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PERSPECTIVES

An Overview of Cancer Biology, Staging, Metastasis, and Treatment Limitations

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Abstract

Cancer represents a highly heterogeneous group of diseases driven by complex genetic, epigenetic, and microenvironmental interactions that result in diverse biological behavior and clinical outcomes. Despite substantial advances in molecular biology, diagnostics, and therapeutic strategies, cancer remains a leading cause of global morbidity and mortality, with advanced-stage disease continuing to pose major clinical challenges. This narrative review provides an integrated overview of fundamental cancer biology, including genetic alterations, hallmark capabilities, tumor microenvironmental influences, and intratumoral heterogeneity, alongside contemporary classification and staging systems. It examines the biological mechanisms and clinical consequences of metastasis, which remains the principal cause of cancer-related death, and reviews current treatment modalities such as surgery, radiotherapy, systemic chemotherapy, targeted therapy, hormonal therapy, immunotherapy, and emerging cellular therapies. The review critically discusses the major limitations of modern cancer treatment, including therapeutic resistance, treatment-related toxicity, immune escape, high cost, and late-stage diagnosis. Particular emphasis is placed on understanding why metastatic (Stage IV) cancer remains largely incurable despite modern therapeutic advances, highlighting the roles of metastatic burden, microenvironmental protection, cellular dormancy, impaired drug delivery, and genetic instability. Finally, emerging future directions including precision oncology, oncolytic virotherapy, gene editing, nanomedicine, tumor vaccines, and liquid biopsy–based monitoring are explored as potential strategies to improve early detection, personalize treatment, and overcome resistance. This review aims to provide a cohesive, biologically informed synthesis to support more effective and personalized approaches to cancer care.

Keywords: Tumor heterogeneity- Therapeutic resistance- Precision oncology- Cancer progression- Treatment failure

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide and continues to pose a major global health challenge. According to recent global estimates, nearly 20 million new cancer cases and approximately 10 million cancer-related deaths occurred in 2022, with a disproportionate burden observed in low- and middle-income countries where delayed diagnosis, limited screening programs, and restricted access to effective treatment contribute to poorer outcomes [1]. Beyond its epidemiological impact, cancer represents a biologically complex group of diseases encompassing more than two hundred distinct tumor types, each characterized by unique molecular and cellular features. This heterogeneity arises from the accumulation of genetic and epigenetic alterations, dysregulation of oncogenes and tumor suppressor genes, and dynamic interactions between malignant cells, the tumor microenvironment, and the host immune system, leading to substantial variability in disease behavior and therapeutic response [2].

A detailed understanding of cancer biology is fundamental to improving patient outcomes and guiding therapeutic development. The biological basis of cancer is underpinned by a defined set of functional capabilities, collectively described as the hallmarks of cancer, which represent common traits acquired during malignant transformation. These include sustained proliferative signaling, evasion of growth suppressors, resistance to programmed cell death, genomic instability, induction or

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access to tumor vasculature, and activation of invasion and metastatic spread [3]. This conceptual framework provides a unifying model that distills the biological complexity of diverse malignancies into shared underlying principles and has become central to modern oncology, informing mechanistic insights as well as the rational development of targeted and immune-based therapies.

Clinical staging is a cornerstone of cancer management, providing critical information for prognostication, treatment planning, and outcome assessment. The tumor–node–metastasis (TNM) classification system offers a standardized method for describing disease extent by evaluating primary tumor characteristics, regional lymph node involvement, and the presence of distant metastasis. By integrating clinical examination, imaging, and pathological findings, TNM staging enables patient stratification and guides therapeutic decision-making across solid tumors [1]. While early-stage cancers may often be effectively treated with localized modalities, advanced-stage disease typically requires systemic or multimodal therapy and is associated with significantly poorer prognoses.

Metastasis remains the principal cause of cancer-related mortality and represents a major barrier to curative treatment. The metastatic process is a complex, multistep cascade involving tumor cell invasion, dissemination through lymphatic or hematogenous routes, and colonization of distant organs, regulated by interactions between tumor-intrinsic factors and the surrounding microenvironment [4]. Once metastatic disease is established, therapeutic options become limited and long-term remission is difficult to achieve. Despite substantial advances in cancer treatment, including molecularly guided therapies and immunotherapeutic approaches, recurrence, resistance, and treatment-related toxicity remain common challenges, underscoring the need for earlier detection and more effective, biologically informed treatment strategies [2].

Despite substantial progress in understanding cancer biology and developing new therapeutic strategies, an integrated perspective that links tumor biology, staging systems, metastatic progression, treatment evolution, and therapeutic limitations is often presented across disparate sources. This article presents a narrative, educational review that provides a comprehensive and integrative overview of these interconnected domains, with the aim of supporting clearer understanding of current challenges and informing biologically grounded and personalized approaches to cancer care.

2. Biology of Cancer

2.1 Genetic alterations

Cancer initiation and progression are driven by the accumulation of genetic and epigenetic alterations that disrupt normal cellular homeostasis. Activating mutations in oncogenes promote constitutive signaling through pathways that regulate cell proliferation, survival, and cellular metabolism, thereby enabling uncontrolled cell growth [5]. In contrast, loss or functional inactivation of tumor suppressor genes, such as TP53 and RB1, removes critical regulatory checkpoints that normally restrain cell cycle progression, preserve genomic integrity, and trigger apoptosis in response to cellular stress [2, 5].

Defects in DNA repair mechanisms including mismatch repair and homologous recombination pathways further contribute to genomic instability, facilitating the accumulation of additional mutations and chromosomal alterations over time [2, 5]. These genetic abnormalities may be inherited, conferring an increased lifetime risk of malignancy, or acquired sporadically as a result of environmental exposures such as tobacco smoke, ionizing radiation, oncogenic viral infections, and chronic inflammation [2, 5]. Collectively, these alterations disrupt key pathways governing cell cycle regulation, apoptosis, growth factor signaling, and genome maintenance, establishing the molecular foundation for malignant transformation and tumor evolution [5].

2.2 Hallmarks of cancer

The hallmarks of cancer describe a set of functional capabilities progressively acquired during tumour development that collectively enable malignant growth. Central to this framework is sustained proliferative signalling combined with evasion of growth-suppressive pathways, allowing continued cell division despite normal regulatory constraints. Cancer cells also acquire resistance to programmed cell death, enabling survival under conditions of oncogenic stress, DNA damage, and metabolic imbalance [3]. Maintenance of telomere integrity permits replicative immortality, allowing tumour cells to bypass intrinsic limits on cellular lifespan. To support sustained growth, tumours induce or co-opt vasculature through angiogenic signalling, ensuring adequate delivery of oxygen and nutrients [3]. Another defining hallmark is activation of invasion and metastatic dissemination, which underlies disease progression and accounts for the majority of cancer-related deaths. More recent expansions of this framework include deregulated cellular metabolism, avoidance of immune destruction, and tumour-promoting inflammation, reflecting the dynamic interactions between cancer cells and their microenvironment [3, 6, 7]. Together, these hallmarks provide a unifying biological framework that has guided the development of targeted therapies, anti-angiogenic agents, metabolic inhibitors, and immunotherapeutic ategies.

2.3 Tumor Microenvironment

The tumor microenvironment (TME) comprises immune cells, stromal fibroblasts, endothelial cells, extracellular matrix components, and soluble signaling factors that surround malignant cells [8]. Rather than acting as a passive scaffold, the TME actively regulates tumor growth, invasion, immune evasion, and therapeutic response [8]. Immune cells within the TME frequently adopt immunosuppressive phenotypes, including tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells, which impair effective antitumor immunity and contribute to resistance to immunotherapy

[9]. Stromal components such as cancer-associated fibroblasts remodel the extracellular matrix and secrete growth factors that promote tumor progression, while hypoxic conditions drive angiogenesis and selection of aggressive cellular phenotypes [8]. In addition, tumor–stromal communication mediated by extracellular vesicles, including exosomes, enhances survival signaling and therapeutic resistance [10].

