INDIVIDUALIZED CANCER: A TARGETED, PROGRESSIVE PROCESS

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INTRODUCTION

The Historical Course of Cancer And The Evolving Conception

Cancer is a group of diseases that can originate from almost any organ or tissue in the body, characterized by uncontrolled cell proliferation, impaired apoptotic mechanisms, and the spread to surrounding tissues (Hanahan & Weinberg, 2011; WHO, 2022). However, this definition is the synthesis of a long process of scientific development. The history of cancer is as old as human history itself, with the first records of cancer dating back to 1600 BCE. The ancient Egyptians described tumor-like masses in papyri, but these descriptions went no further than noting that the tumor was in a hard/solid tissue and had no treatment. The modern cellular and pathological definition of cancer was made in the mid-19th century by Rudolf Virchow. Following the discovery of cells through the first microscopic observations by Antonie van Leeuwenhoek in the 17th century, Virchow and his contemporaries examined cancerous tissue under the microscope. They revealed that, unlike normal tissues, cancerous tissue contained abnormal cells that multiplied uncontrollably and gained the ability to spread (invasion) to surrounding tissues (Virchow, 1855). The understanding that cancer is not a tissue disease but one that develops at a cellular level allowed for a better grasp of the biological basis of the disease. This understanding laid the groundwork for the birth of pathology and formed the basis for diagnostic processes such as the classification of tumors as benign or malignant and tumor grading (Rosai, 2011).

Beginning in the mid-20th century, the revolution in science and technology marked a significant turning point in cancer research. During this period, the genetic foundations of cancer were discovered; oncogenes, tumor suppressor genes, and DNA damage and repair mechanisms were revealed in detail. Thanks to molecular biology, genetics, biochemistry, and genomic technologies, cancer began to be regarded not merely as a "mass," but as a group of diseases caused by specific genetic mutations, signaling pathways, and epigenetic abnormalities. In the modern era, cancer is treated not just as a disease but as a biological process, and treatment strategies are being developed that are customized for each individual's genetic makeup. This paradigm shift has created a scientifically grounded, mechanism-focused transformation in oncology, just as it has in other fields of medicine.

The Pathogenesis of Cancer

Cancer is a complex, multi-stage disease that develops as a result of the disruption of molecular mechanisms that control cell proliferation and death. The pathogenesis of cancer begins with a number of genetic mutations and epigenetic changes, and these alterations progress by affecting intracellular signaling pathways (Hanahan & Weinberg, 2011).

In the pathogenesis of cancer, genes that promote uncontrolled cell growth and division (oncogenes) are activated, while genes that control the cell cycle and repair DNA damage (tumor suppressor genes) are inactivated. For instance, mutations in the TP53 gene, which regulates the cell cycle, allow cells to continue dividing despite DNA damage, thereby paving the way for tumor development (Vogelstein et al., 2013). Similarly, a mutation in the RAS gene, which normally regulates cell growth, division, and lifespan (proto-oncogene), leads to uncontrolled cell proliferation. In addition to these genetic changes, epigenetic factors also play a significant role in cancer development. Specifically, epigenetic changes such as DNA methylation and histone modifications can alter gene expression and initiate tumor formation (Jones & Baylin, 2007). Under normal conditions, cells with DNA damage are eliminated through programmed cell death (apoptosis). However, cancer cells disable this mechanism, allowing mutation-carrying cells to survive and continue to proliferate (Hanahan & Weinberg, 2011). This process, considered one of the key mechanisms in cancer pathogenesis, is defined as the inhibition of apoptosis. These processes, which form the basis of cancer development, lead to an increase in intracellular genetic instability through the impairment of DNA repair mechanisms, which in turn causes the accumulation of more mutations in tumor cells. This condition facilitates both the progression of cancer and the development of resistance to treatment.

The pathogenesis of cancer is a multi-layered process that occurs through the interaction of genetic, epigenetic, cellular, and environmental factors. In modern oncology, understanding these mechanisms makes it possible to both develop early diagnostic methods and apply targeted therapies.

