بنام خدا

The Cancer that changes its mind: Can AI Predict the next move of Pancreatic Cancer?

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Introduction:

Pancreatic cancer is one of those diseases that exposes the limitations of modern medicine not at a single point, but at the intersection of multiple biological and clinical systems. Pancreatic ductal adenocarcinoma (PDAC) is not merely a malignant mass. It is a dynamic biological ecosystem in which malignant cells continuously interact with stromal and immune populations, the extracellular matrix, vascular structures, metabolic conditions, genetic and epigenetic programs, and the selective pressures imposed by therapy. This complexity is central to the extraordinary clinical difficulty of pancreatic cancer.

According to GLOBOCAN ٢٠٢٢, pancreatic cancer accounted for more than ٥٠٠,٠٠٠ new cases worldwide and more than ٤٦٠,٠٠٠ deaths, highlighting the disproportionate mortality burden associated with this malignancy. The narrow gap between incidence and mortality reflects not only the aggressiveness of the disease, but also the persistent limitations of early detection and effective long-term treatment.

Yet the fundamental problem is not simply that pancreatic cancer is lethal. Its deeper challenge lies in its temporal biology. PDAC may undergo substantial molecular, cellular, and ecological evolution long before the disease produces sufficiently specific clinical manifestations. By the time symptoms such as weight loss, abdominal or back pain, jaundice, or metabolic abnormalities prompt definitive investigation, the biological process may already have progressed beyond the stage at which local curative treatment is most feasible.

This temporal disconnect between the biological emergence of disease and its clinical recognition is one of the defining challenges of pancreatic oncology.

The difficulty does not end with diagnosis. Modern research increasingly demonstrates that PDAC should not be conceptualized as a biologically uniform entity. A single tumor may contain multiple cellular populations that differ in their genomic alterations, transcriptional states, metabolic dependencies, phenotypic characteristics, spatial organization, immune interactions, and sensitivity to therapy.

Single-cell and spatial profiling technologies have made this heterogeneity increasingly visible and have challenged the assumption that a single biopsy or bulk molecular profile can fully represent the biology of an entire tumor.

This heterogeneity has direct therapeutic consequences. Treatment may eliminate highly sensitive populations while leaving behind resistant, tolerant, or phenotypically adaptable populations. Therapeutic pressure can therefore alter the composition of the tumor and reshape the selective environment in which surviving cells evolve. The tumor observed after treatment is not necessarily biologically identical to the tumor that existed before treatment. In this sense, therapy does not merely act upon cancer; it can also influence the evolutionary trajectory of cancer.

This observation leads to the central question of this book:

Can we predict the next move of pancreatic cancer?

The phrase *next move* is deliberately metaphorical. Cancer does not possess intention, consciousness, or strategy. Rather, its apparent adaptability emerges from the interaction of clonal variation, natural selection, cellular plasticity, microenvironmental pressures, and treatment-induced selection. What appears clinically as an intentional response is often the emergent consequence of biological evolution.

Accordingly, predicting the next move does not mean predicting the future with certainty. It means estimating the probability of future disease states: treatment response, resistance, progression, recurrence, metastatic dissemination, toxicity-limited treatment failure, or the emergence of a new therapeutic opportunity.

This is where Artificial Intelligence (AI) becomes particularly relevant.

Modern oncology generates an extraordinary volume of multidimensional information. Clinical records, laboratory measurements, radiological imaging, histopathology, genomics, transcriptomics, proteomics, metabolomics, treatment exposure, and longitudinal outcomes each capture different aspects of disease biology. The challenge is no longer merely to acquire more information, but to integrate these heterogeneous streams into a coherent representation of the patient's current disease state and its likely future trajectory.

Artificial intelligence offers a potential framework for performing this integration at a scale that is difficult to achieve through conventional human analysis alone. Machine-learning systems can identify complex nonlinear relationships across large datasets; deep-learning models can extract high-dimensional representations from medical images and pathology; and multimodal approaches can potentially combine clinical, molecular, imaging, and longitudinal information within a single predictive framework.

The emerging literature provides important examples of this direction. The Molecular Twin platform, for instance, demonstrated the potential of integrating multi-omic and computational data to generate outcome predictions in pancreatic adenocarcinoma, illustrating how computational oncology may increasingly move beyond single-variable biomarkers toward multidimensional representations of tumor biology.

Radiomics and computational pathology further extend this paradigm. A medical image is not merely a visual representation; it is a quantitative matrix containing information about intensity, texture, shape, spatial relationships, and tissue characteristics. Similarly, digitized histopathological slides contain morphological information that may be computationally analyzed at a scale and granularity beyond conventional visual interpretation. The convergence of radiomics, pathomics, transcriptomics, and other molecular layers is therefore creating the foundations for increasingly integrated predictive oncology.

However, this book deliberately avoids technological optimism without evidence.

