26 Secondary Tumors of the Central Nervous System	219
27 Cancer of the Skin	230
28 Malignant Melanoma	240
29 Sarcomas	247
30 Cervical Cancer	253
31 Uterine Cancer	259
32 Ovarian Cancer	264
33 Neuroendocrine Tumors	269
34 Hereditary Cancer Syndromes	277
35 Drug Interactions in Oncology	283
REFERENCES	287
ABBREVIATIONS	290

PREFACE

Dear Students,

Oncology is a broad medical discipline focused on the comprehensive management of malignant tumors. Over the past decade, oncology has undergone remarkable and dynamic development driven by new insights into tumor biology and mechanisms of cancer progression. These advances have enabled the introduction of novel therapeutic approaches that have significantly improved patient survival and outcomes.

Oncology encompasses treatment with curative intent as well as palliative, symptomatic, and supportive care. It also includes long-term follow-up of patients after completion of therapy. Modern oncological care relies on both state-of-the-art radiotherapy techniques and systemic treatment modalities.

This textbook is intended to introduce you to the fundamental principles of the management of the most common solid malignant tumors in adults. The introductory chapters focus on the principles and indications of radiotherapy and systemic treatment, including targeted therapy and immunotherapy. Dedicated chapters address the management of symptoms related either to the disease itself or to adverse effects of oncological treatment. The genetic background of cancer development is highlighted in the chapter on hereditary cancer syndromes.

The general chapters are followed by disease-specific chapters devoted to individual tumor entities, prepared by physicians with expertise in the respective fields. These chapters follow a unified structure covering epidemiology, etiology, symptomatology, diagnostics, differential diagnosis, pathology, therapy, post-treatment complications, and follow-up care.

However, it must always be borne in mind that the treatment of an oncology patient is inherently multidisciplinary and team-based, and that the oncologist should appropriately lead and “conduct” this process.

Through this textbook, we aim to provide you with the most up-to-date information that will be essential not only for your oncology examination, but also for your further studies and future medical practice. Unfortunately, epidemiological data remain uncompromising: it is highly likely that each of you will encounter patients with malignant disease in your professional career.

The text was translated from Czech original Renata Soumarová a kol., *Onkologie*, Karolinum 2025, by DeepL Translator and edited by Gape Ragontse.

prof. MUDr. Renata Soumarová, Ph.D.

GENERAL SECTION

1 PREVENTION AND SCREENING IN ONCOLOGY

Oncological prevention is an important part of the National Oncology Program (NOP) of the Czech Republic, which was developed based on the conditions and needs of the Czech Republic and in accordance with the conclusions of the World Health Organization (WHO), adopted for the control of cancer.

The objectives of the National Oncology Program of the Czech Republic are to reduce cancer incidence and mortality, improve the quality of life of cancer patients, and rationalize the costs of cancer diagnosis and treatment in the Czech Republic.

The program is guaranteed by the Czech Oncology Society of the Czech Medical Association of J. E. Purkyně and is distributed to a number of institutions that may have even the slightest influence on the fulfillment of any of its points. Institutions are invited to become signatories to the program and share responsibility for its implementation.

The basic objectives of the NOP include:

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

The main tasks of the NOP are to:

- Provide professional support for cancer prevention education in schools; popularize primary cancer prevention among the general public; reduce smoking among young people and women in particular; and help bring about positive changes in nutrition and lifestyle.
- Ensure the long-term functioning and auditing of programs for the screening of breast cancer, cervical cancer, and colon cancer.
- Improve the early diagnosis of malignant tumors, especially in cooperation with general practitioners; innovate the content of preventive examinations integrating the detection of oncological, cardiovascular, and metabolic diseases.
- Name a network of centers for comprehensive diagnostic and therapeutic oncological care, accredited by the Czech Oncological Society, based on four competencies: qualifications, equipment, self-evaluation, and communication.
- Promote equal access to comparable oncology services and information on the prevention, diagnosis, and treatment of oncological diseases for the entire population.
- Ensure the establishment and stability of palliative and terminal care facilities; support the development of home care; monitor the quality of life and pain management of patients with advanced malignant tumors.

- Support the continuity, stabilization, modernization, and practical use of the Czech National Cancer Registry database for managed preventive and diagnostic-therapeutic care in oncology.
- Support applied oncology research and innovation; introduce HTA (health technology assessment) principles in oncology; and support education in oncology.

In 2022, the Czech government adopted the National Oncology Plan of the Czech Republic 2030 (NOPL ČR 2030), which is a strategic concept for the further development of oncology care, from primary prevention to end-of-life care. The vision of NOPL ČR 2030 is to ensure that every citizen of the Czech Republic has the opportunity to prevent the development of cancer and, in the event of the development of the disease, to ensure the highest possible quality of care and life for everyone, regardless of their geographical location or stage of the disease.

Only by concentrating highly specialized oncology care in the appropriate healthcare facilities can patients be provided with the highest possible quality of care.

In 2005, the Czech Oncology Society (ČSL JEP) institutionalized the establishment of comprehensive oncology centers accredited by ČOS on the principle of four competencies: qualifications, equipment, self-evaluation, and communication. Comprehensive oncology centers co-create a network of oncology services in the regions (regional oncology centers) in cooperation with other departments or outpatient clinics involved in oncology care. Two centers are designated as national oncology centers (NOC) and should cover the latest procedures and international cooperation, including research projects.

In general, the incidence of newly diagnosed oncological diseases is increasing (Fig. 1.1), while mortality is slightly lower (Fig. 1.2), but the prevalence, i.e., the number of living patients who have had cancer, is clearly increasing.

In absolute numbers, 60,000 malignant neoplasms (excluding other skin tumors) are newly diagnosed in the Czech Republic each year, approximately 28,000 deaths from malignant tumors are registered annually, and more than 700,000 people live with a history of any type of neoplasm in their medical records. Every third citizen of the Czech Republic will develop some type of cancer during their lifetime. It can be assumed that by 2030, the prevalence will exceed 750,000 people. Malignant tumors are the second leading cause of death in the Czech Republic and the leading cause of death among people under the age of 65. It is expected that by 2035, cancer will be the leading cause of death in the EU, mainly due to an aging population, insufficient health literacy, and unhealthy lifestyles.

The most common diagnoses, apart from skin tumors, include colon and rectal cancer; malignant prostate tumors in men; breast cancer in women; and tumors of the trachea, bronchi, and lungs.

The main reasons for the high incidence of malignancies are:

- an aging population – most tumors affect middle-aged and older patients, but the increasing incidence of tumors in people between the ages of 20 and 30 is also alarming;
- changes in eating and exercise habits;
- a higher incidence of physical and chemical carcinogens – caused, among other things, by environmental pollution;
- but also improved diagnostics and quality of medical care, which leads to longer life expectancy.