Classification of Cancer

In cancer pathology, which is an approach focused on understanding the fundamental mechanism of cancer formation and the tumorous process, the cellular structure of the tumor, its tissue arrangement, growth pattern, invasion

potential, spread via lymph or blood (metastasis), cell differentiation (level of maturity), and mitotic activity (rate of division) are evaluated using various techniques. The pathological examination process, which is critical for the diagnosis and classification of cancer, also guides the treatment process and, in this respect, holds a crucial importance in both the diagnostic and therapeutic stages of cancer.

Cancer classification can be made according to various characteristics of the tumor. The classification of cancer based on the tissue type of origin remains valid and is widely used today. In this classification, cancers originating from epithelial tissue are classified as carcinoma; cancers originating from connective tissue as sarcoma; cancers originating from neuroectodermal tissue as melanoma; and cancers originating from blood and lymphoid tissue as hematological malignancy (Rosai, 2011). Naming cancer according to the tissue it is located in is a general classification, and more comprehensive classifications are made based on the specific organ where the cancer is localized (e.g., osteosarcoma, multiple myeloma).

Based on histopathological examination and imaging methods, the biological behavior and distribution of cancer can be evaluated, allowing for its classification as either benign or malignant. Benign tumors are a type of cancer that typically grows slowly, does not invade surrounding tissues, and lacks the ability to metastasize. Histologically, the cells are similar in structure to the normal cells from which they originated. Their borders are generally well-defined and can sometimes be surrounded by a capsule. Recurrence is usually not observed when these tumors are surgically removed. In contrast, malignant tumors are characterized by uncontrolled cell proliferation and can invade surrounding tissues, as well as metastasize to other tissues and organs via lymphatic or hematological pathways. Their indistinct borders with surrounding tissues are associated with a high rate of recurrence after surgery. Malignant cells are typically atypical, showing morphological abnormalities compared to their cells of origin (Rosai, 2011; WHO, 2022).

The degree to which cancer cells resemble or differ from normal tissue cells is called tumor differentiation (grade), and this concept indicates how "abnormal" cancer cells appear. Grading is typically done on a scale from 1 to 3 (sometimes up to 4) and is used in predicting cancer prognosis. In this classification, well-differentiated (Grade 1) tumors show morphological features similar to the healthy cells of origin, have a slow growth rate, and a much lower probability of metastasis, representing a good prognosis.

Moderately differentiated (Grade 2) tumors show significant morphological differences compared to the healthy cells of origin, have a more irregular cell structure, and an increased metastatic tendency compared to Grade 1. In poorly differentiated (Grade 3) tumors, the cells are very different from the normal cell morphology and are characterized by aggressive invasion and metastasis. Grade 3 clinically represents a poor prognosis (WHO, 2022).

In the diagnosis and treatment planning of cancer, classifying the degree of disease spread is of critical importance. The TNM system is an internationally accepted standard for classifying the extent of cancer spread. In this system, T (Tumor) indicates the size and depth of the tumor at its localization (T1-T4); N (Node) indicates whether cancer cells have led to regional lymph node involvement (N1-N3); and M (Metastasis) indicates the status of cancer cells spreading to distant parts of the body (M0-M1) (Figure 1) (Edge et al., 2010). The TNM staging system allows for a comprehensive assessment of the cancer, enabling the application of patient-specific treatment selections (Brierley et al., 2017).

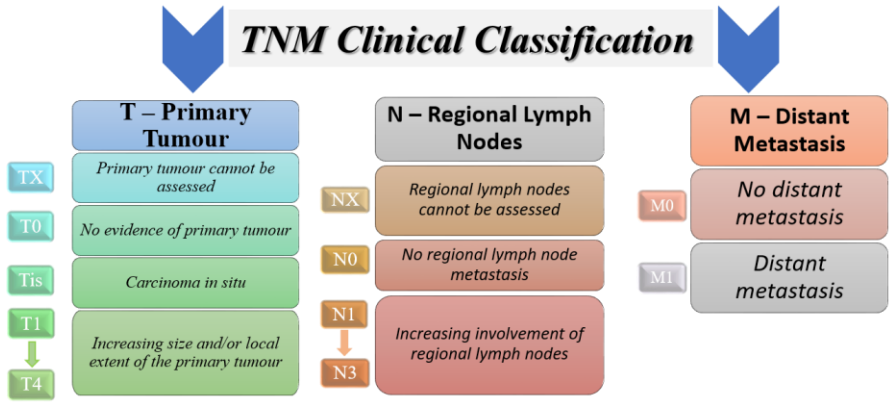

Figure 1. International Classification of Diseases for Oncology (Brierley et al., 2017)