2.4 Tumor Heterogeneity

Tumor heterogeneity refers to the coexistence of genetically, epigenetically, and phenotypically distinct cancer cell populations within the same tumor and across disease sites. This diversity arises through continuous tumor evolution driven by genomic instability, selective pressures from the microenvironment, and therapeutic interventions, resulting in branched clonal architectures [11]. Single-cell sequencing studies have revealed extensive intra-tumoral heterogeneity, identifying rare subclonal populations that contribute to treatment resistance and disease relapse [12]. Inter-tumoral heterogeneity between patients further reflects differences in genetic background, environmental exposures, and tumor biology, complicating the development of universally effective therapies [11].

3. Benign vs Malignant tumours

Benign and malignant tumors represent biologically distinct forms of neoplastic growth that differ in their evolutionary dynamics, growth behavior, invasive capacity, and clinical consequences [13]. Benign tumors arise from localized cellular proliferation and are typically characterized by slow growth, well-circumscribed margins, and preservation of normal tissue architecture, reflecting limited evolutionary selection pressures within the tumor microenvironment [13]. These lesions remain confined to their site of origin, lack the capacity for tissue invasion or metastatic dissemination, and therefore exert minimal impact on overall survival [13]. Many benign tumors retain a high degree of cellular differentiation and may remain asymptomatic throughout life, although they can cause clinical manifestations through mass effect or hormone secretion in specific anatomical settings, such as endocrine tissues [14].

In contrast, malignant tumors are defined by uncontrolled proliferation accompanied by progressive loss of tissue organization, infiltrative growth, and the ability to invade surrounding structures and disseminate to distant organs via lymphatic or hematogenous routes [15]. The capacity for invasion and metastasis represents a fundamental biological distinction between benign and malignant neoplasms and is responsible for the majority of cancer-related mortality [15]. At the cellular level, malignant tumors display marked cytologic atypia, increased mitotic activity, genomic instability, and ongoing clonal evolution, enabling adaptation to environmental and therapeutic pressures and driving disease progression and treatment resistance [13].

These biological differences have profound clinical implications. Benign tumors are often effectively treated with complete surgical excision and rarely recur when adequately removed, reflecting their limited invasive and evolutionary potential [14]. In contrast, malignant tumors frequently require aggressive multimodal treatment strategies, including combinations of surgery, radiotherapy, systemic therapy, and immunotherapy, depending on tumor stage and biological characteristics [15]. Accurate differentiation between benign and malignant lesions is therefore essential for appropriate treatment selection, prognostic assessment, and optimization of patient outcomes.

4. Cancer classification and staging

4.1 Classification

Cancers are commonly classified according to their cell type and tissue of origin, an approach that reflects underlying biology and remains central to diagnosis and clinical management. Carcinomas arise from epithelial cells and constitute the majority of human malignancies, encompassing subtypes such as adenocarcinomas and squamous cell carcinomas that originate from glandular or surface epithelia, respectively [16]. Sarcomas derive from mesenchymal tissues, including bone, muscle, adipose tissue, and connective tissue, and although relatively rare, they often exhibit aggressive biological behavior and marked histologic diversity [16]. Hematologic malignancies including leukemias, lymphomas, and plasma cell neoplasms originate from hematopoietic or lymphoid lineages and are typically characterized by diffuse growth rather than solid tumor formation [17].

Additional categories include melanomas arising from melanocytes, germ cell tumors originating from reproductive cells, and neoplasms of the central nervous system and neuroendocrine system, each reflecting distinct developmental origins. This histogenetic classification framework provides a foundation for prognostication, therapeutic selection, and integration of emerging molecular classification systems in modern oncology.

4.2 TNM Staging

The tumor–node–metastasis (TNM) staging system, developed and periodically updated by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), represents the most widely accepted global framework for describing the anatomic extent of solid malignancies [18]. The TNM system evaluates three core components: the primary tumor (T), regional lymph node involvement (N), and the presence or absence of distant metastatic disease (M), each contributing independently to prognosis and treatment planning [18]. The T category reflects tumor size and the degree of local invasion, while the N category characterizes regional nodal involvement based on the number, size, and distribution of metastatic lymph nodes. Recent studies have highlighted the prognostic significance of tumor deposits discrete tumor nodules lacking identifiable lymph node architecture which are not fully captured by traditional nodal staging and may indicate more aggressive disease biology [19]. The M category denotes distant

metastatic spread, a defining feature of advanced-stage cancer associated with poor prognosis [18]. By integrating clinical evaluation, imaging, and pathological assessment, TNM staging provides a standardized language for communication, research comparison, and evidence-based decision-making. Although primarily anatomy-based, contemporary TNM staging is increasingly refined through periodic updates and, in selected cancers, complemented by biological and molecular markers to improve prognostic accuracy [20].

4.3 Stage Grouping I–IV

Following assignment of individual T, N, and M categories, tumors are grouped into overall stages ranging from Stage I to Stage IV, summarizing disease extent and guiding clinical management [21]. Stage I cancers are typically localized and associated with favorable outcomes following local therapy. Stage II disease generally reflects larger tumors or limited regional extension and may require adjuvant treatment. Stage III cancers demonstrate significant regional spread, including extensive lymph node involvement or invasion of adjacent structures, often necessitating multimodal therapy. Stage IV disease is defined by distant metastasis, representing systemic dissemination and markedly reduced long-term survival. Overall stage grouping is essential for prognostic stratification, treatment selection, and patient counseling, as early-stage cancers may be potentially curable, whereas advanced stages usually require systemic therapy and are associated with poorer outcomes [21].

5. Metastasis

Metastasis is the defining biological feature of malignant tumors and is responsible for the majority of cancer-related deaths worldwide, accounting for more than 90% of cancer mortality [22]. Unlike primary tumor growth, metastatic dissemination is a highly inefficient and selective process in which only a small fraction of tumor cells successfully establishes secondary lesions [23]. The lethality of metastasis arises from the ability of disseminated cancer cells to survive hostile conditions, adapt to distant tissue environments, and generate progressive disease that is difficult to eradicate [22].

5.1 Mechanisms of Metastasis: EMT to Colonization

The metastatic cascade typically begins with epithelial–mesenchymal transition (EMT), a reversible cellular program that enables epithelial cancer cells to lose polarity and cell–cell adhesion while acquiring enhanced migratory and invasive properties [24]. During EMT, epithelial markers such as E-cadherin are downregulated, whereas mesenchymal markers, including N-cadherin and vimentin, are upregulated, facilitating detachment from the primary tumor and invasion into surrounding tissues [24]. EMT is regulated by transcription factors such as SNAIL, TWIST, and ZEB family proteins and frequently occurs in partial or hybrid states that enhance metastatic fitness rather than complete phenotypic conversion [22].

Following local invasion, tumor cells degrade the basement membrane and extracellular matrix through matrix metalloproteinases and subsequently enter blood or lymphatic vessels in a process known as intravasation [22]. This step is promoted by tumor-associated macrophages, inflammatory cytokines, and increased vascular permeability within the tumor microenvironment [22]. Once in the circulation, circulating tumor cells are exposed to mechanical shear stress and immune surveillance, leading to the elimination of most disseminated cells [23]. Survival is enhanced by the formation of circulating tumor cell clusters and interactions with platelets, which shield tumor cells from immune-mediated clearance [23, 25].

Surviving tumor cells adhere to the endothelium at distant sites and migrate across the vascular wall through extravasation [25]. The final and most rate-limiting step of metastasis is colonization, during which disseminated tumor cells must adapt to the metabolic, mechanical, and immune conditions of the secondary organ [26]. Many disseminated tumor cells enter a dormant state that can persist for prolonged periods before reactivation, contributing to late metastatic relapse and therapeutic failure [22]. Successful colonization requires immune evasion, induction of angiogenesis, and remodeling of the local stromal niche, underscoring that metastasis represents a complex evolutionary process rather than simple physical dissemination of cancer cells [22].

5.2 Organ Tropism

Metastatic dissemination is not random, as many cancers exhibit a preference for colonizing specific distant organs, a phenomenon known as organ tropism [27]. This selectivity reflects the interaction between anatomical routes of spread and molecular compatibility between tumor cells ("seeds") and the microenvironment of target organs ("soil"), consistent with the seed-and-soil hypothesis [27]. For example, colorectal cancer frequently metastasizes to the liver due to portal venous drainage, whereas breast cancer commonly spreads to the bone, liver, and lung [28]. Beyond anatomical factors, organ-specific metastasis is driven by molecular mechanisms including chemokine receptor–ligand interactions, integrin-mediated adhesion, metabolic adaptability, and immune permissiveness within target tissues [28]. Tumor-on-chip models further demonstrate that organ-specific microenvironmental cues actively regulate cancer cell survival and colonization, providing experimental validation of organ tropism [29].

