

BACKGROUND

Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death worldwide. GC is a disease of poor prognosis and high mortality, being the overall 5-year relative survival rate about 20% in most areas of the world. Chemotherapy helps to prolong survival in cases of advanced disease, but surgical resection is the most effective treatment for curable gastric cancer [1]. The aim of this analysis was:

1) To develop a model for **effects of first line treatment** in patients with locally advanced GC from whom scarce ordered categorical data were obtained.

2) To investigate the potential **relationship between the risk of development new metastasis and the overall survival**.

METHODS

Data were obtained from 115 patients with locally advanced GC treated at the University Clinic of Navarra with neoadjuvant therapy, divided in two different protocols. One group received neoadjuvant chemotherapy followed by radiotherapy, and the other one just neoadjuvant chemotherapy. Both protocols underwent surgery.

Cancer stage of each individual was set using the TNM classification following the American Joint Comitee on Cancer guidelines (AJCC). This cancer notation system describes the stage of a cancer with alphanumeric codes – T describes the size of the primary tumour, N accounts for regional lymph nodes involved and M address distant metastasis [2]. For modelling purposes the TNM classification was reduced to partial response, stable disease and disease progression depending on the change of stage. At time of diagnosis it was assumed that all patients were on disease progression.

Response measurements were treated as ordered categorical using logistic regression and considering the contribution of first order markovian features. **Tumour response** was described, and **Survival** and **Metastasis** development versus time data were linked and described using the population approach with NONMEM 7.3. Model evaluation was performed through predictive checks.

Table I. Data summary

Patients	N=115. Locally advanced (no-metastatic) gastric cancer unergoing surgery.
Overall Survival	Max = 521.86 weeks; Mean = 181.94 weeks; Median = 136.286 weeks
Metastasis development	55 patients