In contemporary cancer classification, approaches based on the molecular and genetic characteristics of cells are increasingly coming to the forefront. This classification relies on a comprehensive analysis of genetic mutations, epigenetic changes, and gene expression profiles in cancer cells. This allows for a more detailed understanding of cancer biology while also enabling the personalization of treatment strategies (Garraway & Lander, 2013). For example, in breast cancer, the positivity of estrogen and

progesterone hormone receptors and BRCA1/2 gene mutations play a critical role in determining the subtypes of the disease and its response to treatment. In colorectal cancer, KRAS, NRAS, and BRAF mutations are important biomarkers for selecting targeted therapy (Dienstmann et al., 2017). Furthermore, in gliomas, IDH1 and IDH2 gene mutations enable the identification of molecular subtypes that affect tumor prognosis (Louis et al., 2021). These molecular classifications reveal cancer heterogeneity, supporting the development of more effective and personalized treatment approaches.

Diagnosis of Cancer

In the diagnostic process for cancer, which begins with clinical suspicion, various diagnostic methods are used in combination to reach a definitive diagnosis. In the first stage, the patient's medical history and physical examination are important. This step is followed by various imaging techniques and laboratory tests. The main imaging methods used today include ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) (Khan et al., 2019). The use of these techniques varies depending on the tumor's localization, spread, and method of use, but they are complementary in cancer diagnosis. USG is preferred for the initial evaluation of lesions in superficial organs such as the breast, thyroid, and liver due to its lack of radiation and rapid applicability (Khan et al., 2019). CT, on the other hand, is widely used for the localization and staging of masses in the thorax, abdomen, and pelvic regions because it provides high-resolution anatomical images (Brant & Helms, 2020). MRI is prominent in the detailed evaluation of tumors in areas such as the brain, pelvic organs, and spinal cord due to its high soft tissue contrast (Weissleder & Pittet, 2008). PET, meanwhile, plays an important role in the detection of early-stage metastases, monitoring treatment response, and screening for recurrence, as it visualizes cellular metabolism based on the increased glucose metabolism of malignant cells (Hanahan & Weinberg, 2011). The hybrid use of imaging methods increases diagnostic accuracy by providing both anatomical and functional information. However, these methods alone are insufficient for making a definitive diagnosis of cancer. In addition to imaging methods, biopsy and histopathological examination are necessary for a definitive diagnosis. Biopsy is the process of taking a tissue sample from a suspicious area and examining it under a microscope. The biopsy material is histopathologically evaluated under a microscope to examine parameters such as cell morphology and cell structures. This provides

information not only about the presence of malignancy but also about the type of tumor, its degree of differentiation (grade), and its potential for spread (Cagle et al., 2020).

Today, biopsy and histopathological examination are still considered the gold standard for cancer diagnosis. Although imaging and laboratory tests provide important information on the path to diagnosis, a definitive diagnosis cannot be made without direct microscopic examination of malignant cells (Rosai, 2011). In addition, immunohistochemical stains and molecular tests performed after biopsy allow for a better understanding of the type and characteristics of the cancer. While each method used in cancer diagnosis has different advantages and disadvantages, they are often used together and with a holistic approach in current clinical practice.

Cancer Treatment

The main treatment methods for cancer are surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, and their combinations. Surgery, the oldest and most classic method of cancer treatment, is the removal of the tumor from its localized area by a surgical procedure. Although these procedures have become widespread with the use of minimally invasive techniques today, the use of surgery alone is not sufficient in cancer treatment. Preoperative treatments (neoadjuvant) and postoperative treatments (adjuvant) play a critical role in this process.

Radiotherapy is a physical agent that generates electrically charged particles (ions) used to destroy cancer cells. Through the ions it creates, it causes energy accumulation in the cells of the tissues it passes through, damaging the cells' genetic material. Thus, it can kill cancer cells by blocking cell proliferation or cause genetic changes that result in the death of the cancer cell (Baskar et al., 2012).

