MODELLING TUMOUR GROWTH AND PROGRESSION FREE SURVIVAL OF BREAST CANCER PATIENTS TREATED WITH NEOADJUVANT THERAPY

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BACKGROUND

Breast Cancer (BC) is the most commonly diagnosed in the US and European women with 23% (231,840) of new cases and 40,730 estimated deaths in 2015 [1], ranking 5TH as cause of death worldwide [2]. Although early diagnosis offers the best chance for survival, the identification of new prognostic factors is crucial. Early change in tumour size (CTS) has been related to Progression Free Survival (PFS) and Overall Survival (OS) for a number of malignancies [3-5] and may offer a chance for early evaluation of potential clinical benefit.

The aim of this evaluation was: 1) Establish a **semi-mechanistic model for tumour-shrinkage** for the period lasting from diagnosis to tumour resection
2) **Evaluate predictive and prognostic factors** (including model predicted tumour related metrics) **in relation with PFS**

METHODS

Information related to tumour size and survival was obtained from 219 patients diagnosed and treated from BC with neoadjuvant chemotherapy on the Clinc University of Navarra (CUN).
Tumour size was assessed either by ultrasound (US) or by magnetic resonance imaging (MRI). Both measurements were taken into account in the description of the tumour size dynamics.
Tumour size and PFS vs time were linked and described using the population approach with NONMEM 7.3. Model evaluation was performed through predictive checks.

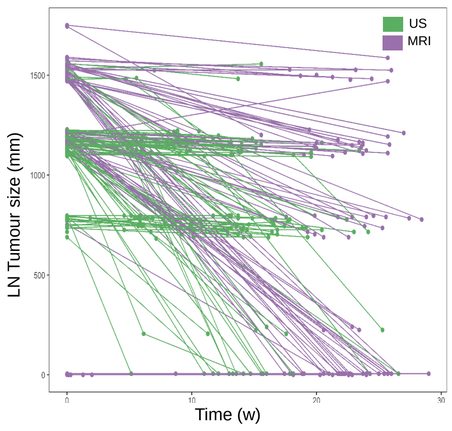

Figure I. Raw data
Tumour size stratified on imaging technique.

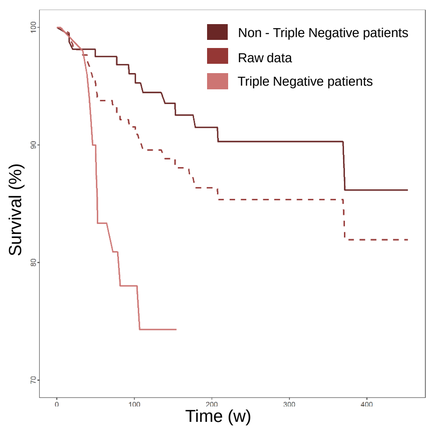

Figure II. Raw data
Kaplan Meier PFS stratified by tumour subtype.

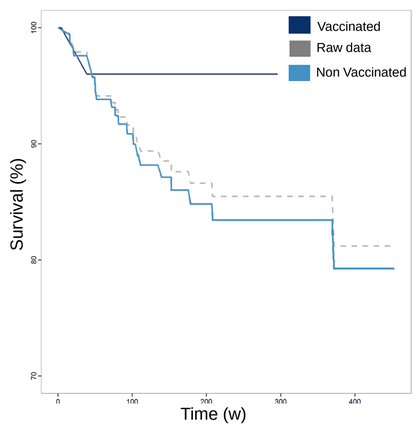

Figure III. Raw data
Kaplan Meier PFS stratified by dendritic cell vaccination.

Table I. Data summary

Patients	N=219. Breast cancer patients treated with neoadjuvant therapy and undergoing surgery.
Tumour size at diagnosis	US (mm) = 29.5 (27) [1,70] ; MRI (mm) = 30.8 (32) [1,77]
Vaccination with dendritic cells	N= 39 (17.8%)
Tumour Subtype	Pure Her-2: 14 (6.4%) ; Luminal A: 51 (23.3%); Luminal B: 100 (45.7%); Triple Negative: 53 (24.2%)