5.3 Why Metastasis Kills

Metastatic disease accounts for the vast majority of cancer-related deaths because it represents a systemic, multi-organ process rather than localized tumor growth [30]. When cancer cells colonize vital organs such as the liver, lungs, brain, or bone, even a limited metastatic burden can disrupt essential physiological functions, ultimately leading to organ failure and death. Population-based analyses show that more than 80% of patients with advanced cancer die as a direct consequence of metastatic progression, with median survival often measured in

months despite therapeutic advances [31]. Biologically, metastases differ from primary tumors by exhibiting increased genetic heterogeneity, phenotypic plasticity, and resistance to therapy, reducing the effectiveness of chemotherapy, targeted agents, and immunotherapy [30]. In addition, metastatic cells exploit protective organ-specific microenvironments that limit drug penetration and promote immune evasion, while dormant disseminated tumor cells can persist for years before reactivation, driving late relapse and poor long-term outcomes [30]. Together, organ dysfunction, biological adaptability, and therapeutic resistance make metastasis the most lethal stage of cancer progression.

6. Current treatments

Cancer treatment has evolved from predominantly local interventions to integrated, biologically informed strategies that combine surgery, radiotherapy, systemic therapies, and immunomodulation. Advances in tumor biology, molecular profiling, and immunology have expanded therapeutic options to include targeted agents, immunotherapies, and cell-based treatments alongside conventional modalities. Contemporary cancer care aims not only to achieve tumor control but also to prolong survival, reduce recurrence, and preserve quality of life. Treatment selection is increasingly individualized, guided by tumor histology, disease stage, molecular alterations, patient-related factors, and healthcare resources. Consequently, most patients are managed through multidisciplinary treatment plans that strategically integrate local and systemic therapies to optimize clinical outcomes [32].

6.1 Surgery

Surgical resection remains a cornerstone of cancer treatment, particularly for early-stage solid tumors. The primary objective of oncologic surgery is complete tumor removal with histologically negative margins while preserving organ function. When disease is localized, surgery alone may be curative, as observed in early breast cancer, colorectal cancer, and many soft tissue tumors [32].

Technological advances have refined surgical practice, with minimally invasive approaches such as laparoscopic and robotic-assisted surgery increasingly adopted. These techniques reduce perioperative morbidity, postoperative pain, and recovery time while maintaining oncologic outcomes comparable to open surgery [33]. Beyond curative intent, surgery serves important diagnostic and palliative roles, including tumor biopsy, relief of obstruction or bleeding, and cytoreduction to enhance the effectiveness of adjuvant therapies. In advanced metastatic disease, surgery is rarely curative and is most effective when integrated with systemic treatment strategies rather than used in isolation [32].

6.2 Radiotherapy

Radiotherapy is a central pillar of modern oncology and is utilized in approximately half of all cancer patients during their disease course [34]. By delivering ionizing radiation, radiotherapy induces DNA damage particularly double-strand breaks that impair tumor cell replication and lead to cell death through apoptosis, mitotic catastrophe, or senescence [34].

Advances in imaging, treatment planning, and radiation delivery have transformed radiotherapy into a highly precise modality capable of achieving durable tumor control while minimizing injury to surrounding normal tissues. Techniques such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy, stereotactic body radiotherapy (SBRT), and proton beam therapy allow conformal dose escalation and improved sparing of critical organs [34]. These innovations have expanded the curative potential of radiotherapy in both early-stage and locally advanced cancers.

Radiotherapy may be administered with curative intent as definitive treatment, for example, in head and neck, cervical, or prostate cancers, or as adjuvant therapy following surgery to reduce local recurrence risk [34]. In metastatic disease, radiotherapy plays a vital palliative role by alleviating symptoms such as bone pain, spinal cord compression, brain metastases, and airway obstruction, thereby improving quality of life [34].

At the molecular level, epigenetic regulation influences radiosensitivity and DNA damage response pathways, creating opportunities for radiosensitization and rational combination with systemic therapies [35]. Nonetheless, radiotherapy is associated with dose- and tissue-dependent toxicities, including fibrosis and organ-specific late effects, underscoring the need for individualized planning and long-term follow-up [36].

6.3 Chemotherapy

Chemotherapy remains a foundational component of systemic cancer treatment and has been used for decades across a wide range of malignancies [37]. Cytotoxic agents primarily target rapidly dividing cells by disrupting DNA synthesis, mitotic spindle formation, or essential metabolic processes, leading to tumor cell death [37]. Because these mechanisms are not tumor-specific, chemotherapy also affects normal proliferating tissues, accounting for its characteristic toxicities.

Multiple classes of chemotherapeutic agents are employed in clinical practice, including alkylating agents, antimetabolites, anthracyclines, and taxanes, each with distinct molecular targets and toxicity profiles [38].

Chemotherapy may be administered in the neoadjuvant setting to reduce tumor burden before local therapy, as adjuvant treatment to eradicate microscopic residual disease, or as palliative therapy to prolong survival and control symptoms in advanced cancer [39]. Combination regimens, such as FOLFOX for colorectal cancer or CHOP for lymphoma, are designed to maximize antitumor efficacy while limiting resistance through non-overlapping mechanisms of action [39].

Despite proven survival benefits, chemotherapy is limited by substantial acute and chronic toxicities, including myelosuppression, neuropathy, cardiotoxicity, mucositis, and fatigue [37]. Tumor resistance either intrinsic or acquired remains a major cause of treatment failure. Mechanisms include genetic mutations, activation

of alternative signaling pathways, increased drug efflux, altered metabolism, epigenetic reprogramming, and protective effects of the tumor microenvironment [38]. Tumor heterogeneity and clonal evolution further promote the selection of resistant subpopulations under therapeutic pressure [37].

6.4 Hormonal Therapy

Hormonal therapy is central to the management of endocrine-dependent malignancies, particularly breast and prostate cancers, where tumor growth is driven by estrogen or androgen signaling [40]. These therapies suppress hormone production or block receptor activity, depriving cancer cells of critical proliferative signals. In breast cancer, agents such as tamoxifen, aromatase inhibitors, and ovarian suppression are widely used across disease stages [41]. Prostate cancer treatment relies on androgen deprivation therapy using LHRH agonists or antagonists, often combined with androgen receptor inhibitors [40]. Although highly effective initially, resistance frequently develops through receptor mutations, intratumoral steroidogenesis, and activation of alternative signaling pathways. Long-term therapy is also associated with metabolic, skeletal, and cardiovascular adverse effects [40, 42].

6.5 Targeted Therapy

Targeted therapies have transformed cancer treatment by selectively inhibiting molecular pathways that drive tumor growth and survival, offering a more precise alternative to cytotoxic chemotherapy [43]. These agents act on defined abnormalities such as activating gene mutations, receptor overexpression, or dysregulated signaling cascades, thereby improving efficacy while reducing damage to normal tissues [43]. Clinically established examples include EGFR inhibitors in non-small cell lung cancer, HER2-directed therapies in breast cancer, BRAF/MEK inhibitors in melanoma, and ALK or ROS1 inhibitors in molecularly defined lung adenocarcinomas [43, 44].

The success of targeted therapy depends on accurate molecular profiling and identification of actionable alterations, highlighting the importance of precision diagnostics in modern oncology [45]. Although targeted agents often produce dramatic initial responses and improved survival, resistance commonly emerges. Mechanisms include secondary mutations, pathway bypass, receptor amplification, and intratumoral heterogeneity that enables clonal escape under treatment pressure [43]. Targeted therapies may also cause off-target toxicities, including cardiotoxicity, dermatologic reactions, hepatotoxicity, and gastrointestinal adverse effects [43]. Despite these limitations, targeted therapy remains a cornerstone of precision oncology and continues to expand through the discovery of new targets and rational combination strategies [43, 44].