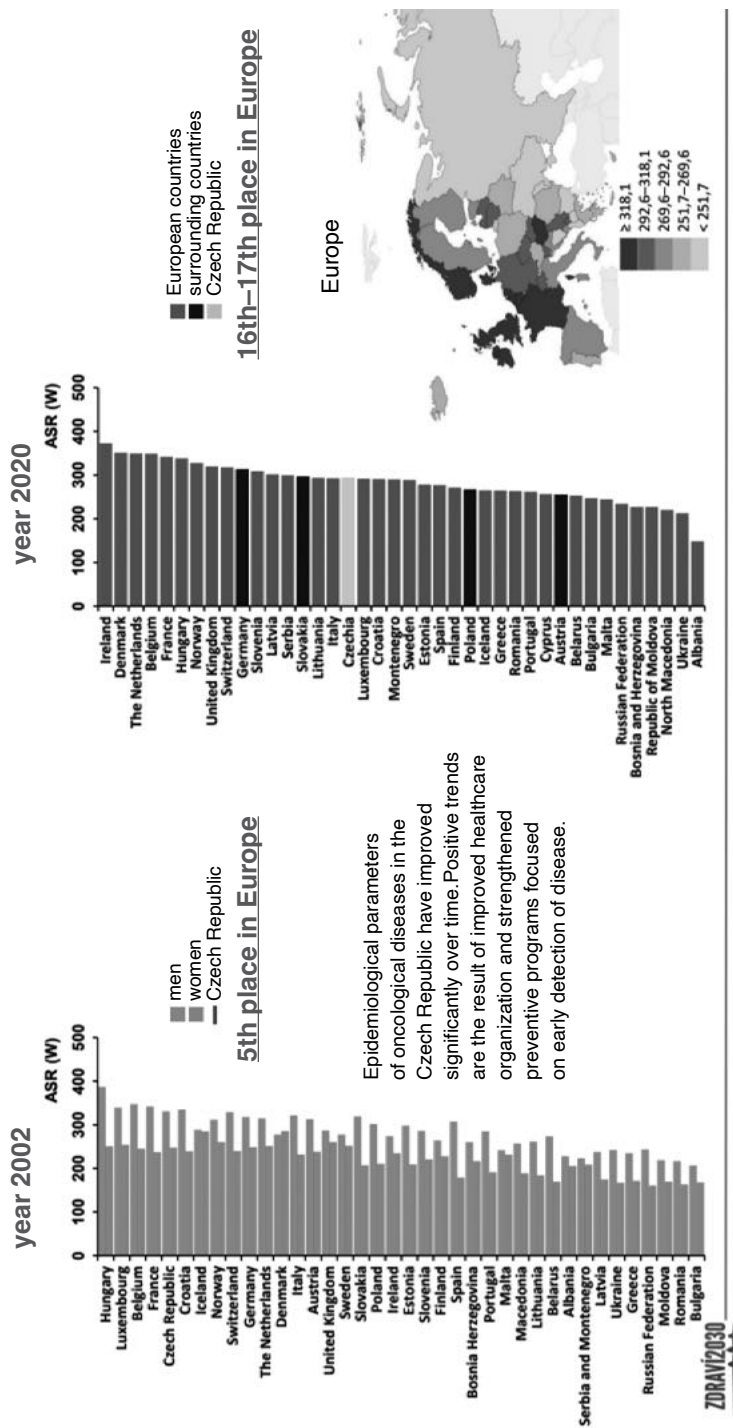


Figure 1.1 Incidence of malignant tumors in international comparison
ASR (W) – Age-standardized incidence rate (World standard population)

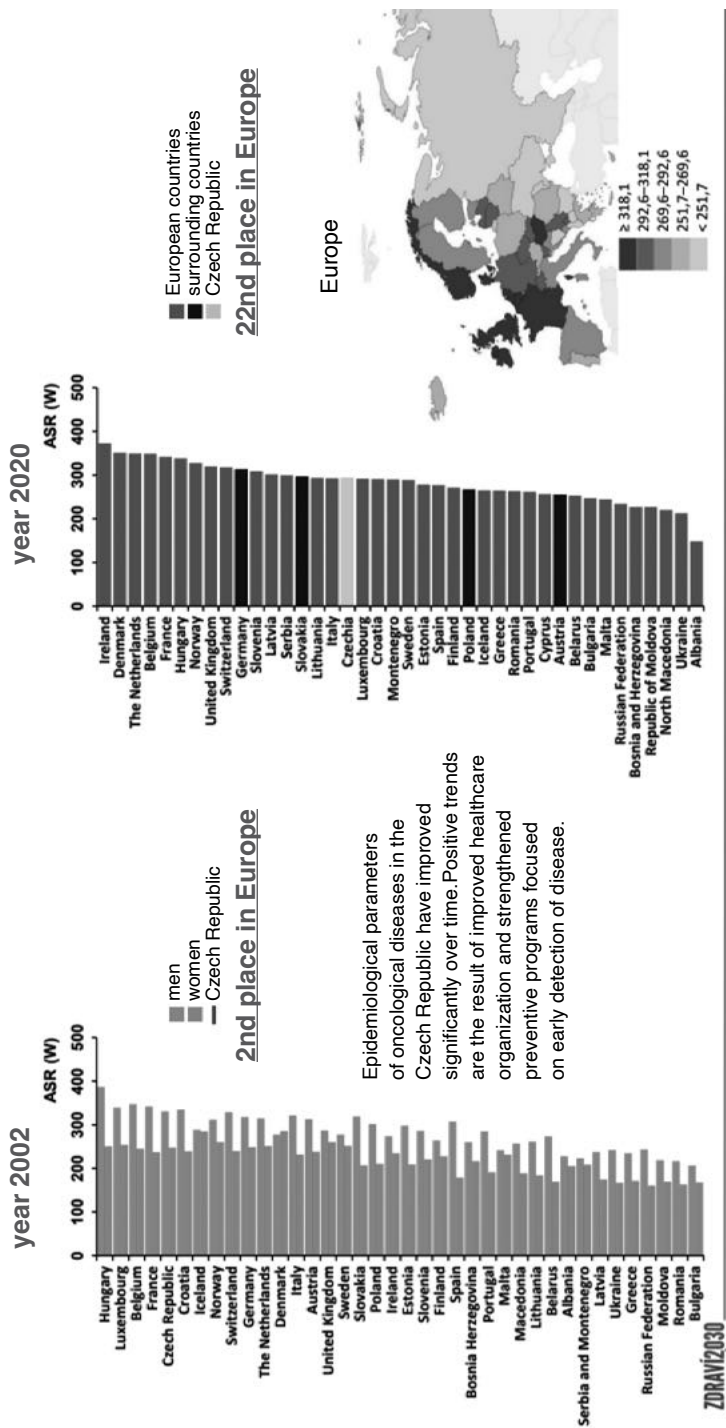


Figure 1.2 Mortality in international comparison
ASR (W) – Age-standardized incidence rate (World standard population)

Malignant tumors in adulthood are partially preventable diseases, i.e., prevention should play a key role in the fight against cancer and is crucial for ensuring the sustainability of the entire healthcare system in connection with the expected increase in the volume of necessary care.

PRIMARY PREVENTION

Most proven or probable risks lead to cancer only after a certain period of time. So, the sooner we start avoiding them, the greater the chance that their impact on our lives will not be fatal. Cancer is hereditary in only about 5% of cases, and at least one-third of tumors are preventable. These include colorectal cancer, cervical cancer, breast cancer, lung cancer, skin cancer, and head and neck tumors (ENT tumors).

The goal of primary prevention in oncology is therefore to:

- reduce the incidence of malignant diseases,
- reduce the side effects of treatment, and
- reduce mortality.

Since smoking, alcohol, and obesity are among the main proven causes of cancer, primary prevention essentially involves changing lifestyle and eating habits. Compared to developed EU countries, the Czech Republic has a high prevalence of risk factors: tobacco consumption (34.4% of adults), alcohol consumption, obesity (28.5% of adults), and lack of exercise (31.1% of adults).

As part of primary prevention, NOPL CR 2030 also focuses on expanding the routine vaccination of girls and boys against human papillomavirus, with the aim of eliminating cervical cancer and other cancers caused by human papillomavirus. The goal is to vaccinate at least 90% of the target population of girls and significantly increase the vaccination coverage of boys by 2030.

SECONDARY PREVENTION

Secondary prevention (screening) focuses on detecting malignant tumors at an early stage, when they are most treatable. Screening is comprehensive, but at the same time focused on a defined part of the population (e.g., regular, repeated mammography examinations for women over 45). Indicators of the level of secondary prevention are the ratio of localized tumor stages to other more advanced stages and the development of mortality from malignant tumors.

The goal of the fight against cancer in the EU is to ensure that 90% of the EU population eligible for breast, cervical, and colorectal cancer screening is offered screening by 2025.

There are already four basic screening programs in the Czech Republic: mammography screening, which began in 2002; cervical screening (cervical cancer), launched in 2008; colorectal cancer screening, which has been running since 2009; and, most recently, lung cancer screening, which was launched in 2023. A fifth program, focused on the early detection of prostate cancer, was starting in 2024. You can read more about all types of screening on the website of the Czech Oncological Society (www.linkos.cz).