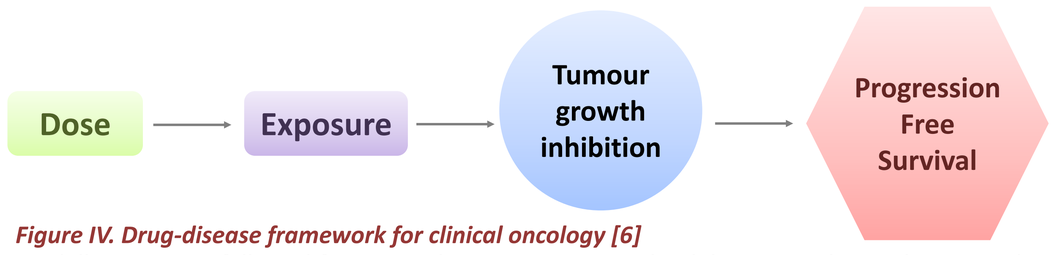

Figure IV. Drug-disease framework for clinical oncology [6]
Modelling strategy followed for our analysis. Tumour Growth Inhibition as a biomarker to predict clinical benefit

RESULTS

The model used to describe the tumour size over time accounts for differences in the imaging technique used to assess the tumour size, and incorporates a drug efficacy part dependent of drug exposure and of administration of immune therapy. Drug exposure was dealt using the KPD approach. The incorporation of a disease progression argument, or resistance development, was not possible. Patients receiving immune therapy had a shrinkage rate 29% higher than those who did not receive this treatment. Predicted tumour dynamics over time were linked to the probability of survival as an argument of the hazard function, which was best described using a Weibull model. Predicted 5-year PFS was 84.7% vs observed - 85.35%. The survival model also included tumour subtype, tumour size at diagnosis and CTS as covariates.

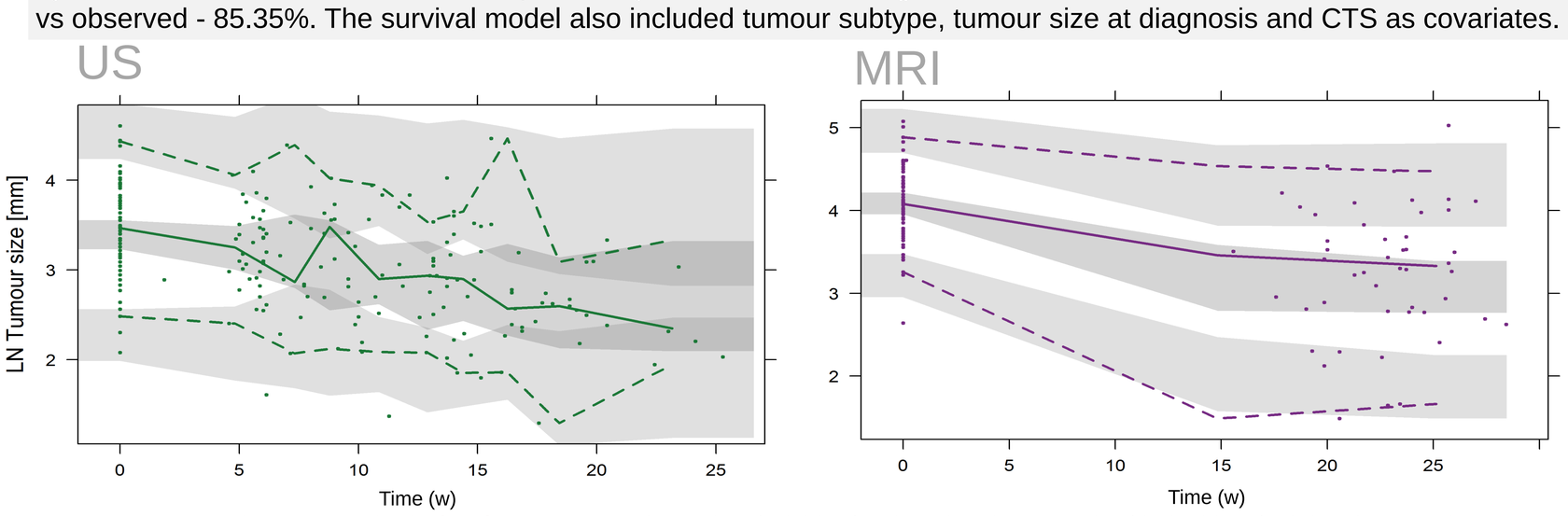

Figure V. Visual Predictive Checks (VPC). Tumour growth; Median (solid line), 5th and 95th percentiles (dashed lines) of the observed data. 95% confidence intervals for median, 5th and 95th percentiles (shaded grey áreas) of the simulated data.