Chemotherapy, a treatment method that uses anti-cancer drugs with cytotoxic effects that target rapidly dividing cancer cells, is used both to shrink the primary tumor and control metastasis, and in combination with surgical or radiotherapy treatment methods. Cancer cells can gain resistance to chemotherapeutic agents due to various factors such as genetic changes and epigenetic factors, both during and after the treatment process. The common side effects and undesirable effects of chemotherapy drugs are factors that limit the treatment process.

Hormone therapy is a treatment method that aims to stop or slow down tumor growth by suppressing the production of hormones or by blocking hormone receptors in tumors where hormones are effective in cell division and growth. In this treatment method, side effects may occur, resistance may develop, and a response to the treatment may not be achieved due to the formation of new mutations in the tumor.

Despite the progress made in the fields of diagnosis and treatment, cancer continues to be a major public health problem worldwide and ranks as the second leading cause of death globally (Zugazagoitia et al., 2016; WHO, 2021). Today, cancer is regarded not as an isolated disease but as a complex spectrum of illnesses, each with hundreds of subtypes possessing unique molecular profiles and genetic mutations (Hoadley et al., 2018).

While traditional treatment methods such as surgery, radiotherapy, chemotherapy, and hormone therapy, which are widely used in cancer treatment, can extend life expectancy in many clinical cases, these approaches often fail to consider the molecular heterogeneity of tumors and can cause off-target effects. For example, although surgical treatment is curative by removing the tumor, it is not sufficient on its own to eliminate the risk of micrometastasis or postoperative recurrence. Although the combined use of this treatment method with other treatment methods is common, the damage to healthy cells as well as cancer cells as an off-target and undesirable effect in the treatment combination limits the effectiveness of the treatment (Zafar et al., 2025). Furthermore, although significant progress has been made in cancer treatment with treatment methods such as immunotherapy, CAR-T cell therapies, and targeted therapies, a response is obtained only in some patients with these methods, and resistance to the treatment can develop during the process (Gupta & Shukla, 2022). In addition to the limitations in treatment methods, the broad and complex molecular background of cancer, intra- and inter-tumoral genetic and epigenetic differences, and the dynamic and variable structure of the tumor microenvironment stand out as factors that further limit the effectiveness of these treatment approaches (MacDonald et al., 2025; Zugazagoitia et al., 2016).

Over the past 20 years, the analysis of the molecular background, which refers to the characterization of tumors, has made significant contributions to understanding cancer development and progression. In particular, genomic and transcriptomic analyses reveal that even subgroups of a single cancer type show significant molecular differences from one another. This highlights the

need for individualized approaches at every stage, from diagnosis to treatment (Perou et al., 2000; Koboldt et al., 2012). Consequently, the heterogeneous nature of cancer limits the effectiveness of classical treatment protocols and necessitates the development of more precise, biologically based approaches. In response to these challenges, precision oncology approaches are coming to the forefront today.

Targeted Therapy: Precision Oncology

Precision oncology is a modern, biomarker-based oncology approach that aims to provide customized cancer treatment based on the genetic, epigenetic, and molecular characteristics of each patient's tumor (Schmidt et al., 2016; Schwartzberg et al., 2017). Unlike traditional treatments that target the treatment process in a similar way for all cancer patients, precision oncology aims to determine the most effective treatment strategies on a per-patient basis by considering specific genetic mutations, biomarkers, and molecular pathways unique to each patient's tumor. This approach can increase treatment efficacy, especially in patients with specific gene mutations (such as BRCA, BRAF, EGFR), and provide better survival outcomes with fewer side effects compared to classical methods (Haslem et al., 2018). With this approach, the extent and volume of the tumor in the body, expressed as tumor burden, and genetic changes can be monitored during treatment. This dynamic monitoring process allows oncologists to evaluate the response to treatment in real-time and, when necessary, change the medication or treatment strategy with an earlier intervention. Furthermore, understanding drug resistance mechanisms (e.g., mutations in intracellular pathways, epigenetic changes, effects of the tumor microenvironment) allows for the development of new targets and the optimization of combination therapies in precision oncology (Khan et al., 2024). This way, treatment efficacy is increased while preventing unnecessary toxicity and time loss. In addition, this approach is also of critical importance for the development of next-generation targeted agents and for making patient-specific therapeutic decisions in parallel with the progress of the technological process. Today, this method is increasingly used, especially in advanced-stage cancers, to monitor treatment sensitivity and the development of resistance, and is supported by artificial intelligence and bioinformatics analyses to obtain more precise and rapid results (Vidal et al., 2023; Srivastava, 2025).

