Tumor Organoids Modeling Reveals Timed Responses and Interplay of Radiotherapy and Chemotherapy in Pancreatic Cancer

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ABSTRACT

Purpose: Model the therapeutic effects of chemotherapy, radiotherapy, and chemoradiotherapy to study the heterogeneous responses of pancreatic cancer patient-derived tumor organoids (PDTOs).

Methods: We proposed novel mathematical forecasting frameworks based on logistic growth ordinary differential equations and the characteristics of tumor responses to model the therapeutic effects of chemo- and radiation-induced killing in PDTOs. To validate the models, we cultured PDTOs from different patients and treated them with radiation (4 Gy and 8 Gy), chemotherapy (FOLFIRINOX), and combined regimens, respectively. The diameters of 20-40 organoids per patient were tracked and measured using brightfield images up to 7 or 9 days following each treatment to capture organoid growth dynamics data, which was used for model fitting. The accuracy of the modeling was evaluated by the average normalized mean squared errors (NMSE) of data fitting.

Results: The proposed mathematical modeling frameworks accurately captured the observed growth dynamics of three PDTO samples after chemotherapy, radiotherapy, and chemoradiotherapy. The fitted parameters, including killing pattern, effect window, and peak killing timing, quantitatively revealed significant heterogeneities in treatment responses across different PDTOs. Chemotherapy shows pronounced effectiveness in the early stage, while radiotherapy exhibits the effect later in the first week (around day 4), and a significantly stronger secondary response occurs one week after radiation treatment (around day 8). Chemoradiotherapy combines the strengths of both modalities, producing pronounced effects in both response phases, with modeling results suggesting that the radiation-induced killing effect may play a dominant role in the combined interaction.

Conclusion: Our modeling frameworks demonstrated high accuracy in modeling the heterogeneous therapeutic responses of PDTOs and provided insights into the dynamic killing effects and interplay between chemotherapy and radiotherapy. The modeling of therapeutic responses of PDTOs provides a valuable tool for optimizing treatment regimens and informing clinical trial design, thereby improving the efficacy of personalized medicine.

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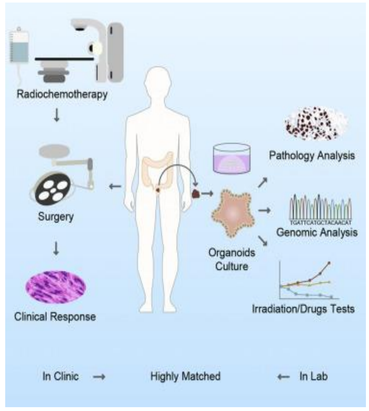
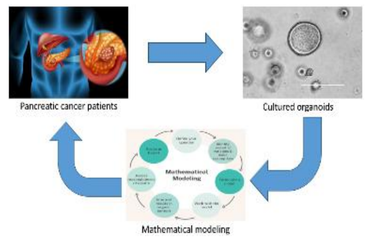
INTRODUCTION

Patient-derived organoids
- 3D in vitro models
- Recapitulate the organ
- Treatment response
- Drug discovery
- Disease modelling



Aims
- ❑ Model killing effects
- ❑ Quantify responses
- ❑ Predict tumor behavior



METHODS AND MATERIALS

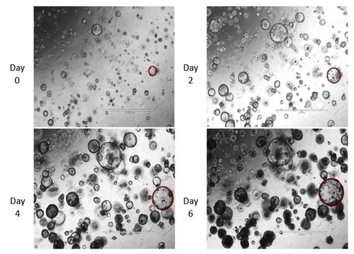
Mathematical models
- Chemotherapy:

$$\frac{dN}{dt} = (\lambda - C(t))N\left(1 - \frac{N}{K}\right)$$

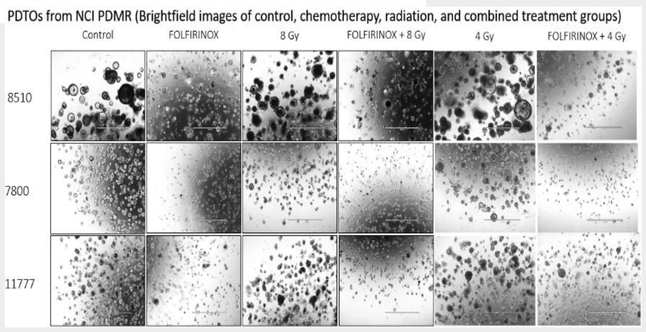
- Radiation:

