Osteosarcoma as a Math Problem: Using Modeling to Guide the Development of New Therapies

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Introduction

- Osteosarcoma metastases could develop through many distinct mechanisms.
- Knowing which mechanism occurs in patients can inform treatment by optimizing when drugs are used and what part of the metastatic cascade should be targeted.
- We seek a mathematical model of osteosarcoma that facilitates this optimization.

Methods

- Our approach is to build models from the ground up, guided by clinical data (see **Table 1**). Mechanisms will only be proposed when necessary. Models not matching the data will be rejected.
- All models that explain the existing data are candidates. We can propose specific future experiments to refine them.

Source	Datapoints Used
Link et al. NEJM 1986	Disease-free survival curve for localized osteosarcoma patients undergoing surgery only; proportion of patients cured by surgery alone; relapse timing and number of lung nodules at relapse.
Balmukhanov et al. Cancer 1982	Distribution of doubling times for primary bone tumor and their metastases.
Bieling et al. JCO 1996	Distribution of primary osteosarcoma tumor sizes at diagnosis.

Table 1: Summary of clinical data used for validating model predictions. For this work, we focused on describing the outcomes of initially localized osteosarcoma patients that underwent surgery alone.

Results

- We compared predictions of the models to clinical data; see **Table 2**. Many were eliminated; some matched the data.
- Mechanisms that were too “independent” in their seeding and growth processes never worked. Some form of “cooperativity” in the seeding process is needed (see **Figure 1**).
- Models with delayed seeding needed a period of accelerated met growth to match the relapse timing distribution.

Future Directions and Proposed Experimental Tests

- Incorporating chemotherapy response into the models could eliminate more mechanisms.
- The models differ on the timing of metastatic seeding. Preclinical experiments disrupting the metastatic seeding process at different times are needed to distinguish them.
- The models agree that there is cooperativity in the seeding process. The predicted genetic variability of micrometastases is small in some cases. Can this prediction be exploited?

Synchronization of Metastases is Needed to Explain the Data

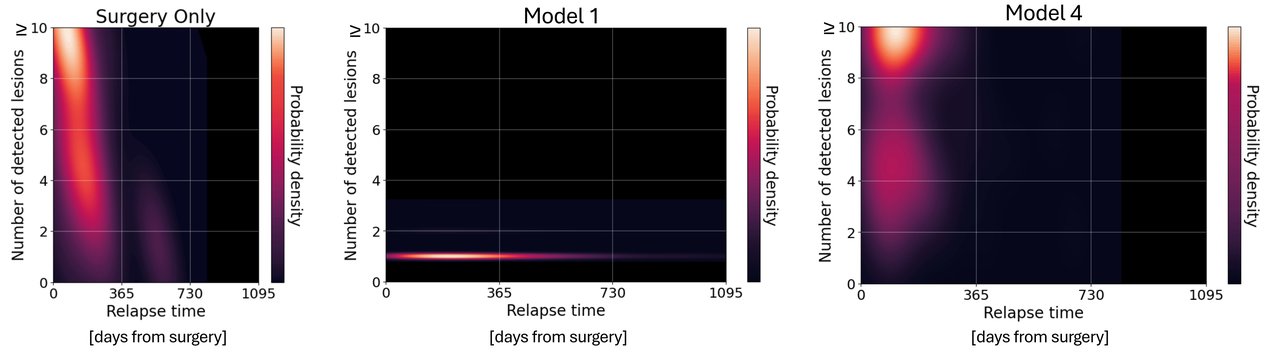

Figure 1: Comparison of Models 1 and 4 to the clinically-observed distribution of relapse times and numbers of lung nodules in localized osteosarcoma treated by surgery only. Model 1 is the simplest model of the metastatic process: tumor seeding happens at a “mass-action” rate, and each seeding is independent. This mechanism fails to capture the relapse distribution. However, when metastatic seeding is restricted and seeding events become cooperative (Model 4), a much closer fit is obtained.

