Building a Risk-Stratification Model for Patients with Osteosarcoma

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Abstract

Osteosarcoma patients exhibit profound molecular heterogeneity, but we remain unable to identify whether patients will have excellent or poor outcomes. The standard of care has remained stagnant since 1982 – surgical resection followed by chemotherapy. This results in ineffective treatment for high-risk patients and unnecessarily harsh treatment regimens for low-risk patients.

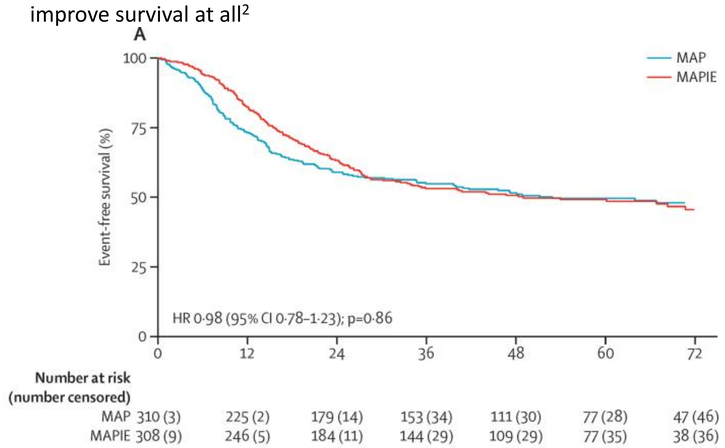
Multiple groups have proposed molecular signatures across multiple sequencing modalities that have associations with prognosis – and potentially even each other.

We hypothesize that several of these patient-stratification frameworks can be consolidated into a single risk prediction model that can inform treatment regimens, which will require the curation of the largest outcome-linked multiomic data resource to date.

Background

Evidence for high- and low-risk patients

- Before the advent of chemotherapy, 10-20% of patients would survive with surgery alone[1]
- In patients with poor response to the traditional chemotherapy regimen (MAP), more aggressive chemotherapy (MAPIE) did not improve survival at all[2]



The Problem: we know there are patients that don't need chemotherapy and others that need alternate treatments, but no way of identifying them at diagnosis.

Funding

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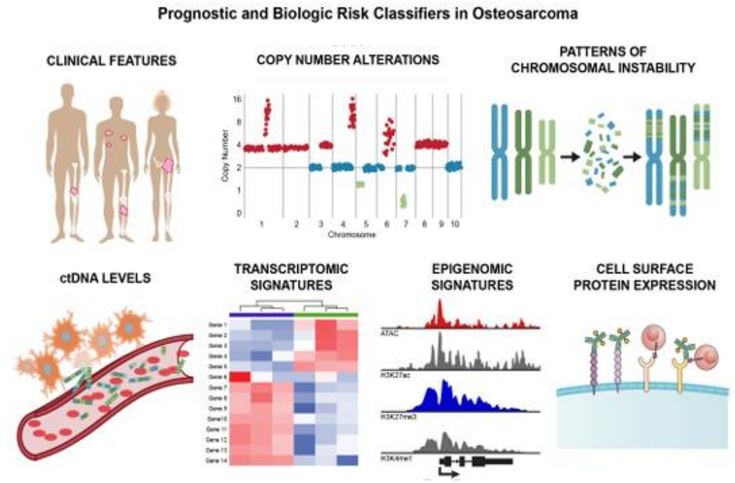
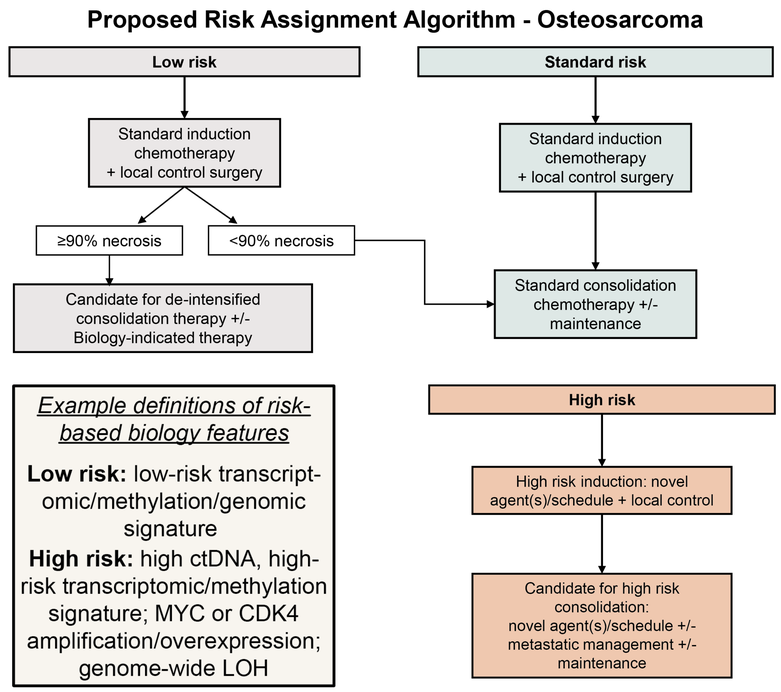
Background (cont.)

