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Machine Learning and Mechanistic Modeling for the prediction of Overall Survival on the basis of 1st line Tumor Dynamics in Head and Neck Squamous Cell Carcinoma

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BACKGROUND

- Prediction of **Overall Survival** and **Response to 2nd line** is a **major challenge** in treatment of HNSCC
- Tumor kinetics during first line** may provide interesting **predictive metrics** for Overall Survival

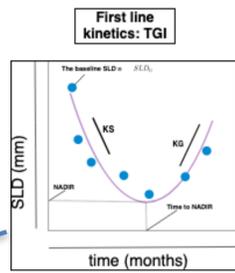
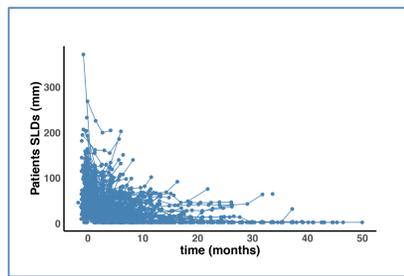
OBJECTIVES

- Propose the best **mathematical model** for the description of the longitudinal measurement of the patients individual SLDs (Sum of the Largest Diameters)
- Predict the **Overall Survival** using the kinetic data of first line and some baseline data

MATERIAL AND METHODS ¹

Clinical data

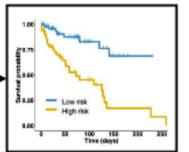
- EXTREME (cetuximab, 5-FU, platinum) vs TPEX (cetuximab, docetaxel, platinum)
- Phase 2 clinical trial**
- 528 patients** enrolled (263 (TPEX) and 265 (EXTREME)).



Kinetic signature

Baseline Features

MACHINE LEARNING



Tumor Growth Inhibition (TGI) models²:

Tumor Growth model with treatment effect

$$SLD(t) = SLD_0 e^{-KS/\lambda(1-e^{-\lambda t}) + KGt}$$

Biexponential model with resistant cells

$$SLD(t) = SLD_0 (\alpha e^{KGt} + (1-\alpha)e^{-KSt} - 1)$$

Biexponential model

$$SLD(t) = SLD_0 (e^{KGt} + e^{-KSt} - 1)$$

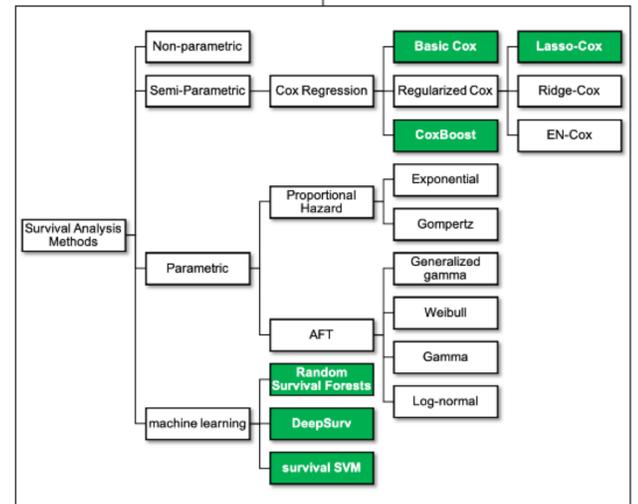
Nonlinear Mixed Effects Modeling (NLMEM)