TERTIARY PREVENTION

Tertiary prevention in oncology aims to detect any recurrence of cancer after primary treatment and an asymptomatic interval in time, i.e., while it is still treatable. Patients with cancer are monitored (followed up) for life. The path to improving tertiary prevention lies primarily in better organization of follow-up care and better communication between specialists and general practitioners. Patients in long-term complete remission can also be monitored by general practitioners.

However, the problem with dispensary examinations is that they often focus only on the original diagnosis or organ. Patients with cured tumors are at risk not only of relapse but also of developing other, secondary tumors. Secondary primary tumors (second primaries) have become the third most common tumor diagnosis. The incidence of multiple primary tumors in the Czech Republic is more than 11% and continues to grow.

QUARTERLY PREVENTION

Quarterly prevention in oncology refers to anticipating and preventing the consequences of progressive and incurable cancer, which can shorten the remainder of a patient's life or reduce its quality. This includes, for example, ensuring the availability of analgesic treatment and specialist pain management care before the pain fully develops. It is also necessary to anticipate and address nutritional measures, psychological support, and social support in cases of limited self-sufficiency in a timely manner. The EU wants to promote the exchange of information between healthcare providers to improve continuity of care, particularly in managing the late and long-term effects of cancer treatment, including meeting psychosocial needs and rehabilitation.

The main indicator of the quality of quaternary prevention is the systematic evaluation of quality of life questionnaires.

2 BIOLOGY OF CANCER

2.1 TUMOR GROWTH

Under physiological conditions, the cells in our bodies undergo cyclical renewal, which involves replacing old, damaged, or mutated cells with new ones. This process is controlled by a number of mechanisms. The control of this process is hierarchical: cell proliferation control mechanisms → cell cycle control mechanisms → cell cycle (Fig. 2.1).

The main characteristic of malignant tumors is the failure of these control mechanisms (due to mutations), which leads to their uncontrolled growth, resistance to apoptosis, and escape from recognition and destruction by immunocompetent cells. The result is local, locoregional growth and the formation of distant metastases, which are the main cause of

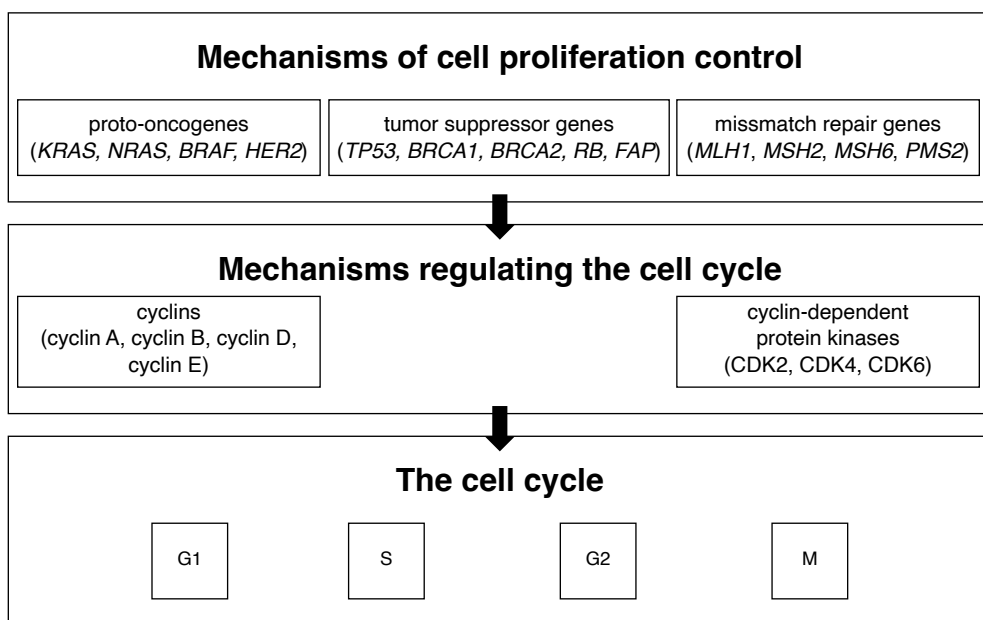


Figure 2.1 Hierarchical control of cell proliferation and the cell cycle

death in patients with cancer. The causes of mutations in genes involved in the control of cell proliferation and apoptosis are both external environmental factors (physical, chemical, biological) and internal environmental factors (especially hormonal influences).

2.2 MECHANISMS OF CELL PROLIFERATION CONTROL

Proto-oncogenes are genes whose products are growth factors, growth factor receptors, signal transducers, and transcription factors. Mutations can cause a proto-oncogene to change into an oncogene, which ultimately stimulates excessive and uncontrolled proliferation. The consequences of (proto)oncogene mutations can include excessive production of growth factors, activating mutations of a number of receptors, intracellular signal transducers, chimeric (fusion) genes, and others. Proto-oncogene mutations are dominant in nature, i.e., a mutation in a single allele will manifest itself in the phenotype. Examples: *KRAS*, *NRAS*, *BRAF*, *HER2/neu*. Knowledge of the presence or absence of mutations in certain proto-oncogenes is currently essential when deciding on the choice of therapy for malignancies, given that a number of mutations in proto-oncogenes have both prognostic and predictive significance (e.g., mtBRAF colorectal cancer is associated with a very poor prognosis compared to wtBRAF, mtRas, wtRas colorectal carcinomas; mtRas tumors are resistant to anti-EGFR antibody therapy).

Tumor suppressor genes are genes whose products have an antiproliferative effect, participate in DNA repair, and induce apoptosis. Their mutation is recessive in nature, i.e., mutation of both alleles is necessary for the mutation to manifest in the phenotype. Heterozygotes with a congenital mutation in one of the tumor suppressor genes have a higher risk of inactivation of these genes (and development of cancer) due to sufficient somatic mutation of the remaining functional allele of the gene. Examples: *TP53*, *BRCA1*, *BRCA2*, *RB*, *FAP*. Even in the case of tumor suppressor genes, knowledge of their status is important in the decision-making process for the treatment of malignancies. For example, mutations in the *BRCA1* and *BRCA2* genes are associated with an increased risk of developing a number of malignancies (breast, ovarian, prostate, and pancreatic cancer). On the other hand, the presence of this mutation is associated with higher sensitivity to platinum-based therapy.

Mismatch repair genes (MMR) are genes (e.g., *MLH1*, *MSH2*, *MSH6*, *PMS2*) whose products participate in the repair of base pairing errors that occur during DNA replication or due to environmental factors. Their mutations are recessive in nature. Currently, in the era of immunotherapy in oncology, the status of MMR gene functionality is routinely examined using immunohistochemical methods, where deficiencies in this repair system manifest themselves in the phenotype as microsatellite instability (MSI-H), which is one of the main predictors of the effectiveness of immunotherapy in malignancies. On the other hand, the presence of a germline mutation in the MMR gene system is associated with Lynch syndrome.

It is important to note that isolated mutations of a single proto-oncogene, tumor suppressor gene, or MMR gene do not usually lead to the development of malignant cell transformation. Several dozens of these mutations in different genes and other internal and external environmental factors are needed for a normal cell to undergo malignant transformation via a pre-malignant lesion. This process usually takes months or even years. In addition, most of these mutations are repaired in time by repair mechanisms, or the mutated cells are removed by the immune system as part of immune surveillance, meaning they do not manifest themselves.

2.3 CELL CYCLE CONTROL MECHANISMS

Cell cycle regulation mechanisms: cyclins and cyclin-dependent protein kinases are controlled by cell proliferation regulation mechanisms (see above).