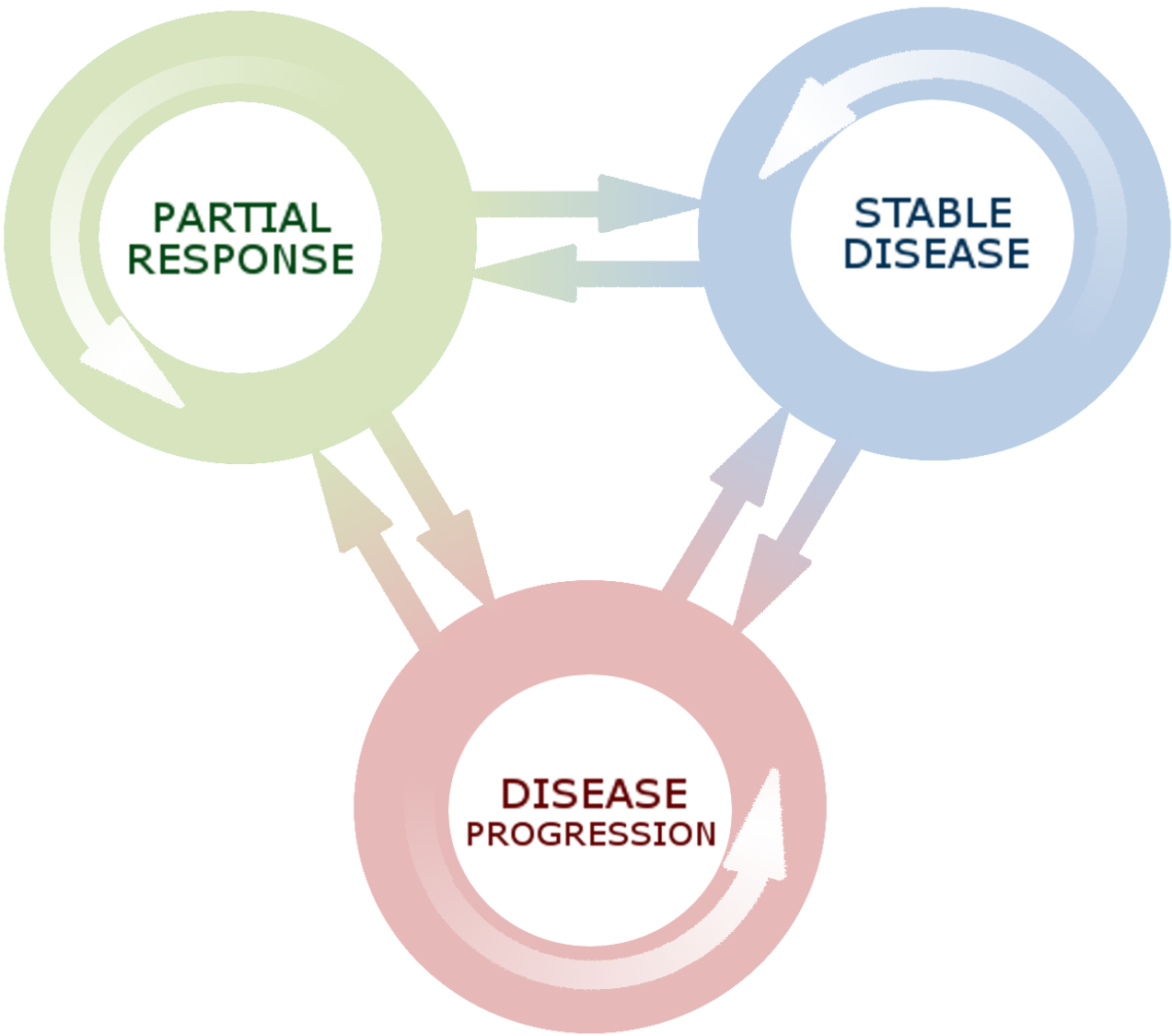


Table II. Response conversion

DV	Meaning	Relation with AJCC staging
0	Partial Response	Downstaging between visits
1	Stable Disease	No change in staging
2	Disease Progression	Upstaging between visits

Figure I. Markovian features. Transition possibilities between responses, according to the conversion made for modeling purpose.