6.6 Immunotherapy

Immunotherapy represents a major paradigm shift in cancer treatment by harnessing the host immune system to recognize and eliminate malignant cells [46]. Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have been particularly transformative, restoring effective T-cell–mediated antitumor immunity by reversing tumor-induced immune suppression [46, 47].

Checkpoint inhibitors have demonstrated durable clinical benefit across multiple malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma, and selected colorectal cancers [47, 48]. Combination strategies, especially dual blockade of PD-1/PD-L1 and CTLA-4, enhance antitumor responses by acting at complementary stages of T-cell activation, although with increased toxicity [49]. Other immunotherapeutic approaches, such as cancer vaccines and adoptive cell therapies, aim to stimulate or augment tumor-specific immune responses [46].

However, immunotherapy is not universally effective. Resistance may arise from low tumor antigenicity, impaired antigen presentation, immunosuppressive microenvironments, or alternative immune escape mechanisms [46, 47]. Immune-related adverse events can affect multiple organs, including skin, gastrointestinal tract, lungs, endocrine glands, and liver, sometimes necessitating immunosuppressive treatment [50]. Despite these challenges, immunotherapy continues to reshape oncology practice, with ongoing research focused on predictive biomarkers, rational combinations, and strategies to overcome resistance [46–49].

6.7 CAR-T Therapy & New Modalities

CAR-T cell therapy is an advanced form of adoptive immunotherapy in which autologous T cells are genetically engineered to express synthetic receptors that recognize tumor-associated antigens independently of major histocompatibility complex presentation [51]. CAR-T therapies have achieved remarkable success in hematologic malignancies, particularly B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma, producing durable remissions in heavily pretreated patients [51, 52].

However, efficacy in solid tumors remains limited due to antigen heterogeneity, poor tumor infiltration, immunosuppressive microenvironments, and antigen escape [52, 53]. CAR-T therapy is also associated with significant toxicities, including cytokine release syndrome and immune-mediated neurotoxicity, requiring specialized management [51]. Emerging strategies include next-generation CAR designs, combination approaches with radiotherapy or checkpoint inhibitors, and novel modalities such as bispecific antibodies, oncolytic viruses, RNA-based therapies, and nanomedicine aimed at enhancing tumor targeting and immune activation [53].

6.8 Palliative and Supportive Care

Palliative and supportive care is an essential component of comprehensive cancer management, focusing on symptom control, psychosocial support, and preservation of quality of life throughout the disease course [54]. Importantly, palliative care is not limited to end-of-life settings. Early integration alongside standard oncologic

treatment has been shown to improve quality of life, reduce depressive symptoms, decrease aggressive end-of-life interventions, and even prolong survival in patients with metastatic cancer [55]. Key interventions include pain and symptom management, nutritional and psychological support, and shared decision-making aligned with patient goals. Supportive strategies such as structured physical exercise further improve functional capacity and well-being in advanced cancer patients [56].

7. Limitations of current treatments

7.1 Therapeutic Resistance

Despite major advances in cancer therapeutics, resistance to treatment remains one of the most significant barriers to durable clinical benefit. Therapeutic resistance may be intrinsic, where tumor cells possess pre-existing molecular features that confer insensitivity to therapy, or acquired, developing over time as a consequence of selective pressure imposed by treatment [57, 58]. Intrinsic resistance is frequently driven by baseline genetic alterations, epigenetic states, or protective interactions within the tumor microenvironment that limit drug efficacy from the outset [58].

Acquired resistance arises through dynamic tumor evolution and involves multiple adaptive mechanisms, including activation of drug efflux transporters, enhanced DNA damage repair, rewiring of oncogenic signaling pathways, metabolic reprogramming, and epigenetic modifications that enable cancer cells to survive therapeutic stress [57]. Targeted therapies are particularly vulnerable to resistance mediated by secondary mutations or compensatory pathway activation, whereas chemotherapy resistance often reflects altered cell-cycle regulation, detoxification pathways, and evasion of apoptosis [57].

The tumor microenvironment plays a central role in resistance development. Cancer-associated fibroblasts, immune cells, and extracellular matrix components create a protective niche that limits drug penetration and promotes survival signaling [58, 59]. Notably, fibroblast-derived extracellular vesicles can transfer regulatory RNAs, proteins, and metabolites to tumor cells, actively inducing resistance across chemotherapy, targeted therapy, radiotherapy, and immunotherapy by promoting epithelial–mesenchymal transition, stemness, metabolic flexibility, and immune evasion [59]. Tumor heterogeneity further exacerbates resistance, as genetically distinct subclones respond differently to treatment, leading to selective enrichment of resistant populations and disease relapse [57]. Overcoming resistance will require rational combination strategies, biomarker-guided therapy selection, and longitudinal monitoring of tumor evolution.

7.2 Toxicity

Treatment-related toxicity remains a major limitation of modern cancer therapy because most anticancer modalities damage normal tissues in addition to malignant cells [60]. Radiotherapy produces dose- and field-dependent adverse effects, including acute inflammation and late complications such as fibrosis, vascular injury, organ dysfunction, and secondary malignancies, which may persist for years after treatment completion [60]. Immunotherapy introduces a distinct toxicity profile characterized by immune-related adverse events resulting from nonspecific immune activation, commonly affecting the skin, gastrointestinal tract, lungs, endocrine organs, and cardiovascular system [61]. These toxicities may be delayed, severe, or life-threatening and often require immunosuppressive therapy and multidisciplinary management [62]. Collectively, treatment-related toxicities limit dose intensity, compromise quality of life, and may necessitate treatment interruption, thereby reducing therapeutic effectiveness.

7.3 Immune Escape

Immune escape represents a major biological barrier to effective cancer immunotherapy and reflects the ability of tumors to evade immune surveillance through both intrinsic and extrinsic mechanisms [63]. Cancer cells may reduce immunogenicity by downregulating tumor antigens, impairing antigen processing, or suppressing major histocompatibility complex expression, limiting recognition by cytotoxic T lymphocytes [64]. In parallel, tumors establish immunosuppressive microenvironments through upregulation of immune checkpoint ligands such as PD-L1, recruitment of regulatory T cells, and expansion of myeloid-derived suppressor cells [63, 65]. These mechanisms contribute to primary resistance and limit the durability of responses to immune checkpoint inhibitors. Overcoming immune escape will require rational combination immunotherapies, improved predictive biomarkers, and strategies aimed at reprogramming the tumor immune microenvironment [65].

7.4 Cost and Late Detection

High treatment costs and delayed diagnosis remain major systemic barriers to effective cancer care worldwide. Many contemporary therapies, including targeted agents, immunotherapies, and advanced radiotherapy techniques, are expensive and inaccessible to large populations, particularly in low- and middle-income countries, leading to financial toxicity and reduced treatment adherence [66]. Late-stage diagnosis further worsens outcomes, as many patients present with advanced disease due to inadequate screening, limited diagnostic infrastructure, nonspecific early symptoms, and socioeconomic disparities [66]. Advanced-stage cancers require complex, costly treatments with lower survival benefit. Improving early detection and reducing economic barriers are essential for equitable global cancer control [66].

8. Why does stage 4 cancer remain incurable?

Stage IV cancer represents the most advanced phase of malignant disease, defined by the dissemination of tumor cells to distant organs [67]. Despite substantial advances in systemic therapy, a durable cure remains rare in metastatic cancer because disease spread fundamentally alters tumor biology, treatment response, and host interactions [67, 68]. Metastatic cancer is characterized by widespread tumor burden, microenvironmental protection, cellular

dormancy, limited drug delivery, and profound genetic instability, which together create a disease state that is intrinsically resistant to eradication [68, 69].

8.1 Metastatic Burden

In Stage IV disease, tumor cells have colonized multiple anatomical sites, resulting in a high and heterogeneous metastatic burden that overwhelms physiological reserve [68]. Unlike localized tumors, metastatic lesions are rarely amenable to complete surgical resection and must be treated primarily with systemic therapies [68, 70]. Multi-organ involvement including liver, lung, brain, and bone metastases leads to progressive organ dysfunction and directly contributes to cancer-related mortality [70]. Large-scale genomic analyses demonstrate that increasing metastatic burden is associated with chromosomal instability and aggressive tumor evolution, increasing the likelihood that resistant subclones are present or emerge during treatment [71].