$$y_j^i = f(t_j^i; \theta^i) + e_j^i$$

observation of individual i at time t_j^i structural model error model

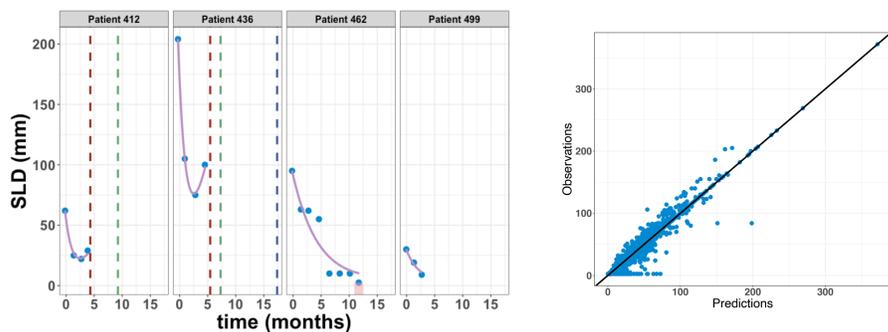
$$\theta^i = \mu \exp(\eta^i) \quad \eta^i \sim \mathcal{N}(0, \omega) \quad \mu \text{ fixed effects, } \eta^i \text{ random effects}$$

$$e_j^i = (\sigma_1 + \sigma_2 f(t_j^i; \theta^i)) e_j^i \quad e_j^i \sim \mathcal{N}(0, 1) \quad \text{combined error model}$$



RESULTS

The Biexponential model provides the best Fit (AIC and identifiability)³

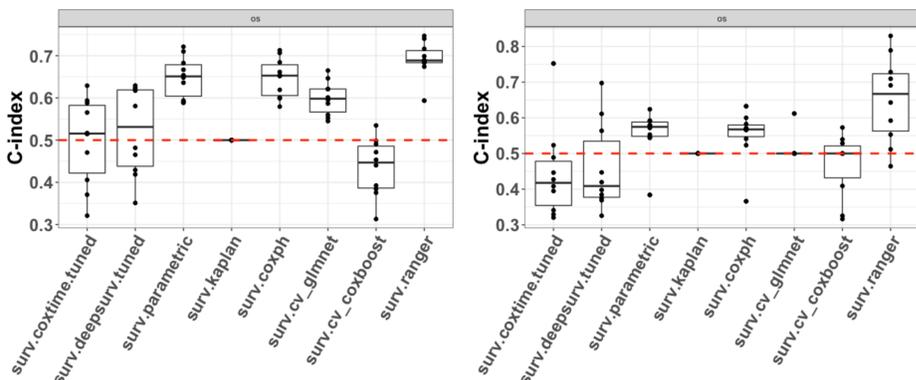


Prediction of the Overall Survival

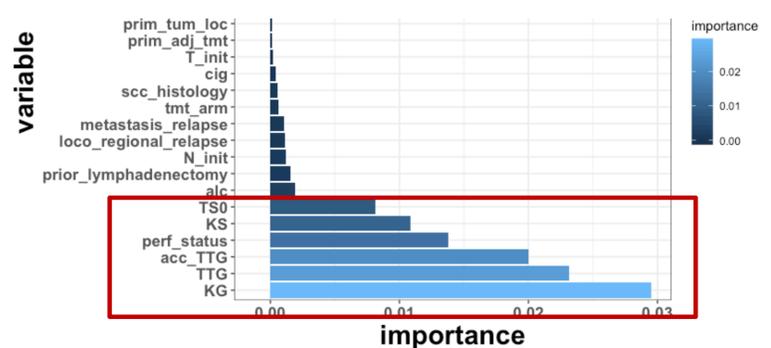
Best performance for Random Survival Forest (C-index= 0.7)

On the training set: 0.7

On the test set: 0.67



KG is the most important parameter for predicting OS



Tumor Kinetic Parameters Outperform All Others

CONCLUSION AND PERSPECTIVES

- A **mechanistic** mathematical model was able to fit the **clinical data** of SLD measurements in a HNSCC clinical trial
 - Mechanistic modeling and Machine learning algorithms were combined to predict **Overall Survival**
 - Predictive power is **only modest so far** but only the SLD measurements was considered
- ==> include **more features** and model **individual lesions kinetics**

References

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- R. Bruno, F. Mercier, L. Claret, Evaluation of Tumor size Response Metrics to predict Survival in Oncology Clinical Trials, Clinical Pharmacology and Therapeutics (2014)
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