$$\begin{cases} \frac{dA}{dt} = (\lambda - R(t))A\left(1 - \frac{A+I}{K}\right) \\ \frac{dI}{dt} = R(t)A\left(1 - \frac{A+I}{K}\right) - \mu I \end{cases}$$

Organoid culture



Organoid treatment groups



RESULTS

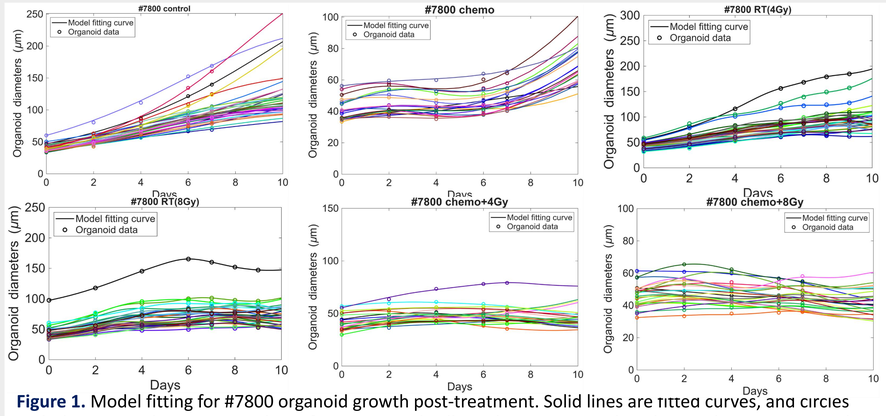


Figure 1. Model fitting for #7800 organoid growth post-treatment. Solid lines are fitted curves, and circles with the same color represent data of one organoid collected on corresponding days. At least 20 organoid lines were collected in each group.

Treatment-induced killing patterns

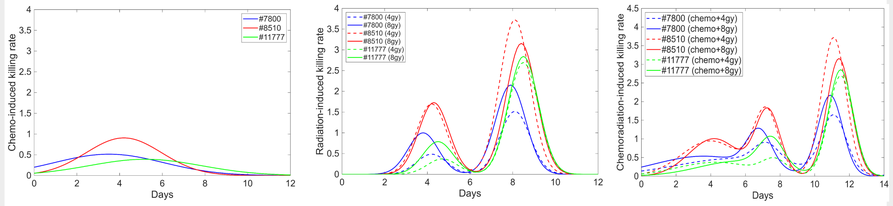


Figure 2. Treatment killing effect over time for #7800, #8510, and #11777 organoids. The chemo-induced killing effect occurs within days 0-12, with the response peak occurring around days 3-6. The radiation-induced killing effect occurs within days 2-11, with the early and secondary response mainly peaking around day 4 and day 8, respectively. The synergistic killing effect of chemoradiotherapy combines the strengths of both modalities, providing a relatively long and strong response window.

Chemotherapy
- Early initiated response
- Slower-growing organoids exhibit stronger drug resistance
- Sensitive organoids have a short drug response window

Radiation
- Second response is much stronger than initial response
- Peak time interval is approximately 4 days
- Radiation fraction interval needs to exceed 10 days

Combined regimes
- More intense response window in combined regimens
- RT on chemo killing is higher than chemo on RT killing
- Higher doses of RT enhance the chemo killing