Table II. Estimated model parameters

Parameters	Typical estimate	Variability	Shrinkage (%)
TS0 US (mm)	29.8	44%	12
TS0 MRI (mm)	58.8	43%	13
KDE (w^{-1})	0.0395	-	-
EFF	0.444	95%	23
EVAC	1.29	-	-
Error [US] log(mm)	0.378	-	25
Error [MRI] log(mm)	0.166	-	58
Base	0.004	-	-
Beta (w-1)	0.898	-	-
ECOdx	0.0237	-	-
CTS ECO	1.78	-	-
Subtype	0.0022	-	-

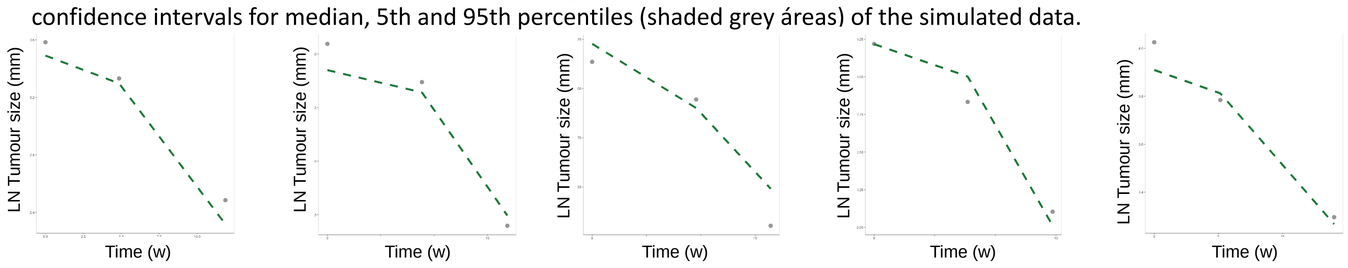

Figure VI. Individual tumour growth profiles. Points, individual observations. Dashed line, individual prediction.

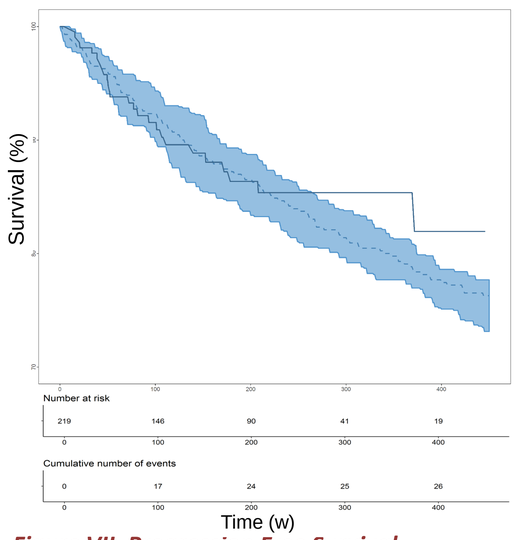

Figure VII. Progression Free Survival
VPC of final PFS. Kaplan Meier from raw data (solid line) is compared to the 95% prediction interval (shaded areas) based on 500 simulations.