Cyclins are proteins that do not have their own enzymatic activity. Their concentration in the cell rises and falls during the individual phases of the cycle. **Cyclin-dependent protein kinases** are proteins that have their own enzymatic activity, but only the cyclin/cyclin-dependent protein kinase complex is active, which controls the progression through the individual phases of the cell cycle. There are a number of these complexes that are specific to certain phases of the cell cycle. Examples: cyclin D/CDK4, 6 – in the G1 phase of the cycle, or the G1/S transition. Their continuous activation and inactivation controls the movement through the individual phases of the cell cycle.

The function of individual complexes in the regulation of the cell cycle and malignant cell transformation is now well understood. In addition, specific inhibitors of these complexes are available and are used as a standard, for example, in the treatment of hormone-positive, HER2-negative breast cancer.

2.4 CELL CYCLE

The cell cycle is the period from the formation of a cell to its division into two daughter cells. It is controlled by cell proliferation control mechanisms and cell cycle regulation mechanisms (see above). It consists of the G0, G1, S, G2, and M phases (Fig. 2.2).

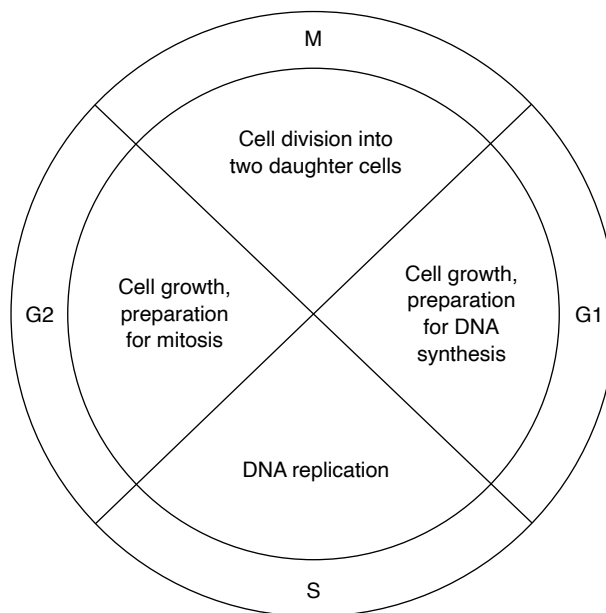


Figure 2.3 The cell cycle and its phases

G0 phase: This is referred to as the resting phase, and most of the cells in the organism are in this phase.

G1 phase: After mitogenic stimulation, cell growth begins, the number and size of cell organelles increases, the cell prepares for DNA replication in the S phase, and the necessary proteins are synthesized. The G1 phase contains the main control point of the cycle – the G1/S checkpoint.

S phase: This is the longest phase of the entire cell cycle, but it is constant for a given cell. Each chromosome is copied according to a template. The result is 46 dichromatid chromosomes.

G2 phase: The cell continues to grow, synthesizing structures, cell organelles, and proteins for the daughter cell. Proteins and structures of the mitotic apparatus are synthesized. This phase contains the second main checkpoint of the cycle – the G2/M checkpoint.

M phase: This represents the actual division of chromosomes and subsequently of the cell into two identical daughter cells. The M phase is a controlled process consisting of several phases: prophase, prometaphase, metaphase, anaphase, and telophase.

2.5 IMMUNE SURVEILLANCE

Immune system cells also play an important role in the process of controlling malignant transformation and tumor growth. This is explained by the so-called immune surveillance theory, according to which tumor cells, as cells foreign to the body, are usually removed from the organism in a timely manner. According to the theory of immune surveillance, there are three phases: elimination – equilibrium – escape, the so-called 3E theory. In the **elimination** phase, tumor cells are recognized and removed by immune system cells in time, so that malignant disease does not develop. Over time, tumor cells begin to actively defend themselves against recognition and destruction by immunocompetent cells. On the one hand, they reduce the expression of surface antigens by which they are recognized, and on the other hand, they produce cytokines that inhibit the functions of immune system cells – and a period of **equilibrium** ensues, when the tumor is present, usually of a subclinical extent, and there is a balance between the formation and removal of tumor cells. In the **escape** phase, the inhibitory mechanisms of tumor cells against the host prevail and further tumor progression occurs, usually already clinically detectable.

This 3E theory and understanding of how tumor cells acquire the ability to escape the immune system has laid the foundation for the successful application of immunotherapy in the treatment of a number of oncological diseases. The application of immunotherapy in a number of malignancies has completely changed the prognosis for these patients. In 2018, the Nobel Prize in Medicine was awarded to scientists Tasuku Honjo and James Allison, who have made significant contributions to our understanding of the relationship between tumors and the immune system. In very simple terms, the principle of immunotherapy is to reactivate the cells of the inhibited immune system to fight the tumor. The options are: activation of activation receptors and inhibition of inhibitory receptors of immune cells.

2.6 APOPTOSIS

Under normal conditions, there is a balance between cell proliferation and apoptosis. Both processes are strictly controlled. In cancer, we most often encounter dysregulation of both processes. The result is accelerated, uncontrolled proliferation and, at the same time, a disorder in apoptosis. In the early stages of cancer, tumor growth is caused by the exponential proliferation of tumor cells, which slows down at the time of clinical manifestation. Nevertheless, the tumor continues to grow, mainly due to the resistance of tumor cells to apoptosis.

Apoptosis is a physiological process, an active process by which old, damaged, and mutated cells are removed in order to maintain the homeostasis of the organism. Apoptosis dysfunction is typical of cancer. Like everything else in the organism, the process of apoptosis is precisely controlled. The BCL2 family of proteins plays a key role. These include apoptosis inhibitors (BCL2) and apoptosis activators (BAX, BAK, BOK). There are two basic pathways of apoptosis: the extrinsic and intrinsic pathways, which then converge into a common pathway.

The external (extrinsic) pathway involves the interaction of so-called death receptors and ligands (Fas-FasL, TNF-TNFR, TRAIL-TRAILR). This is the main pathway of apoptosis mediated by immune system cells. After the ligands bind to the death receptors, the signal is transmitted to the cell and leads to the activation of the extrinsic pathway of apoptosis. Pro-caspase 8 is activated to caspase 8, which further activates pro-caspase 3 to caspase 3, which is already a caspase of the common pathway.

The intrinsic pathway is triggered by so-called genotoxic stress, i.e., DNA damage caused by mutations, chemotherapy, radiotherapy, and other factors. Such damage leads to the activation of the p53 protein, which subsequently stops the cell cycle of the damaged cell. The influence of p53 then leads to increased expression of proapoptotic proteins and, conversely, to reduced expression of antiapoptotic proteins. As a result, signaling leading to the induction of apoptosis prevails. The initiation of this pathway occurs in the mitochondria, which is why this pathway is sometimes referred to as the **mitochondrial** pathway. There is increased permeability of the mitochondrial membrane and release of cytochrome c into the cytoplasm, where, together with the Apaf-1 protein and procaspase 9, they form an apoptosome complex that activates procaspase 9 to caspase 9. Caspase 9 then further activates procaspase 3 to caspase 3, i.e., the caspase of the common apoptosis pathway.

The common apoptosis pathway thus begins with the activation of procaspase 3 to caspase 3, which can be activated by both the external and internal pathways. The effector caspase 3 subsequently initiates chromatin condensation, DNA fragmentation, organelle breakdown, cell shrinkage, and the formation of apoptotic bodies, which are then phagocytosed by immune system cells without the development of inflammation.

2.7 REPAIR MECHANISMS

Defects (mutations) in genes involved in the regulation of cell proliferation can be recognized and repaired by the organism, which is what happens in the vast majority of cases. The cell has several options for repairing the mutation. Most of these repairs are initiated by the recognition of the mutation by the p53 protein, which then stops the cell cycle via cooperating proteins and allows the repair system to repair the damage. If repair is not possible, apoptosis

is indicated. If the repair mechanisms fail, the mutation is fixed and the risk of malignant transformation of the cell increases.