The main principles of precision oncology, which focuses on the patient rather than the disease, include a molecularly targeted approach, biomarker-based patient selection, tumor heterogeneity, the integrated use of genomic information, dynamic patient monitoring, and a patient-centered decision-making process.

In the process of cancer development and progression, genetic mutations directly affect the growth and spread of the tumor. The determination of the levels and types of biomarkers such as existing mutations, gene expression levels, protein levels, and tumor mutation burden from a patient's tumor tissue or blood sample, and the creation of a tumor profile, are handled within the scope of a molecularly targeted approach. The aim of this process is the systematic, multilayered examination of the genetic, epigenetic, transcriptomic, and proteomic molecular characteristics of the tumor sample taken from the patient; and the acquisition of diagnostic, prognostic (related to the course of the disease), and predictive (related to treatment response) information from these characteristics. According to the molecular information obtained from the changes (presence of mutations, changes in gene expression/protein levels) detected in the analyses performed with the samples taken from the patient, the treatment process and scope are shaped on a patient-by-patient basis. With this method, appropriate treatment methods are applied according to the tumor's biomarkers, and since a drug targeting the tumor is given, unnecessary drug use is prevented, possible side effects are minimized, and the treatment process is optimized by better understanding the molecular structure of the tumor.

In precision oncology, the understanding of 'treatment according to cancer type' in classical oncology treatment methods has been replaced by 'treatment according to biomarker'. The biomarker-based approach is one of the main tools that enables the clinical applicability of precision oncology. This approach goes beyond treatment decisions limited to classical demographic and histological criteria and allows for individual treatment planning according to the patient's molecular profile. Biomarkers are defined as any molecule, gene, gene product, or characteristic that can be an indicator of a disease or a response to treatment. In clinical use, biomarkers can be used for diagnostic, prognostic, predictive, pharmacodynamic, and monitoring purposes. Predictive biomarkers are of critical importance in precision oncology. In patients with certain molecular changes, these changes are determined with biomarkers, and a suitable treatment process is shaped for the patient. In addition, predictive biomarkers show the probability of response to

a particular treatment by predicting in advance whether a patient will benefit from a treatment, thus preventing unnecessary drug use and toxicity in the patient.

The success of precision oncology depends on a correct and complete understanding of the tumor's molecular structure. A fundamental element that complicates this process but should not be overlooked is tumor heterogeneity, which is the situation where cells within a tumor or cells in different patients with the same tumor show genetic, epigenetic, phenotypic, or behavioral differences from each other. The heterogeneity of the tumor can lead to the biopsy sample being insufficient to represent the entire tumor and, in the continuation of the process, can cause the incorrect determination of biomarkers and a deviation towards inappropriate treatment. At this stage, considering tumor heterogeneity, liquid biopsy, multi-region biopsy, and re-profiling over time are required, without being limited to a single biopsy.

The integrated use of genomic information encompasses the process of combining genetic/molecular information obtained from a patient's tumor with clinical data to create personalized diagnosis, treatment, and follow-up plans. In this stage of precision oncology, not only the patient's mutations/genetic information but also the patient's age, general condition, suitability for treatment, and accompanying diagnostic tests are evaluated. With integrated analysis, not only existing mutations but also mutations that may cause drug resistance during the process are detected, and treatment is planned accordingly.

Molecular diagnostic methods used in precision oncology include techniques that help develop the most appropriate treatment strategy for the patient by determining the genetic and biological characteristics of cancer. These methods are generally based on the analysis of genetic material obtained from tumor tissue (sometimes from blood/liquid biopsy). One of these methods, NGS (Next Generation Sequencing), is a high-throughput genetic analysis technology. NGS is a technique that allows for the simultaneous, rapid, and very low-cost analysis of all nucleotide sequences or specific gene regions in an individual's genetic materials. The NGS method, which allows cancer to be treated as a unique condition with its own genetic fingerprint rather than "a single disease", can rapidly determine the prognosis of the disease, its potential for recurrence, and mutations responsible for drug resistance. The NGS process generally consists of three main stages: nucleic acid isolation and library preparation, sequencing, and bioinformatic analysis.