Multiple Distinct Models Reproduce the Data

Model #	Model description	# tunable parameters	# cured by surgery only correct?	# metastatic at dx correct?	relapse timing correct?	relapse # mets correct?
Model 1	Exponential growth, mass action stochastic seeding (tunable rate), independent growth rates/primary size from known distribution.	1	Yes	Borderline (low)	No (late)	No (low)
Model 2	Model 1, but seeding does not start until a certain (tunable) size is reached.	2	Borderline (high)	Yes	Yes	No (low)
Model 2+	Model 2, but each seeding establishes more than one met drawn from a Poisson distribution (tunable mean).	3	No (high)	Borderline (low)	Yes	No (low)
Model 4	Model 2+, but all mets seeded at the same time have the same growth rate.	3	Yes	Yes	Yes	Yes
Model 4cap	Model 4, but the met seeding process stops when a (tunable) met cap is hit.	4	No (high)	No (low)	No (late)	No (high)
Model 5	Model 1, but lung mets can seed (tunable rate) and feed (tunable rate) other lung mets.	3	No (low)	No (low)	No (late)	Yes
Model 6	Model 5, but seeding only starts after a (tunable) size threshold and stops at a (tunable) met cap.	5	No (low)	No (low)	No (late)	Yes
Model 7	Model 1, but primary seeds a 3rd site which then seeds the lung (tunable rate).	2	No	Yes	No (late)	No (low)
Model 8	Reverse engineer the observed met timing and number distributions using the known growth rates. Randomly assign patients to met at dx (picking uniform # mets), localized at dx with no mets, localized at dx with mets groups. For mets, assume they all are at detection threshold when they appear.	0	Yes (enforced)	Yes (enforced)	Yes (enforced)	Yes (enforced)
Model 12	Model 1, but multiple mets can be seeded at the same time (tunable mean) all at the same growth rate and multiple mets (tunable mean) are seeded on surgery day.	3	No (low)	Borderline (low)	No (late)	Yes
Model 13	Model 12, but the surgery mets grow very fast (tunable multiple) for a (tunable) time after surgery.	5	No (low)	Borderline (low)	Yes	Yes (roughly)
Model 14	Model 1, but multiple mets are seeded at the same time (tunable mean) with the same growth rate.	2	Yes	Borderline (low)	No (late)	Yes
Model 15	Model 14, but mets grow faster (tunable multiple) until they reach a certain (tunable) size.	4	Yes	Yes (trending high)	Yes	Yes
Model 16	Model 1, but all mets (tunable mean number) are seeded simultaneously (at tunable primary size). They remain dormant until a trigger (tunable probability per day). Dormant mets can be cleared (tunable probability per day).	4	Yes	Yes	Borderline (late)	No (low)
Model 17	Model 16, but each seeding that isn’t eliminated results in multiple mets (tunable mean) that all have the same growth rate.	5	Yes	Yes	Borderline (late)	Yes
Model 18	Model 1, but tumors greater than (tunable) threshold are met at dx. Then, all others seed some (tunable mean) number of mets at surgery.	2	Yes	Yes	No (late)	No (low)
Model 19	Model 18, but multiple mets per seeding (tunable mean multiple).	3	Yes	Yes	No (late)	Yes
Model 20	Model 19, but with a period of rapid growth immediately following surgery (tunable time, tunable growth multiple).	5	Yes	Yes	Yes	Yes

Table 2: Summary of mechanisms tested and their match to clinical data. Models we built that worked were Model 4 (delayed cooperative seeding of metastases), Model 15 (cooperative seeding of metastases), Model 17 (cooperative dormant metastases), and Model 20 (metastases released at surgery). We were also able to reverse engineer the distribution of relapse times and number of lung nodules to create Model 8, which has no free parameters and cannot be tested without more data.

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Summary

- We modeled various osteosarcoma metastasis mechanisms. Comparing to data limits the possibilities.
- Pre-filtering mechanisms using modeling allows for more focused, clinically motivated experiments.
- The model that emerges from this research can be used to optimize future clinical trial design.