The cell repair systems are:

- *base excision repair* – consists of recognizing and excising the incorrect base and replacing it with a complementary base;
- *nucleotide excision repair* – consists of recognizing and excising the entire misplaced nucleotide and replacing it;
- *mismatch repair* – the system repairs incorrect base pairing during DNA replication. A defect in this system leads to microsatellite instability (MSI-H);
- *single-strand break repair system* – the break is repaired according to a complementary template, which is the second strand of DNA;
- *double-strand break repair system* includes two options:
 - *non-homologous end joining* is a repair process that is fast but prone to errors. During the repair of a double-strand break, the break is repaired by randomly filling in the missing bases, nucleotides, which can lead to a mutation of a proto-oncogene or tumor suppressor gene if the breaks and subsequent random repairs occur at the site of this gene;
 - *homologous repair* is a more lengthy process, but it repairs double-strand breaks without error. The repair is carried out according to a complementary template, which is a duplicated identical chromosome during the S phase, when the cell has 2×46 chromosomes. Homologous recombination therefore takes place in the S phase and G2 phase of the cell cycle, when each chromosome in the cell is duplicated. In the G1 phase of the cycle, when the cell does not have a copy of each chromosome available, repair is carried out by the non-homologous end joining system.

2.8 RESISTANCE OF CANCER CELLS

Due to their cause, i.e., mutations in a number of genes, cancer diseases are very difficult to cure permanently. Various modalities are used in treatment with the aim of inducing the long-term remission of the disease with acceptable side effects of oncological treatment. A common cause of the persistence and relapse of the disease is the resistance of tumor cells to therapy.

Even in the early stages of their development, tumors are heterogeneous populations of different cells with varying sensitivity to therapy. In addition to the tumor cells themselves, the tumor population also consists of tumor stroma, vasculature, and immune system cells. Treatment causes the tumor population to shrink, ideally leading to complete remission as determined by imaging methods. However, due to the heterogeneity of the tumor population, there is a small percentage of cells in the tumor population that are resistant to treatment—so-called primary resistance. These cells are often tumor stem cells, which have a number of mechanisms to defend themselves against damage from chemotherapy, radiotherapy, and other modalities of cancer treatment. Even in cases of complete remission according to imaging methods, it is precisely these primarily resistant cells that are often the cause of tumor relapse. **Primary resistance** is therefore “congenital”.

During treatment, we more often encounter the term **secondary resistance** due to the applied treatment. Due to selection pressure, sensitive cells are eradicated and resistant cells persist. Surviving tumor cells undergo further mutations due to the selection pressure of therapy, further increasing their aggressiveness and resistance to therapy. Sooner or later, the originally effective therapy fails and the disease progresses. When the therapy is changed to the next line of treatment, part of the tumor cell population is eradicated again. However, the effectiveness of each subsequent line of treatment decreases as cell resistance increases due to so-called secondary resistance, which is “acquired”.

3 ASSESSMENT OF DISEASE EXTENT AND RESPONSE TO TREATMENT

3.1 ASSESSMENT OF DISEASE EXTENT – STAGING

An important factor determining not only the prognosis of the disease but also the choice of treatment modalities is the extent of the disease. Its accurate determination is also important for selecting the optimal treatment regimen, evaluating treatment outcomes, and comparing treatment results.

A uniform classification system has been developed to enable the accurate description of the extent of disease in most solid tumors. This classification, known as the TNM system, has been adopted worldwide and is also binding in the Czech Republic. It is continuously updated.

3.2 TNM CLASSIFICATION SYSTEM

The classification of malignant neoplasms according to the TNM system is based on the determination of three components:

- **T (tumor)** – determines the extent of the primary tumor. The numbers 1–4 attached to the letter T determine the extent (size or depth) of the primary lesion. This is determined by clinical and imaging examinations. If the primary site cannot be identified by available examinations, the symbol T0 is used. If the size of the tumor cannot be determined or if no available examinations have been performed to identify the primary site, the symbol TX is used. The symbol Tis is used to designate carcinoma in situ.
- **N (nodes)** – status of regional lymph nodes. It is precisely determined which nodes are regional for a given tumor location. The accompanying numbers describe their more precise characteristics (location or number of affected nodes). N1–N3 indicates increasing involvement of regional lymph nodes, N0 means negative findings, and NX means that findings in the nodes cannot be reliably determined.
- **M (metastasis)** – describes the presence or absence of distant metastases, including metastases in non-regional lymph nodes. Category M1 can be further specified according to location (e.g., PUL – pulmonary metastases, OSS – bone metastases, HEP – liver metastases).

It is important to note that once the TNM classification has been determined, it must not be changed for the patient! However, it may be supplemented based on further surgical examination or histology; this is referred to as pathological classification and is denoted by the symbol p – pTNM.

If the surgery is preceded by systemic treatment or radiotherapy (neoadjuvant therapy), the symbol y – ypTN is used.

3.3 DETERMINATION OF RESIDUAL TUMOR POPULATION

While determining the extent of the disease is important for establishing the treatment plan at the start of treatment, information about the existence of so-called residual disease is needed when determining whether to continue or discontinue treatment. The residual tumor population may become the basis for future recurrence or metastasis (generalization of the disease). Until recently, the possibilities for determining residual disease were very limited, but molecular biology and genetic methods now make it possible, in some cases, to determine tumor population residues. These include, for example, the examination of circulating tumor DNA (ctDNA).

3.4 ASSESSMENT OF TREATMENT RESPONSE

Assessing the response to treatment is just as important as staging. A WHO expert committee has attempted to harmonize the various proposals for assessing treatment response.

According to this proposal, an objective treatment response is assessed using four grades:

- **Complete response (CR)** is the disappearance of all measurable signs of disease detected by two observations over a period of at least 4 weeks. For measurable lesions, two dimensions should be reported if possible, namely the longest diameter and the largest perpendicular dimension.
- **Partial response (PR)** means a 30% or greater reduction in measurable changes, again within 4 weeks. In addition, no new manifestations of cancer may appear in other locations during this period.
- **No change (NC or stable disease – SD)** corresponds to either a regression of tumor changes of less than 30% or their progression of less than 20%.
- **Progressive disease (PD)** means an increase in tumor size or existing measurable pathological changes of more than 20%, or the appearance of new, previously undescribed lesions.

However, there are a number of additional criteria that can be used to evaluate the effect of treatment, such as pain relief, improved appetite, etc., but these cannot be accurately assessed and compared.

A uniform criterion is used to assess physical performance. The most commonly used scale is the WHO performance status (PS) and Karnofsky (KI) performance assessment (Table 3.1). Performance must be assessed in this way before the start of treatment and at all check-ups during therapy.

Table 3.1 Assessment of physical performance according to the WHO scoring scale compared to the Karnofsky performance assessment

WHO grade	Corresponding physical activity status	Karnofsky (%)
0	Capable of normal physical activity	90–100
1	Unable to perform heavy physical work, but can perform light work	70–80
2	Self-sufficient, but unable to work. Spends more than 50% of the day out of bed	50–60
3	Limited self-sufficiency. Confined to bed more than 50% of the day	30–40
4	Dependent on others for care. Permanently bedridden	20–30
–	Moribund patient	0–20

3.5 DURATION OF TREATMENT EFFECT

In addition to tumor response, the duration of treatment effect is a parameter used to evaluate the effect of treatment. The most important and most commonly used in clinical oncology studies (usually used to compare new treatments with existing ones) include:

- **overall survival (OS)** – time to death (regardless of cause of death);
- **cancer-specific survival (CSS)** – time to death from the disease being monitored, deaths from other causes are not counted;
- **disease-free survival (DFS)** – the time during which the patient is alive and shows no signs of disease after previous treatment of the primary tumor (surgery, radiotherapy for some tumors);
- **progression-free survival (PFS)** – the time during which the patient is alive and shows no signs of tumor progression; used in patients with unoperated and/or metastatic disease;
- **time to progression (TTP)** – assessed similarly to PFS, but excluding patients who die from other causes without tumor progression.