In the first stage, DNA or RNA is isolated from tumor tissue, blood (liquid biopsy), or another biological sample taken from the patient. The resulting long DNA strands are reduced to sizes that can be read by sequencing platforms and divided into small fragments. To the ends of these DNA fragments, "adapter" sequences are added that allow them to bind to the sequencing surface and be amplified. This process is called DNA library preparation (Mardis, 2017). In the second stage, the sequencing process, the prepared library is loaded into an NGS machine. The machine identifies the identity of each base by sequentially adding fluorescently labeled nucleotides to the DNA strands. This process allows a large number of DNA fragments to be sequenced simultaneously, and the sequence of each fragment is recorded "like a photograph". In this way, millions of base pairs can be read at the same time (Metzker, 2010). In the final stage, bioinformatic analysis, the raw data obtained from the sequencing machine is processed through special software. This data is compared with the human reference genome to identify genetic variants such as nucleotide changes, insertions, deletions, copy number variations, and fusions. The resulting variants are interpreted using mutation databases known in the literature. As a result of this analysis,

With its increasing importance in cancer diagnosis and treatment, the liquid biopsy method, a non-invasive diagnostic method, is based on the molecular analysis of biological materials such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles (e.g., exosomes) obtained from the patient's body fluids (such as blood). In the precision oncology approach, the liquid biopsy method offers significant advantages such as the dynamic monitoring of treatment resistance development, which cannot be accessed with traditional tissue biopsy, detecting the presence of minimal residual disease (MRD), or detecting signs of early recurrence. In addition, in tumors that are difficult to biopsy or in cases where the patient's general condition is not suitable for an invasive procedure, liquid biopsy stands out as a critical alternative. This method, which is effectively used in clinical practice, especially in determining mutations such as EGFR, ALK, KRAS, and BRAF, is guiding in the selection of targeted therapy and immunotherapies. Liquid biopsy is an indispensable component of precision oncology, especially in critical issues such as monitoring the treatment process, detecting drug resistance, and evaluating tumor heterogeneity (Wan et al., 2017; Rolfo et al., 2018).

CONCLUSION

In contemporary oncology, precision medicine approaches are increasingly favored by clinicians. The continuous advancement of diagnostic, imaging, and therapeutic technologies indicates a growing adoption of these personalized strategies. The ability to precisely map an individual's genetic profile from biological samples using high-tech instruments, and to determine patient-specific therapeutic doses for drugs, is of paramount importance in cancer treatment.

The widespread implementation of personalized cancer therapies, guided by molecular and genetic data, is expected to become the norm in modern medicine. This shift is anticipated not only in oncology but also in other medical fields, where tailored treatment approaches based on an individual's unique biological makeup will improve therapeutic outcomes. By minimizing unnecessary drug exposure and optimizing treatment regimens, these methods promise to enhance efficacy and reduce adverse effects. The integration of such data-driven, patient-centric strategies is a key expectation for the future of healthcare, as it moves the focus from a one-size-fits-all model to one that addresses the unique molecular characteristics of each patient.

RECOMMENDATİONS

The fight against cancer, a disease of our time, is growing globally every day. Patients and their families are eagerly awaiting a groundbreaking new method or a permanent cure, placing a significant and increasing responsibility on researchers. We are already witnessing the impact of technological advancements in in vitro and in vivo research, leading to modifications in study topics and areas.

Unfortunately, we know that drugs administered to cancer cells can cause structural damage to healthy cells over time. However, the future may hold promise with smart, nano-sized drugs that can identify and directly target cancer cells without harming healthy ones. What remains clear is the need for more than the current contributions to the literature, with researchers who have or are gaining sufficient knowledge in the field of cancer needing to produce work that pushes the boundaries of existing understanding. This increasing demand for groundbreaking research highlights the urgency of developing more precise, less harmful, and ultimately curative solutions for cancer.

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