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INTEGRATING EMT DYNAMICS IN MODEL-BASED METASTASIS PREDICTION

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ABSTRACT

Introduction

Cancers are a group of diseases characterized by uncontrolled cell proliferation, leading to the disruption of tissue homeostasis and the destruction of adjacent structures. In the global population, lung cancer - specifically Non-Small Cell Lung Cancer (NSCLC) - remains the leading cause of cancer-related mortality. The vast majority of these deaths result from the presence of metastases, a complex process where cancer cells lose intercellular connections and spread to secondary sites. A key mechanism facilitating this transition is the epithelial-to-mesenchymal transition (EMT), which promotes cellular motility and the generation of circulating tumor cells (CTCs) [1].

While Transforming Growth Factor beta (TGF- β) is recognized as a primary regulator of EMT, its effectiveness as a static prognostic biomarker remains a subject of clinical debate [2]. This study aims to demonstrate that the temporal dynamics of TGF- β , rather than its absolute concentration at a single time point, is the crucial factor in predicting metastasis-free survival (MFS).

Methods

The proposed computational framework integrates intracellular signaling with population-level dynamics through a two-stage simulation pipeline.

The core of the approach is an EMT signaling network model adapted from [3], refitted to human lung A549 cells. We extended this model by introducing extracellular TGF- β production stimulated by the tumor micro-environment. By simulating a heterogeneous population of cells, a cumulative density function (CDF) for the probability of metastasis was derived based on the count of cells achieving a full mesenchymal or mesenchymal-like hybrid phenotype.

Population-level dynamics was modeled as a two-compartmental ODE system, incorporating the effects of chemotherapy and radiotherapy with parameters derived from [4]. A cohort of 1000 virtual patients was generated to match the T and M stage distribution of a real clinical dataset of 657 from the National Institute of Oncology in Gliwice.

Simulation outcomes in terms of Overall Survival (OS) and MFS were validated against clinical survival data using the Kaplan-Meier estimator and log-rank statistical test. Additionally, the EMT-based approach was compared to a simple arbitrary metastasis threshold approach.

Results

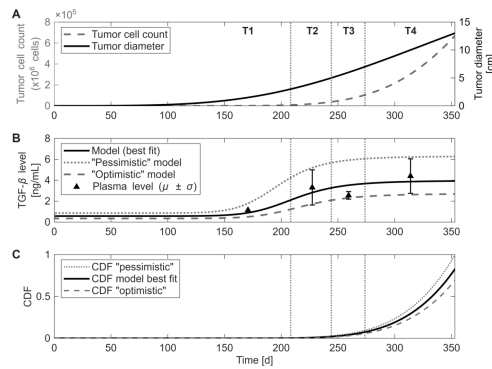


Figure 1. Example simulation results of a model combining tumor growth and intracellular processes **A)** the tumor growth dynamics (expressed as number of cells and tumor diameter), **B)** TGF- β dynamics for different simulation protocols (scenarios) and their comparison with experimental data, and **C)** CDF curves corresponding to different simulation protocols.

The integration of EMT dynamics allowed the model to reproduce OS and MFS curves that were consistent with clinical observations. Analysis of different simulation scenarios revealed that the rate of TGF- β increase significantly influences the metastasis probability (Fig. 1).

In "pessimistic" scenarios, characterized by a rapid rise in TGF- β during early stages (T1-T2), the CDF curves reached critical thresholds much earlier than in "optimistic" scenarios. Furthermore, the EMT-based metastatic switch provided more accurate long-term MFS predictions compared to models using an arbitrary tumor-size threshold.

Conclusions

The findings suggest that the clinical ambiguity regarding TGF- β as a biomarker stems from ignoring its dynamic nature. To improve prognostic accuracy, the study recommends replacing single "snapshot" measurements with time-series monitoring of TGF- β levels. From a modeling perspective, this approach demonstrates how linking intracellular processes to population dynamics can provide results of similar quality but with much better biological grounding. This idea serves as a "proof of concept" for personalized treatment, potentially allowing for the use of treatment protocols based on individual biomarker trajectories.

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