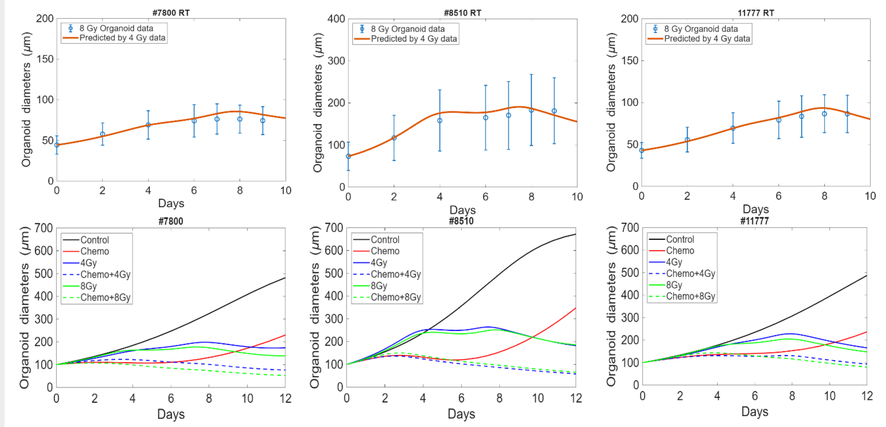


Figure 3. Upper three: Model predictions for 8 Gy RT based on 4 Gy experiments. Lower three: Simulations starting at 100 μm in each group. It shows that CRT at 8 Gy provides the most effective tumor control for #7800 (TR=6.64) and some improvement over 4 Gy for #11777 (TR=5.46), but 4 Gy of CRT is a more effective strategy for #8510 (TR=7.36). TR=treatment response.

Table 1. Treatment responses of each experimental group.

PDTOs ID	Treatment group	Day 7	Day 9
#7800	Chemotherapy	2.71 ± 0.12	
	Radiotherapy at 4 Gy	1.24 ± 0.15	2.15 ± 0.15
	Radiotherapy at 8 Gy	1.62 ± 0.12	2.52 ± 0.12
	Chemoradiotherapy at 4Gy	2.76 ± 0.25	
	Chemoradiotherapy at 8Gy	3.23 ± 0.13	
#8510	Chemotherapy	3.79 ± 0.21	
	Radiotherapy at 4 Gy	1.98 ± 0.20	3.00 ± 0.24
	Radiotherapy at 8 Gy	1.95 ± 0.18	3.01 ± 0.23
	Chemoradiotherapy at 4Gy	4.03 ± 0.18	
	Chemoradiotherapy at 8Gy	3.97 ± 0.16	
#11777	Chemotherapy	1.98 ± 0.15	
	Radiotherapy at 4 Gy	0.69 ± 0.15	1.54 ± 0.15
	Radiotherapy at 8 Gy	1.06 ± 0.15	1.92 ± 0.15
	Chemoradiotherapy at 4Gy	1.89 ± 0.17	
	Chemoradiotherapy at 8Gy	2.01 ± 0.16	

DISCUSSION

Building mathematical models of tumor organoid responses to therapies has clear and increasing clinical value, especially as organoid platforms move closer to routine clinical applications. The major clinical benefits include:

- **Objective, quantitative evaluation of treatment effects.** This enables objective, quantitative, and clinically meaningful understanding, evaluation, and comparison of therapeutic efficacy and timing, moving beyond qualitative or observational assessments of treatment-induced changes in organoid size.
- **Improved prediction of tumor response to different therapies.** This facilitates identification of synergistic treatment strategies and reduces trial-and-error in determining optimal therapeutic regimens in the clinical setting.
- **Integration with multi-omics and clinical data to enhance patient-level prediction.** Incorporating quantitatively modeled PDTO response parameters further strengthens these predictive models and supports treatment customization for precision oncology.

In summary

Mathematical modeling transforms tumor organoid assays from descriptive or observational experiment measurements into quantitative, predictive, integrative, and clinically actionable tools, directly supporting personalized therapy selection and optimization.

CONCLUSIONS

Our modeling frameworks
- demonstrated high accuracy in modeling the heterogeneous therapeutic responses of PDTOs, including killing strength, onset timing, and duration.
- Revealed that chemotherapy effect is predominantly concentrated in the first week, whereas that of radiotherapy is more pronounced next week.
- provides a valuable tool for optimizing treatment regimens and informing clinical trial design, thereby improving the efficacy of personalized medicine.

FUTURE DIRECTIONS

- Coculture modeling (immune cells +CAFs)
- Patient response prediction (Multi-omics + AI)