There is a profound difference between a model that performs impressively on a retrospective dataset and an AI system that can safely influence clinical decisions. Much of the current literature remains limited by retrospective designs, single-center datasets, overfitting, publication bias, limited external validation, and inadequate prospective evaluation. A model may demonstrate excellent discrimination yet fail to generalize to another population, healthcare system, imaging protocol, or clinical workflow. External validation can establish transportability to some extent, but it does not by itself prove clinical utility or improved patient outcomes.

Thus, the relevant question is not simply whether AI can identify patterns that humans cannot.

The more important questions are:

Are those patterns biologically meaningful?

Are they reproducible?

Are they generalizable?

Are they clinically actionable?

And does using them actually improve patient care?

These questions move the discussion from computational performance to clinical translation.

They also introduce issues of explainability, bias, data governance, accountability, privacy, calibration, fairness, and human oversight. An algorithm intended for high-stakes oncology cannot be evaluated solely according to its accuracy. It must be understood within the clinical system in which it operates. The ultimate objective is not a perfectly interpretable algorithm or a perfectly curated dataset, but a clinical environment in which reliance on computational predictions is justified, monitored, and continuously open to challenge.

For this reason, the future envisioned in this book is not one in which an autonomous machine replaces the oncologist.

A more credible future is one in which clinicians and computational systems work in partnership. AI may organize complex longitudinal data, identify subtle patterns, estimate risks, compare possible trajectories, support clinical-trial matching, and highlight information that deserves attention. The oncologist, however, remains responsible for contextual interpretation, clinical judgment, communication, ethical reasoning, and the final decision-making process.

The central objective, therefore, is not human versus machine, but human AI synergy.

This book follows that trajectory. It begins with the biological and clinical paradoxes of PDAC: delayed detection, hidden biomarkers, tumor heterogeneity, and the evolving tumor microenvironment. It then moves toward mechanisms of therapeutic escape and cancer evolution, followed by computational medicine, multi-omics,

machine learning, deep learning, radiomics, and digital pathology. Finally, it addresses the difficult transition from laboratory models to clinical oncology, including validation, interpretability, ethics, governance, and the emerging vision of AI-augmented cancer care.

At its core, this book asks the reader to reconsider what it means to understand a tumor.

A CT scan is a snapshot.

A biopsy is a sample.

A laboratory measurement is a signal.

A molecular profile is a molecular state.

But cancer is a process.

The future of pancreatic oncology may therefore depend not only on obtaining more data, but on learning how to transform fragmented observations into a continuously updated model of disease behavior.

Perhaps the most important question in the oncology of tomorrow will no longer be simply:

What is this tumor?

It may increasingly become:

What is this tumor most likely to become next?

And that is where the real promise and the real responsibility of artificial intelligence begins.

Foreword

Writing about pancreatic cancer is, before anything else, an encounter with one of the most demanding problems in contemporary medicine: how to make meaningful clinical decisions when the disease itself is continuously changing.
Writing about pancreatic cancer is, before anything else, an encounter with one of the most demanding problems in contemporary medicine: how to make meaningful clinical decisions when the disease itself is Yet our ability to predict the future behavior of cancer has not advanced at the same pace. This discrepancy between what we can measure and what we can predict is where this book begins.

The Cancer that Changes Its Mind: Can AI Predict the Next Move of Pancreatic Cancer? was conceived around a simple but consequential idea: if cancer is a dynamic biological process, then our models of cancer should also become dynamic. The title is intentionally provocative.

Pancreatic cancer does not literally “change its mind,” nor does it anticipate the physician in any psychological sense. The apparent strategic behavior of the disease arises from evolution: clones expand or contract, phenotypes change, cellular states shift, microenvironmental conditions evolve, treatment creates selective pressure, and resistant populations may become increasingly dominant. In clinical terms, the “next move” is therefore the next disease state that emerges under these interacting biological forces.

This book is not intended to be a conventional textbook of pancreatic oncology, nor is it simply a review of artificial intelligence in cancer medicine. Rather, it attempts to connect two disciplines that are increasingly becoming inseparable: cancer biology and computational medicine.

The first chapters therefore begin with the biology of the problem.

Why is pancreatic cancer so difficult to detect?

Why can two apparently similar tumors behave so differently?

Why can treatment produce an initial response followed by rapid progression?

How does the tumor microenvironment influence therapeutic resistance?

Why can a cancer cell change its functional state without necessarily acquiring a new driver mutation?

Only after these questions are established does the book turn toward computational approaches. This order is deliberate.

AI can only be as meaningful as the biological and clinical problem it is designed to model. If the underlying disease is heterogeneous, dynamic, spatially organized, and temporally evolving, then a computational framework that treats it as a static classification problem will inevitably capture only part of the phenomenon. The transition from classification to trajectory prediction is therefore one of the central intellectual themes of this book.

A clinically useful AI system should not merely answer: What does the tumor look like now?

It should increasingly help us consider: Given what the tumor looks like now, what biological or clinical state is it most likely to enter next?