

Review

Systems Theory in Oncology: A Narrative Review of an Integrative Framework for Understanding Cancer Complexity

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Abstract

The Systems Theory provides a valuable conceptual framework for analyzing biological complexity, particularly in oncology, where the multiple interactions between biological subsystems can influence tumor initiation, progression, and treatment response. This approach facilitates the integration of data derived from genomics, metabolomics, routine medical analyses, and the clinical examination of the patient, thus overcoming the limitations of the reductionist model. By applying the principles of living systems, new tumor vulnerabilities can be identified, as well as models of cellular, metabolic, and informational organization. The use of systems theory in oncology may contribute to the development of personalized and precision medicine, improving diagnostic and prognostic methods, and enhancing the efficiency of personalized therapies with the aim of improving therapeutic outcomes and the patient’s quality of life.

Keywords: systems theory; genomics; metabolomics; tumor microenvironment; precision medicine



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1. Introduction

Systemic thinking, with roots in classical philosophy and consolidated in the 20th century through the contributions of cybernetics, ecology, and theoretical biology, provides a unifying conceptual model for understanding living organisms as complex, open systems, continuously interacting with their environment [1].

In this context, systems theory proposes a systemic approach, focusing not only on individual components but also on the relationships between them, on organization, and on emergent functions that cannot be deduced solely from the isolated study of system components [2].

In oncology, this paradigm allows for the reinterpretation of biological phenomena associated with tumors—from genomic instability and cellular signaling networks to interactions with the microenvironment and the immune system—as manifestations of systemic imbalance [3].

The tumor is no longer viewed as a mere mass of proliferative cells, but as a subsystem with varying degrees of autonomy, capable of influencing and being influenced by the other subsystems of the organism [4].

Through this review, we aim to analyze the main directions in which systems theory is applied in oncology: from mathematical modeling of cellular interactions and metabolic flow to the interpretation of multi-omic data and the definition of new therapeutic targets.

We will also emphasize the epistemological implications of transitioning from a reductionist to a systemic approach in cancer research [5].

2. Methodology

To conduct this review, we performed a comprehensive search of the literature to synthesize foundational concepts and modern applications. We utilized the PubMed/MEDLINE, Scopus, and Google Scholar databases. Our search strategy combined key terms from two main conceptual groups: (1) terms related to systems theory, such as “systems theory”, “systems biology”, “complex adaptive systems”, “network biology”, “emergent properties” and “informational entropy”; and (2) terms related to oncology, such as “cancer”, “oncology”, “tumor biology”, “carcinogenesis” and “tumor microenvironment”.

Given the theoretical nature of the topic, our inclusion criteria were broad: we included foundational texts on general systems theory to establish the epistemological context, as well as highly cited narrative and systematic reviews. For specific applications, we focused on primary research and modeling studies from the last 10–15 years that explicitly used a systems-level approach to investigate cancer. Exclusion criteria involved articles that were purely reductionist (i.e., did not connect molecular findings to broader systemic properties), case reports and non-English publications. The selected literature was then synthesized to build the narrative argument presented.

3. Results and Discussions

3.1. Theoretical Foundations of Systems Theory

General systems theory, initially formulated by Ludwig von Bertalanffy in the 1940s, emerged as a reaction to the limitations of reductionist approaches in science. Instead of focusing exclusively on analyzing the component parts of a phenomenon, this theory proposes the study of relationships between components, organization, and the collective behavior of the whole [6].

Biological systems, in particular, are regarded as open entities, in continuous exchange of matter, energy, and information with the environment, characterized by a high degree of complexity, adaptability, and self-regulation [7].

Within this conceptual framework, the human organism is interpreted as a hierarchical system, organized across multiple levels—from molecular and cellular, to tissue, organ, and systemic—in which each subsystem influences and is influenced by the others. Health corresponds to coherence among these levels, maintained through dynamic regulatory mechanisms. In contrast, the onset of disease, including cancer, can be interpreted as a loss of informational coherence, balance between feedback mechanisms, and of the capacity for self-organization [8].