8.2 Microenvironment Protection

Metastatic tumor cells are supported by specialized microenvironments that promote survival and therapeutic resistance [72]. Organs such as bone marrow and liver provide stromal- and extracellular matrix–rich niches that deliver anti-apoptotic and pro-survival signals [72, 73]. Collagen-rich extracellular matrix niches have been shown to actively regulate metastatic cell persistence and resistance by enforcing protective cellular states [73]. Interactions with stromal cells, cytokines, and immunosuppressive components alter drug metabolism, enhance repair pathways, and suppress immune-mediated clearance, rendering metastatic lesions less responsive to therapy than primary tumors [73, 74].

8.3 Dormant Cells

Dormant disseminated tumor cells represent a major barrier to curative therapy in Stage IV cancer [69]. These cells persist in a quiescent or slow-cycling state, enabling them to evade treatments that primarily target proliferating cells, such as chemotherapy and radiotherapy [69, 73]. Dormant cells may remain clinically undetectable for prolonged periods before reactivating and driving late metastatic relapse [73]. Their survival is regulated by distinct microenvironmental and stress-response pathways, making them poorly susceptible to conventional therapeutic approaches [69, 73].

8.4 Drug Penetration Limits

Effective eradication of metastatic disease is further limited by inadequate drug delivery to tumor sites [74]. Abnormal tumor vasculature, dense extracellular matrix, and elevated interstitial pressure restrict uniform drug penetration within metastatic lesions [74, 75]. Certain organs, such as the brain, are protected by physiological barriers that limit the entry of many systemic agents [75]. Hypoxic regions within metastases further reduce sensitivity to radiotherapy and promote more aggressive phenotypes [74]. Although nanoparticle-based delivery systems show promise in improving intratumoral drug distribution, these strategies remain largely investigational [75].

8.5 Genetic Instability

Metastatic cancers exhibit marked genetic and epigenetic instability, resulting in diverse subclonal populations with variable therapeutic sensitivities [71]. Comprehensive sequencing studies reveal that metastatic progression is accompanied by ongoing chromosomal alterations and organ-specific evolutionary trajectories [71, 76]. Under therapeutic pressure, cancer cells rapidly adapt through acquisition of resistance mutations, pathway reprogramming, and antigen loss [76]. This dynamic evolutionary landscape makes simultaneous targeting of all malignant clones extremely difficult, contributing fundamentally to the incurability of Stage IV cancer [68, 71].

9. Future directions

9.1 Personalized Medicine

Personalized medicine represents a paradigm shift in oncology, aiming to tailor treatment according to the unique molecular and biological characteristics of an individual patient's tumor rather than population-based averages [77]. Advances in next-generation sequencing have enabled comprehensive genomic profiling, facilitating the identification of actionable mutations and guiding the selection of targeted therapies and immunotherapies matched to specific oncogenic drivers [78]. This approach has already transformed the management of non-small cell lung cancer, melanoma, and selected hematologic malignancies, where molecular alterations increasingly dictate treatment decisions [77]. Beyond genomics, integration of transcriptomic, proteomic, immunomic, and metabolomic data provides deeper insight into tumor behavior, therapeutic vulnerability, and resistance mechanisms [78]. Machine learning and artificial intelligence are being applied to integrate these multidimensional datasets, predict treatment response, and optimize combination strategies. However, clinical implementation remains limited by tumor heterogeneity, evolving resistance, cost, and unequal access to molecular diagnostics, underscoring the need for robust biomarkers and scalable precision oncology frameworks [77, 78].

9.2 Oncolytic Viruses

Oncolytic virotherapy employs naturally occurring or genetically engineered viruses that selectively infect, replicate within, and destroy cancer cells while sparing normal tissues [79]. Tumor selectivity arises from defects in antiviral signaling, dysregulated cell-cycle control, and impaired interferon responses characteristic of malignant cells [79, 80]. Viral replication induces direct tumor cell lysis and releases progeny virions that propagate infection within the tumor mass [79]. Importantly, oncolytic viruses also promote immunogenic cell death, releasing tumor antigens and inflammatory signals that enhance antitumor immune responses [86]. Clinical translation has been demonstrated by the approval of talimogene laherparepvec (T-VEC) for advanced melanoma [79].

Ongoing trials are evaluating diverse viral platforms and combination strategies with immune checkpoint inhibitors, radiotherapy, and targeted agents to overcome immune suppression and enhance efficacy [79, 80].

9.3 CRISPR and Gene Editing

CRISPR–Cas gene-editing technology offers unprecedented precision for modifying genetic alterations that drive cancer initiation, progression, and treatment resistance [81]. Using programmable guide RNAs, CRISPR enables targeted disruption or regulation of oncogenes, tumor suppressor genes, and resistance-associated pathways [81]. In oncology, CRISPR-based loss-of-function screens have identified novel drug targets and synthetic lethal interactions, accelerating therapeutic discovery [81, 82]. In immuno-oncology, CRISPR is used to engineer immune cells by enhancing tumor recognition and effector function, with early-phase clinical trials demonstrating feasibility and acceptable safety [81, 82]. Challenges remain, including off-target effects, delivery limitations, immune reactions, and long-term genomic stability, although advances in high-fidelity Cas variants and improved delivery systems continue to expand clinical potential [82].

9.4 Nanomedicine

Nanomedicine applies nanoscale materials to improve cancer diagnosis and therapeutic precision by overcoming biological barriers that limit conventional treatments [83]. Nanoparticles can encapsulate chemotherapeutic agents, nucleic acids, or imaging probes, enhancing tumor-specific delivery while reducing systemic toxicity [83, 84]. Their physicochemical properties enable preferential tumor accumulation through the enhanced permeability and retention (EPR) effect [83]. Advanced nanocarriers incorporate active targeting and stimuli-responsive release mechanisms, responding to pH, enzymes, or hypoxia within the tumor microenvironment [84]. Several nanomedicines have achieved clinical approval, validating translational potential [83], though challenges such as variable EPR effects, immune clearance, long-term safety, and scalable manufacturing persist [83, 85].

9.5 Tumor Vaccines

Tumor vaccines aim to stimulate antitumor immunity by targeting tumor-associated antigens or patient-specific neoantigens derived from somatic mutations [86]. Advances in sequencing and epitope prediction have enabled personalized neoantigen vaccines that avoid immune tolerance and induce robust $CD4^+$ and $CD8^+$ T-cell responses in early clinical studies [87]. Vaccine platforms include peptide, dendritic cell, viral vector, and mRNA-based approaches [86]. However, clinical efficacy remains limited by tumor heterogeneity, antigen loss, and immunosuppressive microenvironments. Combination strategies with immune checkpoint inhibitors and adjuvants are therefore central to improving durability and clinical benefit [86].

9.6 Liquid Biopsy and MRD Monitoring

Liquid biopsy enables non-invasive detection of tumor-derived biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells, and extracellular vesicles, allowing real-time assessment of tumor dynamics [88]. Its most impactful application is monitoring minimal residual disease (MRD), defined as microscopic tumor burden persisting after treatment and preceding clinical relapse [89]. Prospective studies demonstrate that ctDNA positivity strongly predicts recurrence and inferior survival, particularly in colorectal cancer [90]. Longitudinal monitoring enables early detection of resistance and treatment failure, often months before imaging, supporting personalized surveillance and adaptive therapy strategies [88-90].

In conclusion, cancer represents a highly complex and heterogeneous group of diseases driven by dynamic genetic, epigenetic, and microenvironmental interactions. This review has outlined the fundamental biological mechanisms underlying cancer initiation and progression, including genetic alterations, hallmark capabilities, tumor microenvironmental influences, and intratumoral heterogeneity. It has further examined the clinical distinction between benign and malignant tumors, contemporary classification and staging systems, and the pivotal role of metastasis in cancer-related mortality. Despite substantial advances in surgery, radiotherapy, systemic therapies, and immunotherapy, treatment resistance, toxicity, and disease recurrence particularly in advanced-stage cancer remain major challenges.