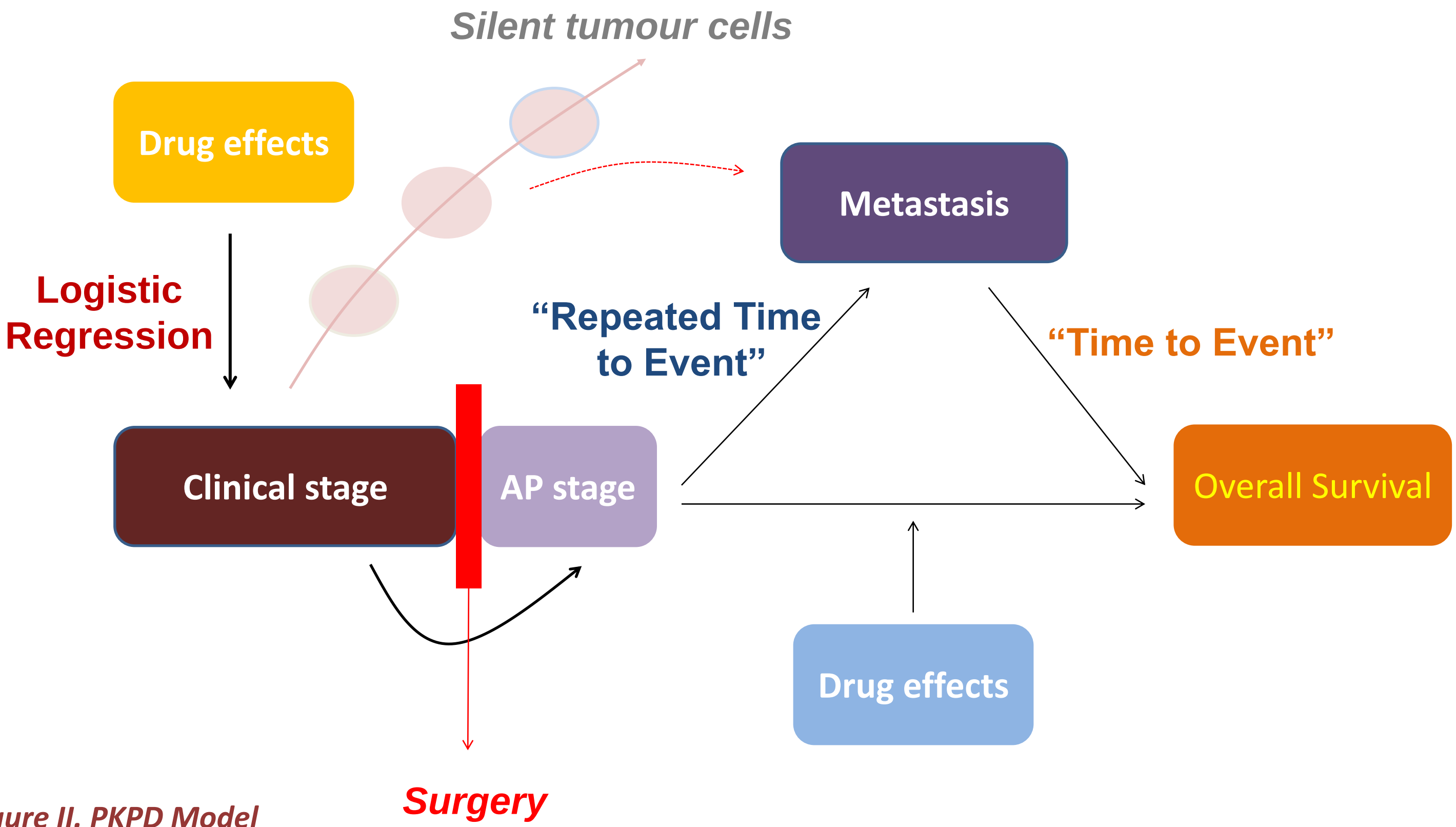


Figure II. PKPD Model Drug effects are linked to the changes between stages (clinical vs anatomopathological (AP)), and those are intended to be taken into account in the overall survival model and in the first new lesion development model.

RESULTS

The model used to describe the effects of first line treatment, regarding change in stage over time, incorporates differences in staging assessment (clinical vs pathological). Predicted tumour response was translated to the probability to undergo stage changes. Treatment effect was implemented as a factor when time is greater than 0, increasing the probabilities of a partial response. The Markov component was included regarding the stage in the previous time step. Differences in protocols shown no significance.

Progression free survival, taking into account only the first new lesion development, is described using an exponential model. Regarding the overall survival analysis was described again with an exponential model. The study of the link between the risk of metastasis development and survival was successful. The overall survival model included linitis plastic (agressive form of GC) and AJCC stage at diagnosis as covariates.