4 PREDICTIVE AND PROGNOSTIC MARKERS – MOLECULAR TESTING

Oncology is characterized by its multimodal approach to the treatment of cancer. In addition to surgery, which is considered one of the oldest treatment options not only for cancer, other specific therapeutic approaches can also be used in treatment. The first mentions of the use of radiotherapy in the treatment of tumors date back to the end of the 19th century. In the 20th century, the first cytostatic drugs were developed and the possibilities of immunotherapy and hormone therapy began to develop. Recently, research interest has turned mainly towards the use of targeted therapy.

However, the more therapeutic options we have at our disposal, the more pressing the question becomes as to which treatment algorithm to choose for a particular patient. It is not desirable to apply all known treatment methods indiscriminately, because clinical practice and numerous studies have shown that not all therapies are effective against every type of cancer, nor are they equally effective. Furthermore, some treatments may not be effective at all clinical stages of a given cancer, or their efficacy may vary depending on the stage. Similarly, not all treatments work for every histological variant of a tumor, or their effectiveness may differ between variants. Finally, even among patients with the same type of cancer, clinical stage, and histological subtype, treatment responses can vary significantly. The role of the oncologist includes developing an individual treatment plan that includes therapeutic methods and combinations thereof to offer maximum efficacy with minimal side effects, thereby maintaining the highest possible quality of life for the patient. Specific molecules on the surface or inside tumor cells, whose presence (expression), excessive presence (overexpression), or structural change (mutation) may have prognostic and/or predictive significance, can be helpful in this regard.

4.1 MOLECULAR TESTING

Molecular testing in oncology is a key diagnostic and prognostic tool that focuses on the analysis of the molecular and genetic characteristics of a patient's tumor cells. This method provides important information about the biology of the tumor, which forms the basis for personalized treatment.

Molecular testing in oncology has several areas of application, primarily:

- **Biomarker tests for more accurate diagnosis:** Molecular testing can be used to identify biomarkers that help diagnose certain types of cancer more accurately. Such diagnostics

include the detection of specific proteins, receptors, or gene alterations associated with specific types of tumors.

- **Genetic analysis of tumor mutations:** Molecular tests can identify specific genetic mutations in tumor cells. This can include the analysis of mutations associated with a response to certain drugs, resistance to therapy, or the presence of predictive markers.
- **Predictive markers for personalized treatment:** Analysis of molecular markers allows doctors to predict how a patient will respond to certain forms of treatment. This includes identifying genetic changes that may affect a tumor's sensitivity to chemotherapy, immunotherapy, or targeted therapy.
- **Monitoring minimal residual disease:** Molecular testing can be used to detect minimal residual disease, i.e., tumor cells that are still present in the body after cancer treatment. This information is crucial for evaluating treatment effectiveness and prognosis.
- **Tumor genomic profiling:** Comprehensive molecular analysis allows the creation of a genomic profile of a tumor, which includes the identification of all genetic changes and mutations in the tumor genome. Genomic profiling is increasingly used for more accurate tumor classification and the selection of therapeutic strategies.

4.2 DEVELOPMENT OF TARGETED DRUGS

Molecular testing plays a key role in the research and development of targeted drugs; the identification of specific molecular targets allows the creation of drugs that are aimed directly at these characteristics of the tumor, which increases the effectiveness of therapy and minimizes its side effects.

Molecular testing in oncology is an important tool for personalized medicine, helping physicians better understand the tumor and select the most effective and generally appropriate therapeutic strategies for each patient. Therefore, a significant portion of oncology research is focused in this direction. Recent advances in molecular genetics, particularly the use of *next-generation sequencing* (NGS), have strengthened the development of methods for analyzing *circulating tumor DNA* (ctDNA) and *circulating tumor cells* (CTCs), often referred to as **liquid biopsies**. These methods, based on the detection of released tumor cells or DNA and RNA molecules in patient serum, provide a relatively non-invasive means of obtaining information about tumor activity. The benefits of liquid biopsies for diagnosis, monitoring therapeutic response, and detecting treatment resistance have so far been described mainly in hematological malignancies. In solid tumors, their application should be approached with caution, as they are still the subject of much scientific research and are not yet considered the method of choice in clinical practice.

Another trend in molecular diagnostics is the detection of **microRNA** (miRNA) molecules. MicroRNAs are short, non-coding RNA molecules that regulate gene translation and influence biological processes including differentiation, proliferation, and carcinogenesis (they are not themselves the basis of proteins, but suppress the translation of other genes by binding to their target miRNA molecules, or even lead to their degradation). These endogenous molecules offer new perspectives in the diagnosis and monitoring of cancer.

4.3 PROGNOSTIC MARKERS

Prognostic markers provide information (not absolutely, but with a certain degree of probability) about the expected course of a disease – for example, the risk of recurrence, the expected overall survival time, etc. They are important for physicians because their presence or absence may influence the treatment plan (without, however, indicating whether the patient will respond well to the treatment), but it should not be forgotten that one of the first questions an oncology patient asks their oncologist is about the prognosis of their disease. It is essential to have an idea of the likely course of the disease and, consequently, the severity of the disease in a given patient.

Prognostic markers can be associated with the patient from a broader perspective (patient age, comorbidities, performance status, etc.) or they can result directly from the tumor itself – in which case it is appropriate to refer to the terms typing, grading, and staging, which are well established in oncology. However, there is a relatively new group of prognostic markers, which we refer to as **biomarkers**. These are characteristics that are objectively measurable and evaluable as indicators of a physiological or pathological process (or pharmacological response). Biomarkers can be detected in various ways – from blood, urine, but also by much more invasive methods necessary to obtain a tissue sample, which is then subjected to detailed examination, most often immunohistochemical, DNA or RNA analysis. The importance of using new biochemical methods and methods of molecular biology and genetics is growing in all areas of medicine, including oncology.

Below is a sample of some of the prognostic markers used. The list is by no means complete; many markers are still the subject of much research, many are yet to enter routine practice, and the vast majority have yet to be elucidated.

Estrogen and progesterone receptors in patients with breast cancer: Patients with breast cancer who test positive for hormone receptors have a much higher five-year survival rate than those who test negative – 83% vs. 69%, respectively. It is important to note that hormone receptor status can change over time. With disease progression and the occurrence of metastatic lesions, re-biopsy and re-testing should always be considered (only if the result would lead to a change in therapy).

HER2/*neu* in patients with breast tumors: The *HER2/neu* gene encodes the epidermal growth factor receptor (EGFR) type 2, which belongs to a group of growth factors important for the regulation of cell growth and differentiation. Mutations in this gene, especially its amplification, have a major impact on the development of certain cancers, particularly breast cancer. Several pathophysiological mechanisms have been described, including upregulation of *HER2/neu* with receptor overexpression, activation of signaling pathways (especially mitogen-activated protein kinase and phosphatidylinositol-3-kinase, which are important for cell cycle control, cell survival, and proliferation), and uncontrolled cell growth and inhibition of apoptosis. As a result of the changes described, uncontrolled cell growth occurs with prolonged cell survival and inhibition of apoptosis, which ultimately leads to a more aggressive course of the disease and a poorer overall prognosis.

c-KIT in patients with gastrointestinal stromal tumors: c-KIT is a transmembrane tyrosine kinase receptor for the growth factor SCF (stem cell factor), which plays an important role in cell proliferation, differentiation, and survival. Mutations in the gene encoding this receptor are important in the pathogenesis of gastrointestinal stromal tumors (GIST). The tumor cells of most patients with this tumor express the c-KIT receptor. Specific types of

mutations in this gene are prognostically significant because different mutations are associated with different tumor aggressiveness (mutations in the extracellular part of the receptor are associated with a better prognosis than mutations in the intracellular part).

KRAS in patients with colorectal cancer: Mutations in the *KRAS* oncogene can lead to excessive activation of this signaling pathway, which stimulates continuous cell growth. In some types of tumors, particularly colorectal cancer, mutations in the *KRAS* gene are associated with resistance to certain forms of targeted therapy (such as epidermal growth factor inhibitors), may cause shorter survival, and generally worsen the patient's prognosis. In colorectal cancer, they occur in up to 30–40% of patients with this type of tumor!