Importance of Early Diagnosis

Early diagnosis is one of the most effective strategies for improving cancer outcomes. Detection at localized stages enables curative treatment with less intensive therapy, reduces treatment-related morbidity, and significantly improves survival. In contrast, delayed diagnosis often results in advanced or metastatic disease, where therapeutic options are limited and prognosis is poor. Expanding access to screening programs, improving diagnostic infrastructure, and integrating emerging tools such as liquid biopsy for early detection and minimal residual disease monitoring are essential components of effective cancer control, particularly in resource-limited settings.

Hope From Upcoming Therapies

Rapid advances in precision oncology, immunotherapy, gene editing, nanomedicine, and real-time disease monitoring offer renewed hope for transforming cancer care. Personalized treatment strategies, rational combination therapies, and early intervention guided by molecular profiling have the potential to overcome resistance and improve long-term outcomes. Continued translational research and equitable implementation of these innovations will be critical to reducing the global cancer burden and moving closer to durable disease control.

Declarations

Conflict of Interest

The author declares that there are no conflicts of interest related to this work.

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Ethical Approval

Not applicable. This article is a narrative review and did not involve human participants or animal experiments.

Informed Consent

Not applicable.

Data Availability

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References

1. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries - Bray - 2024 - CA: A Cancer Journal for Clinicians - Wiley Online Library [Internet]. [cited 2025 Dec 9]. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21834..
2. Hassanpour S, Dehghani MA. Review of cancer from perspective of molecular. Journal of Cancer Research and Practice. 2017 07 01;4:127-129. https://doi.org/10.1016/j.jcrpr.2017.07.001
3. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discovery. 2022 01;12(1):31-46. https://doi.org/10.1158/2159-8290.CD-21-1059
4. Ji H, Hu C, Yang X, Liu Y, Ji G, Ge S, Wang X, Wang M. Lymph node metastasis in cancer progression: molecular mechanisms, clinical significance and therapeutic interventions. Signal Transduction and Targeted Therapy. 2023 09 27;8(1):367. https://doi.org/10.1038/s41392-023-01576-4
5. Zhang S, Xiao X, Yi Y, Wang X, Zhu L, Shen Y, Lin D, Wu C. Tumor initiation and early tumorigenesis: molecular mechanisms and interventional targets. Signal Transduction and Targeted Therapy. 2024 06 19;9(1):149. https://doi.org/10.1038/s41392-024-01848-7
6. Senga SS, Grose RP. Hallmarks of cancer-the new testament. Open Biology. 2021 01;11(1):200358. https://doi.org/10.1098/rsob.200358
7. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: Still emerging. Cell Metabolism. 2022 03 01;34(3):355-377. https://doi.org/10.1016/j.cmet.2022.01.007
8. Sabit H, Arneth B, Abdel-Ghany S, Madyan EF, Ghaleb AH, Selvaraj P, Shin DM, et al. Beyond Cancer Cells: How the Tumor Microenvironment Drives Cancer Progression. Cells. 2024 Oct 09;13(19):1666. https://doi.org/10.3390/cells13191666
9. Xiang X, Wang J, Lu D, Xu X. Targeting tumor-associated macrophages to synergize tumor immunotherapy. Signal Transduction and Targeted Therapy. 2021 02 23;6(1):75. https://doi.org/10.1038/s41392-021-00484-9
10. Jin Y, Xing J, Xu K, Liu D, Zhuo Y. Exosomes in the tumor microenvironment: Promoting cancer progression. Frontiers in Immunology. 2022;13:1025218. https://doi.org/10.3389/fimmu.2022.1025218
11. Vendramin R, Litchfield K, Swanton C. Cancer evolution: Darwin and beyond. The EMBO journal. 2021 09 15;40(18). https://doi.org/10.15252/embj.2021108389
12. Feng D, Zhu W, Wang J, Li D, Shi X, Xiong Q, You J, et al. The implications of single-cell RNA-seq analysis in prostate cancer: unraveling tumor heterogeneity, therapeutic implications and pathways towards personalized therapy. Military Medical Research. 2024 04 11;11(1):21. https://doi.org/10.1186/s40779-024-00526-7
13. Butler G, Baker J, Amend SR, Pienta KJ, Venditti C. Divergent evolutionary dynamics of benign and malignant tumors. Proceedings of the National Academy of Sciences of the United States of America. 2025 Nov 11;122(45). https://doi.org/10.1073/pnas.2519203122
14. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro LV, Raverot G, Reincke M, et al. Clinical Biology of the Pituitary Adenoma. Endocrine reviews. 2022 Nov 25;43(6). https://doi.org/10.1210/endrev/bnac010
15. Li Y, Liu F, Cai Q, Deng L, Ouyang Q, Zhang XH, Zheng J. Invasion and metastasis in cancer: molecular insights and therapeutic targets. Signal Transduction and Targeted Therapy. 2025 02 21;10(1):57. https://doi.org/10.1038/s41392-025-02148-4
16. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. Pathologica. 2021 04;113(2):70-84. https://doi.org/10.32074/1591-951X-213
17. Alig SK, Chapuy B, Ennishi D, Dunleavy K, Hodson DJ. Evolving molecular classification of aggressive B-cell lymphoma. Histopathology. 2025 01;86(1):94-105. https://doi.org/10.1111/his.15350
18. Pan J, Mai H, Ng WT, Hu C, Li J, Chen X, Chow JCH, et al. Ninth Version of the AJCC and UICC Nasopharyngeal Cancer TNM Staging Classification. JAMA oncology. 2024 Oct 10;10(12):1627-1635. https://doi.org/10.1001/jamaoncol.2024.4354
19. Chauhan A, Chan K, Halfdanarson TR, Bellizzi Am, Rindi G, O'Toole D, Ge PS, et al. Critical updates in neuroendocrine tumors: Version 9 American Joint Committee on Cancer staging system for gastroenteropancreatic neuroendocrine tumors. CA: a cancer journal for clinicians. 2024 08;74(4). https://doi.org/10.3322/caac.21840
20. Yu J, Yao R, Han N, Lu L, Chen L, Reyila A, Wang X, et al. Evaluating the prognostic significance of tumor deposits in gastric cancer and strategies for their integration into the TNM staging system: a single-center retrospective study. Cellular oncology (Dordrecht, Netherlands). 2025 06;48(3). https://doi.org/10.1007/s13402-025-01046-9
21. Flanary JT, Lin J, Shriver CD, Zhu K. Cancer stage at diagnosis: Comparison of insurance status in SEER to the Department of Defense Cancer Registry. Cancer Medicine. 2023 Nov;12(22):20989-21000. https://doi.org/10.1002/cam4.6655
22. Castaneda M, Hollander P, Kuburich NA, Rosen JM, Mani SA. Mechanisms of cancer metastasis. Seminars in Cancer Biology. 2022 Dec;87:17-31. https://doi.org/10.1016/j.semcancer.2022.10.006
23. Miranda I, Jahan N, Shevde LA. The metastatic cascade through the lens of therapeutic inhibition. Cell Reports. Medicine. 2025 01 21;6(1):101872. https://doi.org/10.1016/j.xcrm.2024.101872
24. Ghafoor S, Garcia E, Jay DJ, Persad S. Molecular Mechanisms Regulating Epithelial Mesenchymal Transition (EMT) to Promote Cancer Progression. International Journal of Molecular Sciences. 2025 05 03;26(9):4364. https://doi.