Complex biological systems, such as the human organism or a solid tumor, are characterized by a series of fundamental properties, without which their emergent behavior and internal dynamics cannot be understood. These properties, extensively described, in general, systems theory and contemporary systems biology, include nonlinearity, structural interdependence, feedback loops, self-organization, emergence, robustness, contextuality and hierarchical complexity [9–16]. Instead of detailing each in the text, we have provided a comprehensive summary of these properties and their direct implications in oncology in Table 1. We refer the reader to this table for a structured breakdown, as these characteristics form the basis for why a simple reductionist approach is insufficient.

Table 1. Fundamental properties of biological systems relevant to oncology.

System Property	Essential Idea	Example/Detail	Relevance to Cancer
Nonlinearity	Small inputs can produce disproportionate effects.	A point mutation in a key gene triggering extensive oncogenesis.	Explains unpredictable tumor behavior; nonlinear models needed [9].
Structural and Functional Interdependence	Components’ behavior depends on context and network interactions.	Protein activity depends on molecular context and feedback loops.	Genes/proteins cannot be studied in isolation for cancer biology [10].
Feedback and Multiple Regulation	Negative feedback stabilizes systems; positive feedback amplifies instability.	Negative feedback maintains hormonal homeostasis; positive feedback accelerates tumor progression.	Targets for therapies to stabilize or disrupt tumor networks [11].
Self-organization	Systems form organized structures without central control using energy (negative entropy).	Formation of invasive tumor structures or adaptive resistance.	Explains tumor resilience and adaptive behavior [12].
Emergence	Properties arise from interactions, not from the sum of parts.	Tumor aggressiveness emerges from genome–environment–immune interactions.	Supports integrative modeling of cancer dynamics [13].
Robustness and Fragility	Systems resist fluctuations via redundancy and plasticity but have exploitable weak points.	BRCA1/2-mutated tumors are robust via alternative DNA repair but fragile to PARP inhibition (synthetic lethality).	Identifies vulnerabilities for therapeutic targeting [14].
Contextuality and Internal Determinism	System behavior shaped by environment but governed by internal rules; cancer retains reprogrammable logic.	Genetic/epigenetic algorithms guide cellular responses.	Enables prediction of tumor adaptation and evolution [15].
Hierarchical Complexity	Organization spans multiple levels (genetic, molecular, cellular, tissue, systemic) with interdependence.	In metastatic melanoma: Genetic —BRAF/NRAS mutations activate MAPK signaling → Molecular —abnormal phosphorylation cascades and cytokine secretion → Cellular —melanoma cells interact with macrophages and T cells → Tissue —ECM remodeling and angiogenesis → Systemic —exosomes/cytokines prepare pre-metastatic niches.	Explains emergent properties and multi-scale tumor interactions [16].

These characteristics make it impossible to adequately understand cancer through a linear and reductionist approach. When a biological system is divided into independent subsystems, emergent properties disappear, and the capacity for self-regulation and adaptation becomes difficult to capture. Thus, health can be understood as an emergent state of functional coherence, resulting from stable interactions between subsystems of the organism. Conversely, disease reflects a loss of this coherence, an informational and functional imbalance among system components [17].

A central concept in this paradigm is informational entropy. In a healthy system, biological processes are governed by ordered flows of information—from gene transcription to cellular communication. In pathological contexts, however, this balance deteriorates, and the system produces increasingly high informational noise—represented by mutations, aberrant transcriptions, and contradictory signals. Thus, the ratio between valid (functional, coherent) information and informational noise becomes an indicator of systemic coherence or fragility [18].

This vision provides a rigorous explanation for the adaptive and self-regulating nature of living systems. Self-organization, as an emergent process, allows the formation of stable structures without explicit centralized control, through the redistribution of informational and energetic resources according to external and internal stimuli. In tumor biology, this property can be observed in the ability of tumors to generate invasive architectures, stromal support networks, or adaptive resistance to therapies [19].

Therefore, in understanding complex biological phenomena, systems theory is not merely an alternative framework but an epistemological necessity. It allows the study of emergent phenomena, functional instability, and biological variability as intrinsic features of the human organism, especially in pathological contexts such as cancer [20].

3.2. Applications in Oncology

The integration of systems theory into oncological research has generated a new conceptual framework, capable of overcoming the limitations of traditional linear and reductionist approaches. Beyond identifying isolated genetic or molecular alterations, the systemic perspective proposes analyzing cancer as the outcome of complex interactions across multiple levels of biological organization—from the genome and cellular organelles to functional networks, the tumor microenvironment, and the host organism [21].