4.4 PREDICTIVE MARKERS

Predictive markers in oncology are a key element in the individualization of cancer treatment. They provide information that allows doctors to predict how patients are likely to respond to a particular treatment. Personalizing therapy based on predictive markers is not only more effective, but also reduces the risk of unwanted side effects, improving patients' quality of life.

Some of the prognostic markers used in oncology mentioned above can also be used as predictive markers, as certain tumor characteristics provide information not only about the expected course of the disease, but also about the response to specific treatments. For example, the aforementioned **HER2/*neu* gene mutation**, which predicts a more aggressive form of tumor and has negative prognostic significance, is also a predictive marker. Based on the *HER2/neu* status, it can be predicted that a patient would benefit from the use of drugs that act as inhibitors of excessive HER2/*neu* receptor activity on the cell membrane and thus significantly affect the growth and survival of tumor cells. This is known as *anti-HER2* therapy, represented by trastuzumab. (Conversely, if there are no mutations of the *HER2/neu* gene in tumor cells, it does not make sense to use inhibitors in the treatment strategy.)

In the case of breast cancer, it is not necessary to look to molecular genetics for examples of predictive markers; **hormone receptors** can also be demonstrated as significant predictive markers. Patients with tumors that test positive for estrogen receptors (ER) may benefit from hormone therapy, while other therapeutic approaches are preferred for ER-negative tumors. The identification of hormone receptors helps to select the most effective treatment with minimal risk of side effects.

Another important predictive marker is the **presence of mutations in the epidermal growth factor receptor** (EGFR) in patients with lung cancer. Patients with these mutations are often more sensitive to EGFR inhibitors gefitinib and erlotinib. Identifying this genetic change allows for better targeting and selection of cancer treatment, which can significantly increase its success.

The above illustrates the fine line between prognostic and predictive markers. It is important to realize that a negative prognostic factor may at first glance indicate a poor prognosis for a patient, but when it comes to predicting a patient's response to a specific treatment, the same biomarker may offer the patient a target for targeted treatment and thus increase their chances of recovery.

Prognostic and predictive markers in oncology are a key tool for personalizing treatment, as they allow for more selective and effective intervention in tumor growth. The integration of these biomarkers into clinical practice can lead to a significant improvement in patient prognosis and the provision of specific, precisely targeted treatment for each of our patients.

5 SYSTEMIC THERAPY FOR SOLID TUMORS

5.1 CHEMOTHERAPY

The treatment of cancer can be divided into local/locoregional and systemic treatment. Locoregional procedures include surgical methods and radiotherapy, while systemic procedures include chemotherapy, hormone therapy, immunotherapy, biological treatment, radiotherapy in the form of whole-body irradiation, and supportive therapy.

Chemotherapy remains one of the basic treatment modalities used in the treatment of malignant tumors. The history of chemotherapy, i.e., the use of chemical compounds with cytotoxic effects, began in the first half of the last century. The 1940s marked a turning point in the status of anticancer chemotherapy. Paradoxically, the development of chemotherapy was due to World War I and the use of the chemical bis(2-chloroethyl)sulfide near the city of Ypres, when the world became acquainted with the blistering agent yperite. As part of wartime research into chemical warfare agents, the Americans replaced sulfur with nitrogen in mustard gas, creating chloralkylamine, still known today as nitrogen mustard (mustargen). Its ability to inhibit the proliferation of rapidly growing tissues i.e., its potential anticancer efficacy, was soon discovered. This substance became the first significant chemical to be used in the treatment of malignant tumors (mustard gas under the name TS-160). These compounds were still being used in the second half of the last century to treat Hodgkin's disease.

The success of chemicals in destroying tumor cells led to the rapid research and development of new substances. However, this development is a very complex, time-consuming, and costly process. Of the tens of thousands of molecules that enter research and development, only one substance will "catch on" in clinical practice, and this process takes seven to ten years.

The cost of drug research cannot be specified, but it is estimated to be comparable to the cost of launching a space shuttle. Chemotherapy has an irreplaceable place in the treatment of cancer, but it must be used judiciously and in combination with other treatment modalities.

There have been turning points in recent history, with discoveries of new molecules that have advanced the therapeutic possibilities of oncology. These milestones are shown in Table 5.1.

Table 5.1 Milestones in the development of systemic chemotherapy

Time period	Therapy (Drug)
1940s	Nitrogen mustard, actinomycin
1960s	Antimetabolites
1970s	anthracyclines, platinum derivatives
1990s	taxanes
present day	biological therapy, immunotherapy
future	gene therapy

Unfortunately, the effect of cytostatic drugs is not selective. From a general perspective, cytostatic drugs do not distinguish between tumor cells and healthy cells. This limits their use and leads to a number of undesirable side effects.

5.1.1 Mechanism of action

In terms of their mechanism of action, cytostatic drugs are divided into several groups:

1. **Substances leading to the inhibition of nucleic acid synthesis** – antimetabolites: purine analogues – fludarabine, cladribine; pyrimidine analogues – 5-fluorouracil, capecitabine; cytidine analogues – cytarabine, gemcitabine; folic acid analogues – methotrexate, raltitrexed;
2. **substances leading to the disruption of the structure of already formed nucleic acids:**
 - a) alkylating agents: cyclophosphamide, cisplatin, carboplatin, carmustine, lomustine,
 - b) intercalating agents: anthracyclines – doxorubicin, epirubicin; actinomycins,
 - c) topoisomerase I inhibitors: irinotecan, topotecan,
 - d) topoisomerase II inhibitors: etoposide, teniposide,
 - e) radiomimetics: substances that cleave the DNA molecule – bleomycin;
3. **substances altering microtubular structures during mitosis:**
 - a) polymerization inhibitors: vincristine, vinblastine, vindesine,
 - b) depolymerization inhibitors: paclitaxel, docetaxel;
4. **substances disrupting protein synthesis:** L-asparaginase;
5. **substances with combined effects:** procarbazine, dacarbazine, temozolomide, thalidomide.

5.1.2 Method of treatment

Chemotherapy is sometimes used as a standalone method in the treatment of malignant tumors, but it is more often combined with other treatment methods (surgery, radiotherapy, hormone therapy). Due to the demanding nature of cancer treatment and its side effects, supportive treatment is an integral part of properly administered cancer therapy. The most common **combination with surgical procedures** is the administration of chemotherapy as neoadjuvant or *preoperative treatment*, e.g. in breast cancer, where chemotherapy is used – in

addition to the systemic treatment objective – to reduce the primary tumor, facilitate surgery, and enable breast-conserving surgery.

Postoperative chemotherapy, administered after surgery, can be used for two therapeutic purposes. As adjuvant therapy – after successful surgery, or as palliative therapy – where surgery could not be radical (e.g., due to the detection of liver metastases, lymph node or intraperitoneal dissemination). Metastatic cancer is incurable, and despite all advances in treatment, oncology is currently unable to permanently cure such patients. On the other hand, there are diseases, such as breast cancer, colorectal cancer, malignant ovarian tumors, or testicular tumors, which we are able to treat repeatedly and long-term, even in stage IV, and bring to complete remission or long-term stabilization. This state of the disease can last for several years, but unfortunately, the surviving aggressive clones of malignant tumor cells ultimately prevail over the efforts of the physician and patient.

Postoperative chemotherapy in the form of adjuvant chemotherapy offers patients the best chance of survival or at least a significant prolongation of the time to disease recurrence. This treatment is used in patients after radical surgery where the risk of disease relapse is high. The presence of *risk factors* indicates a high probability of tumor recurrence and the possibility of existing subclinical dissemination of the disease. These factors may vary from disease to disease, but generally include the size of the tumor, the extent of regional lymph node involvement, the histological type of tumor, and its detailed examination (grading, angiogenicity, specific histological features detected by immunohistochemical examination, e.g., receptor markers, etc.). The optimal outcome of adjuvant chemotherapy is patient survival without signs of disease recurrence. There is no clinical correlate available for this treatment modality to evaluate the effectiveness and usefulness of the therapy, as there is no measurable tumor lesion.