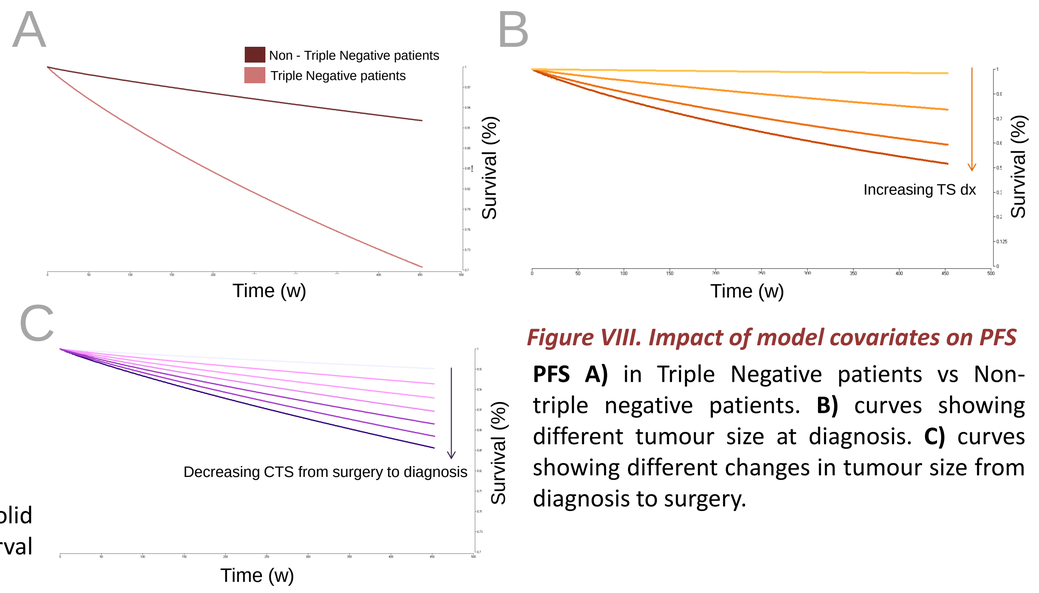

Figure VIII. Impact of model covariates on PFS
PFS A) in Triple Negative patients vs Non-triple negative patients. **B)** curves showing different tumour size at diagnosis. **C)** curves showing different changes in tumour size from diagnosis to surgery.

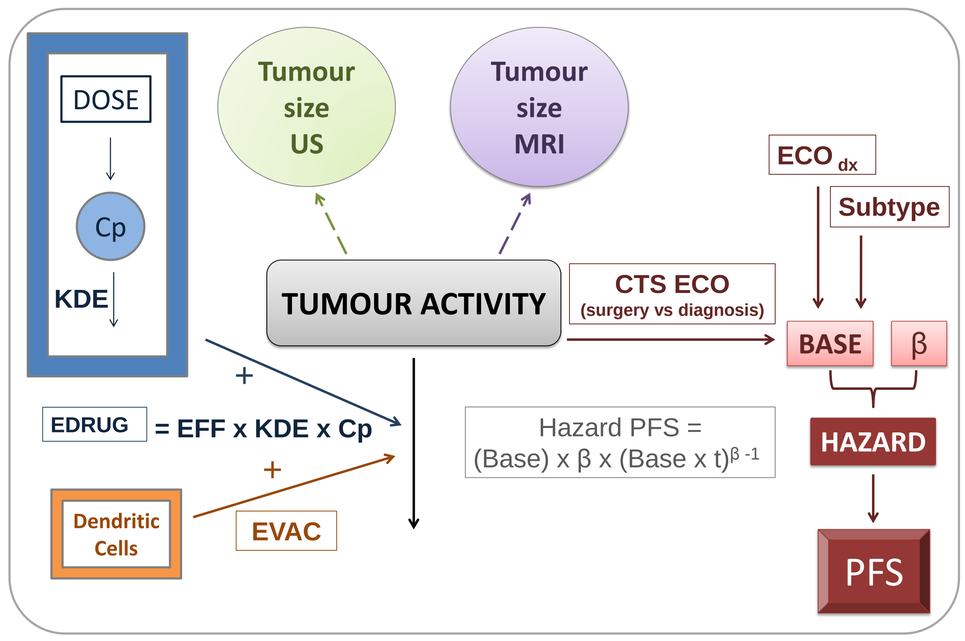

Figure IX. Tumour growth model linked to PFS model
KDE – Drug elimination constant; **EFF** – drug efficacy parameter; **Cp** – plasmatic drug concentration; **EDRUG** – Drug Effect; **EVAC** – dendritic cell - vaccine effect; **CTS ECO** – change in tumour size assessed by ECO; **ECOdx** – Tumour size at diagnosis assessed by ECO.

CONCLUSIONS & FUTURE PERSPECTIVES

Routine clinical data in general, and in oncology in particular, are sparse and scarce and represent a challenge from the modelling perspective.
This modelling exercise describes the efficacy of the neoadjuvant therapy in terms of tumour growth inhibition and survival of patients with BC.
It is expected to have a potential benefit in optimising the standard treatment of patients receiving neoadjuvant therapy by predicting the likelihood of treatment success.
The model building process in terms of modelling the biomarkers and toxicity to complete the full modelling framework is still ongoing.

References

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