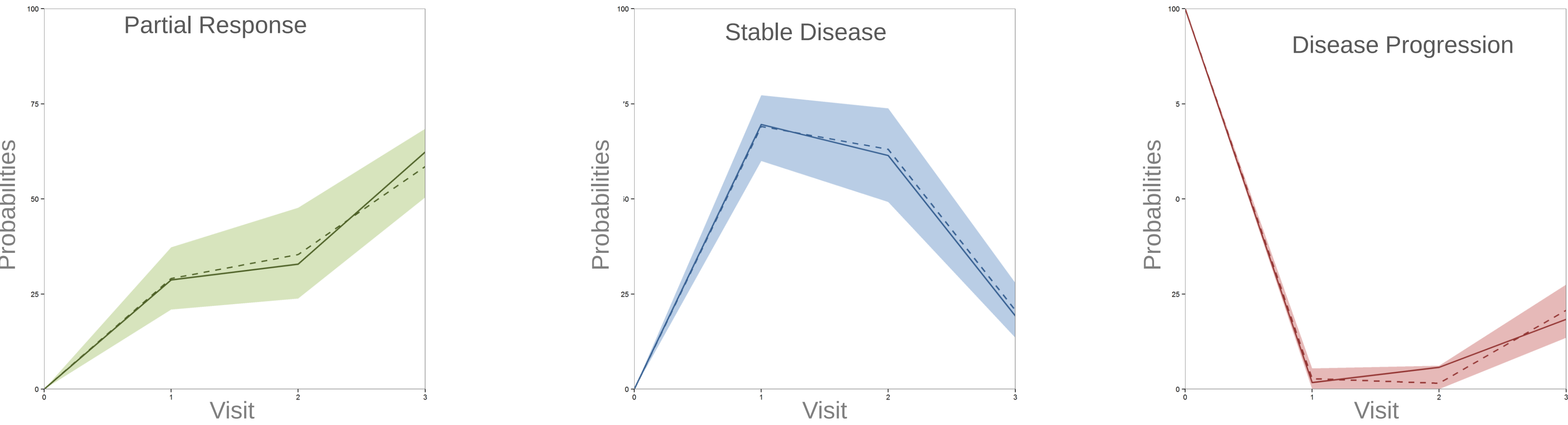


Figure III. Model Evaluation. Visual Predictive Check Probabilities (solid lines) for the observed data. Median (dashed lines), 95 % confidence Intervals (shaded areas) of the simulated data. Displayed according to the response codification: (I) Partial Response, (II) Stable Disease and (III) Disease Progression.

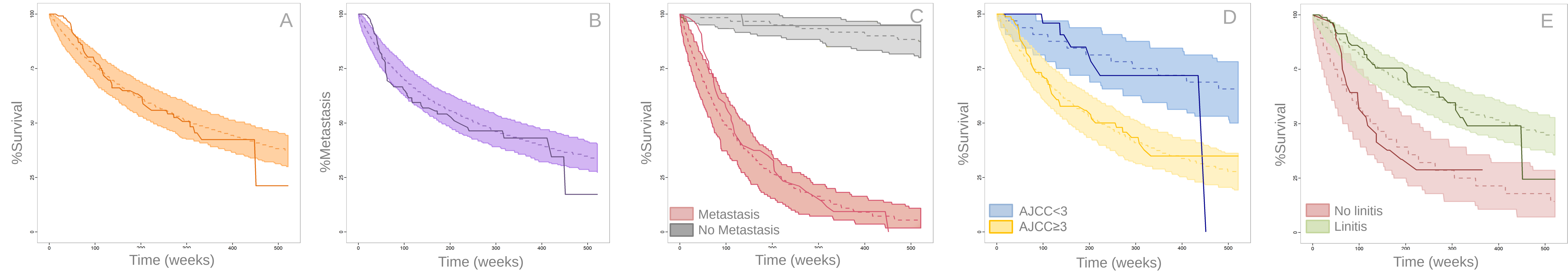


Figure IV. Survival – First New Lession Development Model Evaluation. Visual Predictive Check VPCs of final Survival – first new lesion development for Kaplan–Meier curves. The observed Kaplan–Meier (solid line) is compared to the 95% prediction interval (shaded areas) based on 500 simulations. A–OS model evaluation; B–First lesion development model evaluation; C–Survival depending on metastasis appearance; D–Survival depending on AJCC classification at diagnosis; E–Survival depending on Linitis Plastic at diagnosis

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. Herein it is shown that expressing data in terms of down-, upstage and no change represents an alternative to characterize drug effects using logistic regression. Our analysis shown that markovian features were present in our data. Overall survival and metastasis development could be successfully linked. The study of the link between predicted response and survival is still ongoing.

References

[1]Ferlay J et al. Int J Cancer. 2015;136:E359–86
[2] Washington K. Ann Surg Oncol 2010; 17:3077-9