The administration of **chemotherapy in combination with radiotherapy** is the second option for combining both treatment modalities. We can proceed sequentially or concomitantly. *Sequential administration* is used in cases where there is a need for high control of both the locoregional (provided by radiotherapy) and systemic (where chemotherapy is more important) levels. Both methods are used separately, with chemotherapy usually being administered first, followed by radiotherapy.

Concomitant, simultaneous administration of chemotherapy and radiotherapy is a very demanding procedure for the patient. This method is associated with a higher incidence of side effects, which are cumulative from both methods. It is used, for example, in preoperative chemoradiotherapy for rectal tumors or head and neck tumors.

In some cases, chemotherapy is administered as a **standalone method**, either for curative or palliative purposes.

Curative chemotherapy is used only for highly chemosensitive cancers, which include childhood tumors, hematological malignancies (Hodgkin's lymphoma, non-Hodgkin's lymphomas, and some forms of leukemia), and solid tumors in adults, such as choriocarcinoma, testicular tumors, and some ovarian tumors. In radical chemotherapy, relatively significant side effects that may temporarily worsen the quality of life of patients are acceptable because there is a realistic chance of a permanent cure.

Palliative treatment, used in advanced stages of the disease, does not aim to permanently cure the patient. Its goal is to stabilize the disease, delay its progression, and prolong the patient's life. Side effects of treatment are acceptable in proportion to the expected effectiveness of the treatment.

Symptomatic treatment (chemotherapy) does not monitor the effect of therapy on the size of the tumor. Its goal is to eliminate or alleviate the problems (symptoms) caused by the tumor in the patient. Side effects of treatment must be minimal and must not cause a deterioration in the quality of life.

5.1.3 Effectiveness

The effectiveness of the chemotherapy used depends on three limiting factors:

1. the number of tumor cells and their heterogeneity,
2. chemosensitivity and chemoresistance,
3. the patient's overall condition and comorbidities.

The number of tumor cells is determined by the size of the tumor itself. In tumors at the limit of diagnostic capabilities, measuring 1 cm, the number of cells is estimated at 10^9 . Such a tumor has already undergone thirty doublings (whereas tumors with 10^6 cells can already form distant metastases). With the number of tumor cells, the number of different cell clones increases, and thus their heterogeneity. Tumor heterogeneity is probably the most important factor in chemotherapy failure; the existence of even one resistant clone causes the “survival” of tumor cells and subsequent disease progression.

Chemosensitivity and chemoresistance are primary and secondary. Primarily, there are types of tumors that are sensitive to chemotherapy. This sensitivity may be lost secondarily during the life of the tumor and its treatment – due to acquired resistance (multi-drug resistance) and the effect of the treatment, where the elimination of sensitive cell clones enhances the activity of less sensitive and resistant strains.

The chemosensitivity of tumor cells is determined by the type of tumor:

- The first group of tumors most sensitive to chemotherapy includes all childhood tumors, hematological malignancies, and solid tumors such as choriocarcinoma and testicular tumors.
- The second group of tumors less sensitive to chemotherapy includes ovarian carcinomas, breast tumors, and small cell lung cancer.
- The third group with lower chemosensitivity includes gastrointestinal tract (GIT) tumors and ENT tumors.
- The fourth group of the least chemosensitive diseases includes thyroid tumors, pancreatic tumors, and non-small cell lung cancer.

The overall condition of the patient, their age and comorbidities determine the intensity of any oncological treatment.

Pharmacological knowledge of individual cytostatic drugs is essential for the proper administration of chemotherapy. The classification of cytostatic drugs according to their mechanism of action is discussed above. Other knowledge is also necessary, such as the resorption of cytostatic drugs, their possible binding to proteins and distribution in the body, and their biotransformation, whether anabolic (conversion to an active, effective substance) or catabolic (deactivation). Of course, knowledge of the method of excretion of cytostatic drugs (via the liver or kidneys) is also essential, because slowed excretion of cytostatic drugs could increase the effectiveness of treatment, but unfortunately also – and sometimes much more – its toxicity. Details of this information can be found in any pharmacology textbook and oncology monograph.

The mechanism of action of individual cytostatics shows that they only affect tumor cells at a certain stage of their division cycle (always only in the G1 and M phases, not in cells in the G0 resting phase). Tumor cells are found in different phases of the cell cycle, which is why cytostatic drugs are only able to kill some of the cells during their limited existence in the body. *For example:* antimetabolites act in the S phase, which lasts 2–6 hours, while antibiotics (anthracyclines) act during the transition between the G1 and S phases, i.e., for a slightly longer period. Mitotic poisons (vinca alkaloids and taxanes) only act during part of the M phase, which lasts 0.5–2 hours. Alkylating agents have the longest effect on tumor cells, acting for almost the entire duration of the G1 phase, which guarantees the longest effective action on tumor cells, but also the longest action on healthy cells. This is why they cause the greatest chronic toxicity, as the largest number of sensitive stem cells are permanently damaged. The mechanism of action of cytostatic drugs is shown in Figure 5.1.

Prolonging the action of cytostatic drugs in the body increases the number of tumor cells killed, but is dangerous in terms of long-term damage to the body.

So how can the **effectiveness of chemotherapy** be increased? One option is to increase the dose, assuming that a higher dose = more cells killed. However, this is not always true. The limit is the aforementioned duration of the cytostatic drug's effect in the cell phase and the percentage of cells in this phase. Another limit is the potential capacity of transport mechanisms and anabolic activation of the cytostatic drug. Nevertheless, various dosing regimens can be used to increase the effectiveness of chemotherapy by using the dose of the cytostatic drug, or more precisely, the dose intensity of the cytostatic drug (drug dose/duration of action). Dosing in cytostatic regimens is usually expressed in terms of the drug dose per body surface area of the patient, measured in square meters, regardless of whether it is monotherapy (one cytostatic drug used) or polychemotherapy (several cytostatic drugs used simultaneously). The second principle of a chemotherapy regimen is the time at which the next dose is to be administered, i.e., the repetition of the cycle. The dose intensity can be increased by simply increasing the dose, shortening the interval between doses, or both. In the latter case, hematological toxicity increases significantly and careful and active supportive therapy is necessary.

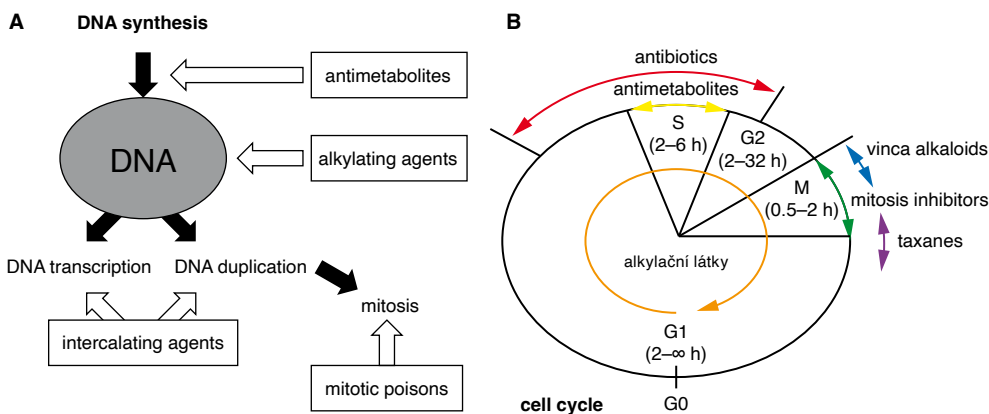


Figure 5.1 Mechanism of action of cytostatic drugs in terms of cell division and the cell cycle

Vážení čtenáři, právě jste dočetli ukázkou z knihy ***Oncology***.

Pokud se Vám ukázka líbila, na našem webu si můžete zakoupit celou knihu.