org/10.3390/ijms26094364
25. Zhan Q, Liu B, Situ X, Luo Y, Fu T, Wang Y, Xie Z, et al. New insights into the correlations between circulating tumor cells and target organ metastasis. Signal Transduction and Targeted Therapy. 2023 Dec 21;8(1):465. https://doi.org/10.1038/s41392-023-01725-9
26. Drapela S, Gomes AP. Metabolic requirements of the metastatic cascade. Current Opinion in Systems Biology. 2021 Dec;28:100381. https://doi.org/10.1016/j.coisb.2021.100381
27. Sellner F, Thalhammer S, Klimpfinger M. Isolated Pancreatic Metastases of Renal Cell Carcinoma-Clinical Particularities and Seed and Soil Hypothesis. Cancers. 2023 01 04;15(2):339. https://doi.org/10.3390/cancers15020339
28. He C. Activating Invasion and Metastasis in Small Cell Lung Cancer: Role of the Tumour Immune Microenvironment and Mechanisms of Vasculogenesis, Epithelial-Mesenchymal Transition, Cell Migration, and Organ Tropism. Cancer Reports. 2024 Oct;7(10):e70018. https://doi.org/10.1002/cnr2.70018
29. Del Piccolo N, Shirure VS, Bi Y, Goedegebuure SP, Gholami S, Hughes CCW, Fields RC, George SC. Tumor-on-chip modeling of organ-specific cancer and metastasis. Advanced Drug Delivery Reviews. 2021 08;175:113798. https://doi.org/10.1016/j.addr.2021.05.008
30. Gerstberger S, Jiang Q, Ganesh K. Metastasis. Cell. 2023 04 13;186(8). https://doi.org/10.1016/j.cell.2023.03.003
31. Mani K, Deng D, Lin C, Wang M, Hsu ML, Zaorsky NG. Causes of death among people living with metastatic cancer. Nature Communications. 2024 02 19;15(1):1519. https://doi.org/10.1038/s41467-024-45307-x
32. Liu B, Zhou H, Tan L, Siu KTH, Guan X. Exploring treatment options in cancer: Tumor treatment strategies. Signal Transduction and Targeted Therapy. 2024 07 17;9(1):175. https://doi.org/10.1038/s41392-024-01856-7
33. Full article: Robotic versus laparoscopic surgery for colorectal cancer in older patients: a systematic review and meta-analysis [Internet]. [cited 2026 Jan 4]. Available from: https://www.tandfonline.com/doi/10.1080/13645706.2024.2359705?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed..
34. Verginadis II, Citrin DE, Ky B, Feigenberg SJ, Georgakilas AG, Hill-Kayser CE, Koumenis C, et al. Radiotherapy toxicities: mechanisms, management, and future directions. Lancet. 2025 01 25;405(10475):338-352. https://doi.org/10.1016/S0140-6736(24)02319-5
35. Wang Y, Han Y, Jin Y, He Q, Wang Z. The Advances in Epigenetics for Cancer Radiotherapy. International Journal of Molecular Sciences. 2022 05 18;23(10):5654. https://doi.org/10.3390/ijms23105654
36. Yu Z, Xu C, Song B, Zhang S, Chen C, Li C, Zhang S. Tissue fibrosis induced by radiotherapy: current understanding of the molecular mechanisms, diagnosis and therapeutic advances. Journal of Translational Medicine. 2023 Oct 09;21(1):708. https://doi.org/10.1186/s12967-023-04554-0
37. Nussinov R, Tsai C, Jang H. Anticancer drug resistance: An update and perspective. Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy. 2021 Dec;59:100796. https://doi.org/10.1016/j.drup.2021.100796
38. Gu Y, Yang R, Zhang Y, Guo M, Takehiro K, Zhan M, Yang L, Wang H. Molecular mechanisms and therapeutic strategies in overcoming chemotherapy resistance in cancer. Molecular Biomedicine. 2025 01 06;6(1):2. https://doi.org/10.1186/s43556-024-00239-2
39. Chaft JE, Rimner A, Weder W, Azzoli CG, Kris MG, Cascone T. Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. Nature Reviews. Clinical Oncology. 2021 09;18(9):547-557. https://doi.org/10.1038/s41571-021-00501-4
40. Michael P, Roversi G, Brown K, Sharifi N. Adrenal Steroids and Resistance to Hormonal Blockade of Prostate and Breast Cancer. Endocrinology. 2023 01 09;164(3):bqac218. https://doi.org/10.1210/endocr/bqac218
41. Kim J, Bang H, Seong C, Kim E, Kim SY. Transcription factors and hormone receptors: Sex specific targets for cancer therapy (Review). Oncology Letters. 2025 02;29(2):93. https://doi.org/10.3892/ol.2024.14839
42. Kesztyüs D, Kämpfer J, Kesztyüs T. Intermittent Use of Anti-Hormonal Agents for the Endocrine Therapy of Sex-Hormone-Dependent Breast and Prostate Cancer: A Protocol for a Systematic Review. International Journal of Environmental Research and Public Health. 2022 Nov 22;19(23):15486. https://doi.org/10.3390/ijerph192315486
43. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nature Reviews. Cancer. 2013 Oct;13(10):714-726. https://doi.org/10.1038/nrc3599
44. Ciappina G, Toscano E, Ottaiano A, Capuozzo M, Consolo P, Maiorana E, Carroccio P, et al. Negative Hyperselection in Metastatic Colorectal Cancer for First-Line Anti-EGFR Therapy: A Narrative Review. International Journal of Molecular Sciences. 2025 02 28;26(5):2216. https://doi.org/10.3390/ijms26052216
45. Ecker J, Selt F, Sturm D, Sill M, Korshunov A, Hirsch S, Capper D, et al. Corrigendum to 'Molecular diagnostics enables detection of actionable targets: the Pediatric Targeted Therapy 2.0 registry' [Eur J Cancer 180 (2023) 71-84]. European Journal of Cancer. 2023 05;184:200-201. https://doi.org/10.1016/j.ejca.2023.02.024
46. Zhang M, Liu C, Tu J, Tang M, Ashrafizadeh M, Nabavi N, Sethi G, Zhao P, Liu S. Advances in cancer immunotherapy: historical perspectives, current developments, and future directions. Molecular Cancer. 2025 05 07;24(1):136. https://doi.org/10.1186/s12943-025-02305-x
47. Cheng W, Kang K, Zhao A, Wu Y. Dual blockade immunotherapy targeting PD-1/PD-L1 and CTLA-4 in lung cancer. Journal of Hematology & Oncology. 2024 07 27;17(1):54. https://doi.org/10.1186/s13045-024-01581-2
48. Song D, Hou S, Ma N, Yan B, Gao J. Efficacy and safety of PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors in the treatment of advanced colorectal cancer: a systematic review and meta-analysis. Frontiers in Immunology. 2024;15:1485303. https://doi.org/10.3389/fimmu.2024.1485303
49. Park J, Skålhegg BS. Combination of PD-1/PD-L1 and CTLA-4 inhibitors in the treatment of cancer - a brief update. Frontiers in Immunology. 2025;16:1680838. https://doi.org/10.3389/fimmu.2025.1680838
50. Chhabra N, Kennedy J. A Review of Cancer Immunotherapy Toxicity: Immune Checkpoint Inhibitors. Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology. 2021 Oct;17(4):411-424. https://doi.org/10.1007/s13181-021-00833-8
51. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer Journal. 2021 04 06;11(4):69. https://doi.org/10.1038/s41408-021-00459-7
52. Umut Ö, Gottschlich A, Endres S, Kobold S. CAR T cell therapy in solid tumors: a short review. Memo. 2021;14(2):143-149. https://doi.org/10.1007/s12254-021-00703-7