This section explores the main directions of applying systems theory in oncology, highlighting how this approach contributes to modeling tumor dynamics, the integrative interpretation of multi-omic data, the understanding of emergent cellular behavior, and the definition of therapeutic vulnerabilities from the perspective of biological network architecture [22].

3.3. The Tumor Cell as a Complex Adaptive System

From the perspective of systems theory, the tumor cell is not merely a dysfunctional entity, but a complex adaptive system, capable of reorganizing its internal functions to withstand selective pressures imposed by the microenvironment, therapies, and its own energetic and informational constraints. This system is characterized by openness (continuous exchanges with the environment), self-regulation, emergence, and information-processing capacity—properties reflected in the organization and functioning of cellular organelles [23].

Each organelle contributes to maintaining the functional coherence of the cellular system, fulfilling specific roles that can be mapped onto the core dimensions of a complex system. For example, the Nucleus acts as the governor of systemic identity and memory, the Mitochondria as the hub for energetic control, the Plasma Membrane as the boundary for signaling, and Lysosomes as regulators of entropy and waste. To provide a clear, structured overview of this concept, we have summarized the systemic function of each major organelle, along with its key associated molecular drivers in oncology (Table 2). We refer the reader to this table for a detailed breakdown of this functional mapping.

Table 2. Mapping of cellular organelles to systemic functions in tumor cells.

System Property	Essential Idea	Example/Detail	Relevance to Cancer
Nucleus	Identity and memory	Governs informational stability via transcriptional control, DNA repair, and epigenome maintenance; TP53, RB1, BRCA1/2 act as central regulators of system integrity.	Maintains genetic fidelity; mutations disrupt identity and promote oncogenesis [24].
Endoplasmic reticulum (ER) & Ribosomes	Information processing	Translate and modulate cellular responses through protein synthesis; persistent UPR activation via IRE1, PERK, ATF6 supports tumor survival under stress (e.g., pancreatic adenocarcinoma).	Supports stress adaptation and protein quality control in cancer cells [25].
Mitochondria	Energetic control	Metabolic reprogramming (Warburg effect): shift from oxidative phosphorylation to aerobic glycolysis for biosynthesis and hypoxia adaptation; involves HIF-1 α , PDK1, HK2, PKM2.	Ensures energy supply and biosynthetic precursors for rapid proliferation [26].
Plasma membrane	Boundaries and signaling	Regulates perception of stimuli and intercellular communication via EGFR, HER2, VEGFR receptors—often hyperactivated in breast, colorectal, and lung cancers.	Drives uncontrolled proliferation and signal transduction in tumors [27].
Cytoskeleton & Golgi apparatus	Mechanical and chemical regulation	Govern migration, polarity, secretion; Rho GTPases (RhoA, Rac1) coordinate cytoskeletal reorganization during invasion/metastasis, especially in prostate and pancreatic cancers.	Enables tumor cell motility, invasion, and metastatic spread [28].
Lysosomes & Autophagy	Entropy control and waste elimination	Maintain homeostasis via recycling; autophagy (mTOR, ATG5, ULK1) protective in early phases, supports survival in advanced melanoma and breast cancer.	Dual role: tumor suppression early, survival mechanism later [28,29].
Golgi vesicles & Exosomes	Modularity and long-distance communication	Facilitate material and signal exchange; tumor-derived exosomes (Rab GTPases, ESCRT complexes) remodel microenvironment and evade immune response (gliomas, prostate cancer).	Supports microenvironment manipulation and immune evasion [30].

Table 2. Cont.

System Property	Essential Idea	Example/Detail	Relevance to Cancer
Centrosomes, Cyclins & CDKs	Temporal coordination	Control cell cycle progression; dysregulation of Cyclin D1, CDK4/6 or centrosome amplification causes chromosomal instability (glioblastoma, triple-negative breast cancer).	Drives uncontrolled proliferation and genomic instability [31].
Inter-organelle interactions	Adaptability	Integrated JAK/STAT, NF-κB, MAPK signaling networks regulate responses to inflammatory, nutritional, or therapeutic stimuli.	Coordinates adaptive responses under environmental or treatment pressures [32].