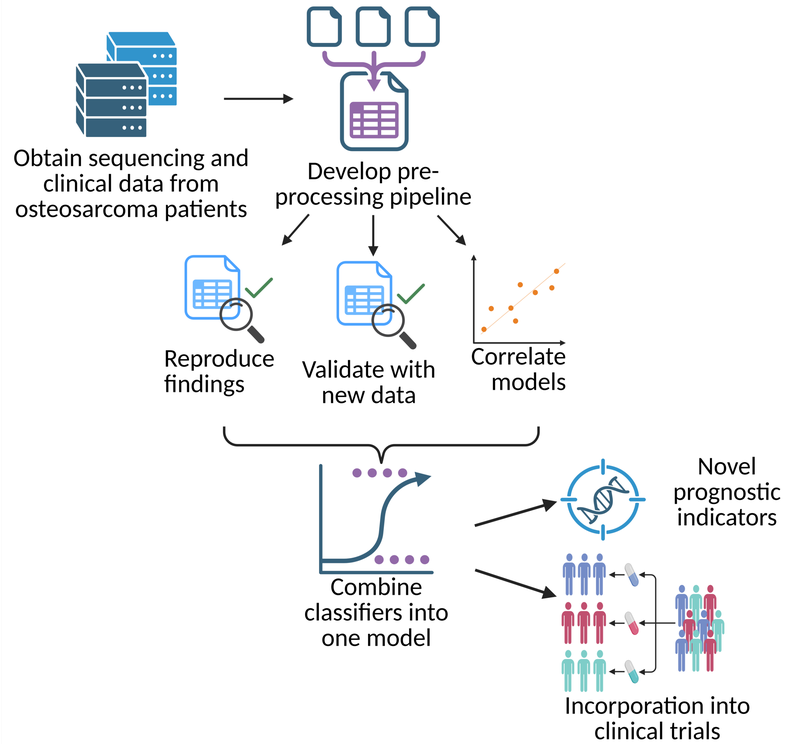
Recent efforts to stratify patients by risk status have leveraged next-generation sequencing technologies[3]



Deployment of a robust risk-stratification model[3]



Analysis Plan



Conclusions, Future Directions

- There is a need for a shift away from the "one size fits all" approach to osteosarcoma treatment
- Multiomic patient heterogeneity reveals risk-associated signatures
- This data resource will enhance our ability to validate proposed classifiers
- A model combining significant classifiers will enable personalized treatment
- Correlation analysis between classifiers provides insights into osteosarcoma tumor biology at large

References

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3. Marinoff, A.E., Nathrath, M., Shulman, D.S. et al. An international framework for clinical translation of molecular classifiers in osteosarcoma. npj Precis. Onc. (2026). https://doi.org/10.1038/s41698-026-01456-4