53. Zhong L, Li Y, Muluh TA, Wang Y. Combination of CAR T cell therapy and radiotherapy: Opportunities and challenges in solid tumors (Review). Oncology Letters. 2023 07;26(1):281. https://doi.org/10.3892/ol.2023.13867
54. Rabben J, Vivat B, Fossum M, Rohde GE. Shared decision-making in palliative cancer care: A systematic review and metasynthesis. Palliative Medicine. 2024 04;38(4):406-422. https://doi.org/10.1177/02692163241238384
55. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. The New England Journal of Medicine. 2010 08 19;363(8):733-742. https://doi.org/10.1056/NEJMoa1000678
56. Rodríguez-Cañamero S, Cobo-Cuenca AI, Carmona-Torres JM, Pozuelo-Carrascosa DP, Santacruz-Salas E, Rabanales-Sotos JA, Cuesta-Mateos T, Laredo-Aguilera JA. Impact of physical exercise in advanced-stage cancer patients: Systematic review and meta-analysis. Cancer Medicine. 2022 Oct;11(19):3714-3727. https://doi.org/10.1002/cam4.4746
57. Garcia-Martinez L, Zhang Y, Nakata Y, Chan HL, Morey L. Epigenetic mechanisms in breast cancer therapy and resistance. Nature Communications. 2021 03 19;12(1):1786. https://doi.org/10.1038/s41467-021-22024-3
58. Sherman MH, Beatty GL. Tumor Microenvironment in Pancreatic Cancer Pathogenesis and Therapeutic Resistance. Annual Review of Pathology. 2023 01 24;18:123-148. https://doi.org/10.1146/annurev-pathmechdis-031621-024600
59. Lin Z, Li G, Jiang K, Li Z, Liu T. Cancer therapy resistance mediated by cancer-associated fibroblast-derived extracellular vesicles: biological mechanisms to clinical significance and implications. Molecular Cancer. 2024 09 07;23(1):191. https://doi.org/10.1186/s12943-024-02106-8
60. Radiation therapy-associated toxicity: Etiology, management, and prevention - Wang - 2021 - CA: A Cancer Journal for Clinicians - Wiley Online Library [Internet]. [cited 2026 Jan 4]. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21689.
61. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. The New England Journal of Medicine. 2018 01 11;378(2):158-168. https://doi.org/10.1056/NEJMra1703481
62. Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, Hamad L, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. Journal for Immunotherapy of Cancer. 2017 Nov 21;5(1):95. https://doi.org/10.1186/s40425-017-0300-z
63. Spranger S, Gajewski TF. Mechanisms of Tumor Cell–Intrinsic Immune Evasion. Annual Review of Cancer Biology. 2018 03 04;2(Volume 2, 2018):213-228. https://doi.org/10.1146/annurev-cancerbio-030617-050606
64. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews. Cancer. 2012 03 22;12(4):252-264. https://doi.org/10.1038/nrc3239
65. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, Coussens LM, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nature Medicine. 2018 05;24(5):541-550. https://doi.org/10.1038/s41591-018-0014-x
66. Sharma R, Abbasi-Kangevari M, Abd-Rabu R, Abidi H, Abu-Gharbieh E, Acuna JM, et al. Global, regional, and national burden of colorectal cancer and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. Gastroenterology & Hepatology. 2022 07;7(7):627-647. https://doi.org/10.1016/S2468-1253(22)00044-9
67. Gion M, Saavedra C, Perez-Garcia J, Cortes J. Oligometastatic Disease: When Stage IV Breast Cancer Could Be "Cured". Cancers. 2022 Oct 25;14(21):5229. https://doi.org/10.3390/cancers14215229
68. Nguyen B, Fong C, Luthra A, Smith SA, DiNatale RG, Nandakumar S, Walch H, et al. Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. Cell. 2022 02 03;185(3):563-575.e11. https://doi.org/10.1016/j.cell.2022.01.003
69. Agudo J, Aguirre-Ghiso JA, Bhatia M, Chodosh LA, Correia AL, Klein CA. Targeting cancer cell dormancy. Nature Reviews. Cancer. 2024 02;24(2):97-104. https://doi.org/10.1038/s41568-023-00642-x
70. Fukuokaya W, Mori K, Yanagisawa T, Urabe F, Rajwa P, Briganti A, Shariat SF, et al. Tumor burden and heterogenous treatment effect of apalutamide in metastatic castration-sensitive prostate cancer. Cancer. 2025 04 01;131(7):e35819. https://doi.org/10.1002/cncr.35819
71. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, Srinivasan P, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nature Medicine. 2017 06;23(6):703-713. https://doi.org/10.1038/nm.4333
72. Borriello L, DeClerck YA. Tmicroenvironment and therapeutic resistance process. Medecine Sciences: M/S. 2014 04;30(4):445-451. https://doi.org/10.1051/medsci/20143004021
73. Di Martino JS, Nobre AR, Mondal C, Taha I, Farias EF, Fertig EJ, Naba A, Aguirre-Ghiso JA, Bravo-Cordero JJ. A tumor-derived type III collagen-rich ECM niche regulates tumor cell dormancy. Nature Cancer. 2022 01;3(1):90-107. https://doi.org/10.1038/s43018-021-00291-9
74. Zhang J, Wang S, Zhang D, He X, Wang X, Han H, Qin Y. Nanoparticle-based drug delivery systems to enhance cancer immunotherapy in solid tumors. Frontiers in Immunology. 2023;14:1230893. https://doi.org/10.3389/fimmu.2023.1230893
75. Yngve E, Ingvast S, Korsgren O, Yu D. Evaluation of drug delivery vehicles for improved transduction of oncolytic adenoviruses in solid tumor tissue. Upsala Journal of Medical Sciences. 2025;130. https://doi.org/10.48101/ujms.v130.11217
76. Gillies RJ, Verduzco D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nature Reviews. Cancer. 2012 06 14;12(7):487-493. https://doi.org/10.1038/nrc3298
77. Fountzilas E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. Genome Medicine. 2022 08 31;14(1):101. https://doi.org/10.1186/s13073-022-01102-1
78. Koirala M, DiPaola M. Overcoming Cancer Resistance: Strategies and Modalities for Effective Treatment. Biomedicines. 2024 08 08;12(8):1801. https://doi.org/10.3390/biomedicines12081801
79. Mozaffari Nejad AS, Noor T, Munim ZH, Alikhani MY, Ghaemi A. A bibliometric review of oncolytic virus research as a novel approach for cancer therapy. Virology Journal. 2021 05 12;18(1):98. https://doi.org/10.1186/s12985-021-01571-7
80. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Silva Souza JV, Rocha Pinheiro SL, Souza WR, Sande Loureiro M, Melo FF. Oncolytic virus therapy in cancer: A current review. World Journal

of Virology. 2021 09 25;10(5):229-255. https://doi.org/10.5501/wjv.v10.i5.229
81. Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, Shafieizadeh M, Mahmoudi E, Eskandari F, Rashidi M, et al. Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. Molecular Cancer. 2024 01 09;23(1):9. https://doi.org/10.1186/s12943-023-01925-5
82. Ding S, Liu J, Han X, Tang M. CRISPR/Cas9-Mediated Genome Editing in Cancer Therapy. International Journal of Molecular Sciences. 2023 Nov 15;24(22):16325. https://doi.org/10.3390/ijms242216325
83. Tran S, DeGiovanni P, Piel B, Rai P. Cancer nanomedicine: a review of recent success in drug delivery. Clinical and Translational Medicine. 2017 Dec 11;6(1):44. https://doi.org/10.1186/s40169-017-0175-0
84. Zocchi MR, Tosetti F, Benelli R, Poggi A. Cancer Nanomedicine Special Issue Review Anticancer Drug Delivery with Nanoparticles: Extracellular Vesicles or Synthetic Nanobeads as Therapeutic Tools for Conventional Treatment or Immunotherapy. Cancers. 2020 07 13;12(7):1886. https://doi.org/10.3390/cancers12071886
85. El-Saadony MT, Saad AM, Sitohy M, Alkafaas SS, Dladla M, Ghosh S, Mohammed DM, et al. Chitosan nanoparticles: Green synthesis, biological activities, and sustainable frontiers in targeted drug delivery and cancer nanomedicine - A comprehensive review. Materials Today. Bio. 2025 Dec;35:102358. https://doi.org/10.1016/j.mtbio.2025.102358
86. Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal Transduction and Targeted Therapy. 2023 Dec 13;8(1):450. https://doi.org/10.1038/s41392-023-01674-3
87. Lang F, Schrörs B, Löwer M, Türeci Ö, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. Nature Reviews. Drug Discovery. 2022 04;21(4):261-282. https://doi.org/10.1038/s41573-021-00387-y
88. Nakamura Y, Watanabe J, Akazawa N, Hirata K, Kataoka K, Yokota M, Kato K, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. Nature Medicine. 2024 Nov;30(11):3272-3283. https://doi.org/10.1038/s41591-024-03254-6
89. Bohaumilitzky L, Gebert J, Doeberitz MVK, Kloor M, Ahadova A. Liquid biopsy-based early tumor and minimal residual disease detection: New perspectives for cancer predisposition syndromes. Medizinische Genetik: Mitteilungsblatt Des Berufsverbandes Medizinische Genetik e.V. 2023 Dec;35(4):259-268. https://doi.org/10.1515/medgen-2023-2049
90. Crisafulli G. Liquid Biopsy and Challenge of Assay Heterogeneity for Minimal Residual Disease Assessment in Colon Cancer Treatment. Genes. 2025 01