These components do not function in isolation but within an interconnected network, where disruption of a single link can have emergent effects on the entire system. Thus, the tumor is not the result of a punctual dysfunction but the expression of systemic disturbance, simultaneously affecting the identity, adaptability, informational coherence, and energetic balance of the cell [33].

This mapping of systemic functions at the organelle level provides not only a deeper understanding of tumor biology but also an operational framework for identifying vulnerable points within the tumor architecture—paving the way for network-based therapeutic strategies, directed not at a single molecule but at the functional flow of the system [34].

Indeed, this network-based approach is not merely theoretical. It has already been translated into tangible clinical applications.

- In diagnostics, for example, researchers are moving beyond single-molecule biomarkers to develop “network biomarkers” [35]. Rather than relying on the level of a single gene or protein, these signatures are based on the altered state of an entire interaction module or a ‘rewired’ sub-network. Such network-based classifiers are proving to be more robust for predicting patient prognosis or response to therapy, as they capture the collective, dysfunctional behavior of a pathway rather than a single, isolated component.
- In therapeutics, one of the most successful applications of a systems-level concept is the strategy of “synthetic lethality” [36]. This approach directly targets the fragility of the cancer network (a property discussed in Table 1). The prime clinical example is the use of PARP inhibitors (e.g., Olaparib) in patients with tumors harboring BRCA1 or BRCA2 mutations. Healthy cells possess redundant DNA repair pathways. Cancers with BRCA mutations have lost one of these pathways (homologous recombination). The PARP inhibitor drug systemically blocks a second, compensatory pathway (base excision repair). While healthy cells tolerate this inhibition by relying on their intact BRCA pathway, the cancer cells—lacking both redundant pathways—suffer catastrophic DNA damage and cell death. This is a quintessential systems-level intervention, as it targets a specific, context-dependent network vulnerability that exists only in the cancer subsystem, rather than targeting a single overactive oncogene.

3.4. Mathematical Modeling in Oncology

Mathematical modeling represents one of the most advanced applications of systems theory in oncology, allowing the quantitative simulation of tumor dynamics, prediction of therapeutic responses, and testing of hypothetical interventions in silico before their application in vivo or in clinical trials [37].

Ordinary and partial differential equations have been widely used to describe the growth of tumor populations, the dynamics of the cell cycle, and interactions with the immune system. Agent-based models offer a complementary perspective, simulating the behavior of individual cells and their local interactions, thus enabling the study of tumor heterogeneity and emergent phenomena at the tissue level [5,38,39].

Stochastic models add another dimension, integrating random variability inherent in biological systems. For example, simulations of the emergence of resistant clones under therapeutic pressure demonstrate that resistance is not merely a deterministic process but results from the interaction between mutation rates, selective pressures, and stochastic events of cellular proliferation [40,41].

In clinical practice, mathematical models have begun to be applied to optimize chemotherapy regimens, predict tumor growth under radiotherapy, and identify optimal combinations of targeted therapies. Multiscale models, which integrate molecular, cellular, tissue, and systemic dynamics, represent the most ambitious direction. Recent progress in this area is now focused on creating dynamic “digital twins” of the patient—a virtual representation of tumor biology that can be used to personalize treatment strategies by continuously integrating real-time clinical, imaging, and multi-omic data, rather than relying on a single static snapshot [42–45].

Despite these advances, challenges remain, particularly regarding the validation of models with heterogeneous clinical data and the translation of mathematical results into therapeutic decisions. Nevertheless, the potential of modeling to anticipate tumor behavior and to guide interventions underscores the central role of systems theory in building predictive oncology [46].

3.5. Genomic and Epigenomic Analysis

Genomic instability represents a defining trait of cancer cells, favoring the progressive accumulation of mutations that sustain uncontrolled proliferation, immune evasion, and resistance to therapies. In a systemic approach, the genome is no longer perceived merely as a passive substrate of genetic information, but as an active node in a complex network of signaling, regulation, and feedback. Any alteration in its structure or function can have emergent effects on the entire cellular system and, by extension, on the organism [25].

Viewed through the lens of information theory, genomic instability generates an imbalance between the quantity of valid information—necessary for coherent functioning—and informational noise produced by mutations, aberrant transcriptions, and chromosomal rearrangements. In this sense, valid information represents the subset of genetic instructions faithfully transcribed and translated into functional proteins, while informational noise refers to errors, redundancies, or dysfunctional signals that disrupt systemic coherence. This noise can be interpreted as a vulnerability of the tumor system, since the efficiency of biological processes—such as replication, DNA repair, or intercellular communication—depends on the fidelity of information transmission. Thus, overloading correction and adaptation systems may lead to functional collapse under certain therapeutic conditions [47].

From a systemic perspective, information is not a simple molecular attribute, but an emergent property of functional organization. Modifications in genomic architecture—such as topological reorganization of chromatin or epigenetic alterations—may modify not only gene expression but also the way the cell “perceives” and responds to stimuli. In this sense, genomic instability reflects a loss of informational coherence within the cellular system, creating the premises for emergent, unpredictable behaviors, but also for potential therapeutic strategies based on overloading this vulnerability [48].

3.6. Cellular Interactions and the Tumor Microenvironment

Tumor progression cannot be fully understood without analyzing the bidirectional interactions between cancer cells and the microenvironment. This includes fibroblasts, endothelial cells, immune cells, extracellular matrix, and soluble signaling factors. From the perspective of systems theory, the tumor represents an ecosystem in which each component contributes to maintaining or destabilizing dynamic equilibrium [49].

This ecosystem is not only self-contained but is also highly susceptible to inputs from the broader organismal and external environment. A prime example of this systemic interaction is the role of environmental endocrine-disrupting chemicals (EDCs) in oncogenesis. As highlighted by Modica et al. [50] EDCs can contribute to processes like breast carcinogenesis not through a single point of action, but via complex, multi-level mechanisms. These include the modulation of key signaling hubs like the aryl hydrocarbon receptor (AhR), which in turn disrupts genomic stability, epigenetic programming, and cellular signaling pathways. This illustrates how external environmental stimuli can introduce systemic perturbations that alter the coherence of the internal ecosystem, reinforcing the need for a systemic, rather than isolated, analysis of tumor progression.

For example, tumor-associated fibroblasts (CAFs) restructure the extracellular matrix and secrete growth factors that support angiogenesis and invasion. Endothelial cells, under the influence of VEGF, form new blood vessels, ensuring nutrient and oxygen supply but also generating heterogeneous gradients that influence cellular adaptation. Immune cells, such as macrophages, T lymphocytes, and myeloid-derived suppressor cells, may act either as effectors of anti-tumor response or as facilitators of immune evasion, depending on context [51,52].

This dynamic network of interactions explains phenomena such as therapy resistance. The tumor does not adapt only through internal genetic mutations but also by reprogramming its environment to neutralize therapeutic effects. Thus, any systemic approach to oncology must consider the tumor not as an isolated entity but as part of a functional and co-adaptive microenvironment [29,53].

3.7. Cancer Stem Cells

Cancer stem cells (CSCs) represent a distinct cellular subpopulation within tumors, defined by their capacity for self-renewal, multipotent differentiation, and long-term tumorigenic potential. From the perspective of systems theory, CSCs can be viewed as strategic nodes within the tumor network, ensuring both cellular heterogeneity and dynamic plasticity [54–56].

These cells can remain in a quiescent state for long periods, evading the effects of chemotherapy and radiotherapy, only to be reactivated under favorable conditions. Thus, CSCs represent a reservoir of resistance and recurrence. Epigenetic mechanisms, interactions with the microenvironment, and signaling pathways such as Wnt, Notch, and Hedgehog play essential roles in maintaining stemness and adaptive potential [57,58].

Understanding CSCs within a systemic framework highlights the need for therapies not only aimed at reducing tumor mass but also at disrupting the nodal architecture that maintains tumor self-renewal. Targeting CSCs in isolation may not be sufficient; interventions must integrate the systemic context, considering the interconnections between CSCs, differentiated tumor cells, and the microenvironment [59–61].

4. Challenges and Future Directions

Despite the theoretical and practical progress achieved, the application of systems theory in oncology faces multiple and significant challenges. On one hand, the extraordinary heterogeneity of tumors, both inter- and intra-individual, complicates the construction of

universal models [62,63]. On the other hand, integrating multi-omic data, clinical information, and patient-specific parameters requires advanced computational infrastructure and interdisciplinary collaboration.

However, as this review has argued for the potential of computational models, it is critical to provide a realistic assessment of the barriers hindering their translation into clinical practice. These challenges are not trivial and represent the active frontier of systems-based oncology research.

- **Model Reliability and Parameterization:** A primary hurdle is model reliability, which is deeply tied to calibration and parameter identifiability. Mechanistic and multiscale models often depend on a large number of biological parameters (e.g., reaction rates, cell motility coefficients) that cannot be directly measured in a patient. This uncertainty, if not properly managed, can undermine the predictive accuracy of the model and complicate its clinical interpretation. This underscores the absolute necessity of embedding rigorous sensitivity analyses and quantitative uncertainty assessment as fundamental components of responsible model design.
- **Validation in the Clinic:** Secondly, external validation of these complex models remains exceptionally difficult. Ideal validation requires large, independent patient cohorts, but in oncology, these are often limited. Furthermore, ethical restrictions and the sheer scarcity of longitudinal datasets (i.e., data collected at multiple time points) that can capture dynamic disease progression make it incredibly challenging to confirm a model's predictive accuracy in a real-world setting.
- **The “Black Box” Problem:** As models, particularly those using artificial intelligence, become more complex, their interpretability often decreases. There is a pressing need for explainable and auditable model architectures (XAI). For a clinician to trust and act on a model's prediction, the model must be able to provide a clear, understandable rationale for its output. This aligns with the broader, critical debate on responsible and ethical AI in biomedical research.
- **The Regulatory and Implementation Gap:** Finally, even a well-calibrated and validated model faces a translational gap. At present, mechanistic and multiscale models are rarely applied directly in clinical decision making. This is largely due to the absence of standardized validation protocols and clear regulatory guidelines (e.g., from bodies like the FDA or EMA) for their development, approval, and implementation as medical devices.

Bridging this comprehensive gap—from parameter uncertainty to regulatory approval—requires large-scale validation studies, standardized methodologies, and active integration of clinicians, data scientists, and regulatory bodies into the systemic research process [64]. Gathering and analyzing real-world data from specific clinical cohorts, for instance, is a critical component of this validation effort, providing essential evidence on therapeutic efficacy and safety outside of controlled trial settings [64].

In the future, the convergence between systems theory, artificial intelligence, and precision medicine may generate powerful tools for diagnosis, prognosis, and therapeutic design. The field is rapidly moving beyond simple machine learning-based pattern recognition. The current frontier involves using AI for mechanistic integration—developing hybrid models that combine data-driven deep learning with mechanistic simulations to infer the underlying network dynamics and emergent properties of a patient's tumor [65,66]. The concept of the “digital twin” of the patient—a computational representation of tumor dynamics—illustrates this direction, with the potential to simulate therapeutic scenarios in real time and personalize medical interventions with unprecedented precision [67–70].

5. Conclusions

Systems theory provides a robust conceptual framework for understanding cancer as a complex, emergent, and adaptive disease. Unlike the reductionist approach, which analyzes biological elements in isolation, the systemic perspective highlights the interdependencies between cellular, molecular, and microenvironmental components, as well as the collective behaviors emerging from these interactions.

Throughout this article, we have demonstrated that integrating systemic theories into oncology allows for:

- Interpreting genetic and epigenetic dynamics not as isolated events but as part of self-regulated informational networks [45,71].
- Understanding the tumor cell as an adaptive system, capable of structural and functional reorganization under stress conditions [72].
- Emphasizing the role of the tumor microenvironment as an active participant in disease progression [73].
- Defining cancer stem cells as strategic nodes in the hierarchy and plasticity of the tumor network [74].
- Last, but not least, it allows for anticipating points of systemic vulnerability, therapeutically exploitable by targeting key nodes or emergent properties of the network [75].

The concrete application of systems theory in oncology is already reflected in the use of molecular networks to prioritize biomarkers, in the development of predictive mathematical models, and in the application of artificial intelligence algorithms for treatment personalization [76]. Nevertheless, continued development of methodologies and deeper collaboration among disciplines—biology, medicine, mathematics, informatics—is required to transform this integrative approach into a clinical standard for evaluation and intervention [77].

In conclusion, systems theory is not only an explanatory tool but an epistemological key necessary to overcome the limits of traditional medicine and to build an oncology that is truly personalized, predictive, and effective. In the face of tumor complexity, systemic thinking provides not only a map of the disease but also a compass for the future of research and clinical practice.

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