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A Survival Modeling Analysis Evaluating the Use of Positron Emission Tomography with [(18)F]-fluorodeoxyglucose for Predicting the Prognosis in Advanced Non-Small Cell Lung Cancer Patients First-Treated with Erlotinib

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Background & Objectives

- Tumor metabolic dynamics measured using positron emission tomography (PET) with [(18)F]-fluorodeoxyglucose (FDG) was promoted over tumor size for evaluating response to novel anticancer agents [1-3].
- Using data from advanced non-small cell lung cancer (NSCLC) patients treated with the tyrosine kinase inhibitor erlotinib[3], we aimed to:
  - describe the survival of the cohort and evaluate different factors including tumor metabolic dynamics (SUV of FDG) as overall survival (OS) predictors.
  - quantify and compare the prognostic abilities of different SUV quantification criteria, namely SUV_{max}, SUV_{peak} and SUV_{50} as defined below[4] and shown in fig. 1.

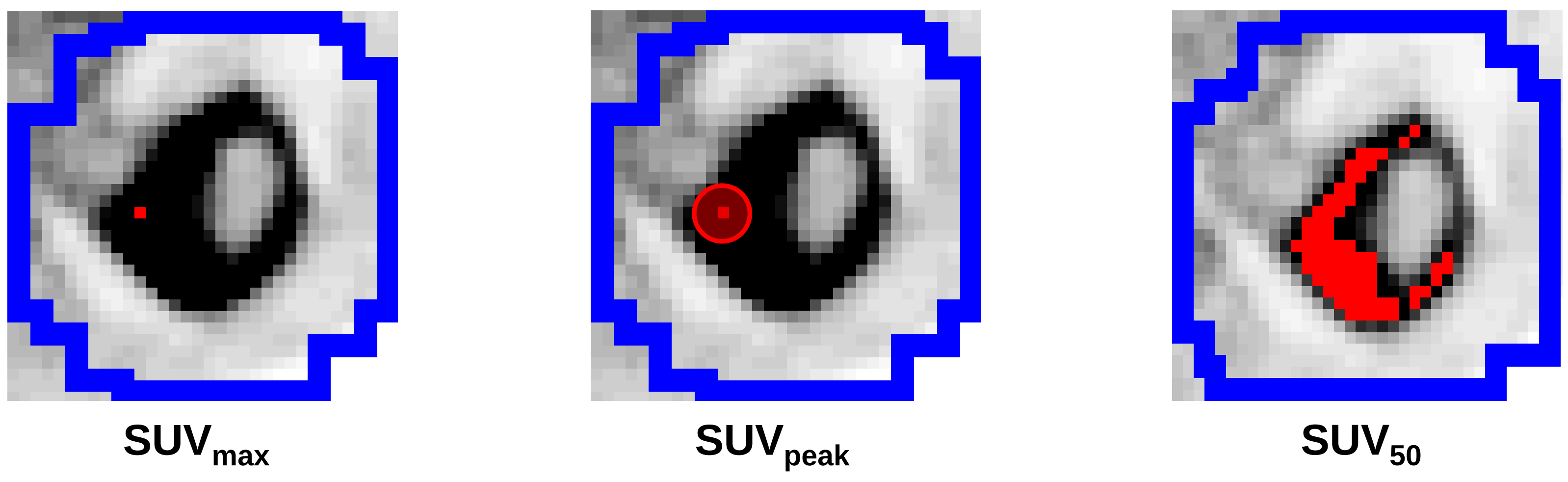


Fig.1. Images for different SUV (standardized uptake value) quantification criteria.

SUV_{max}: The voxel with the maximal activity concentration.

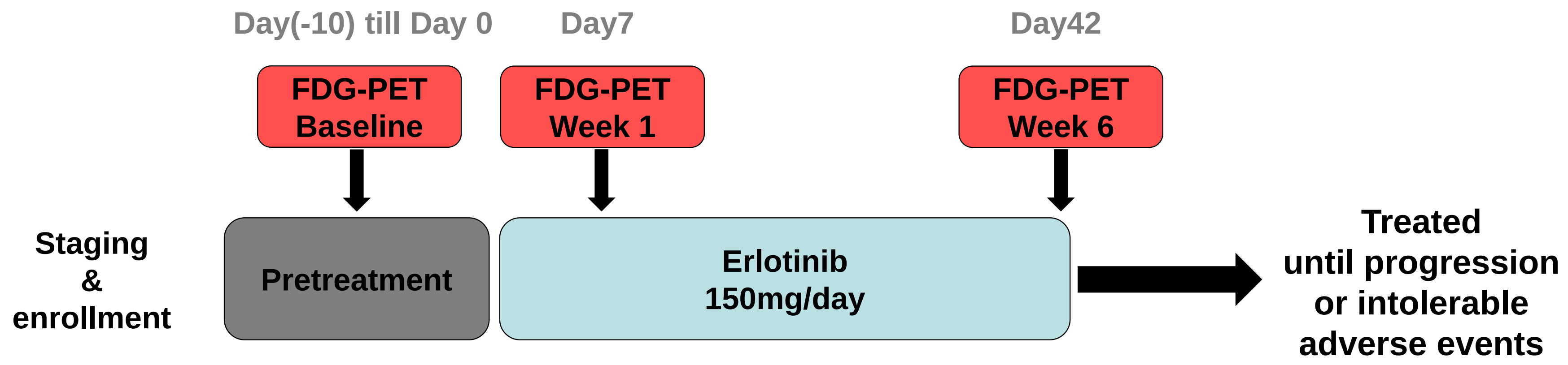
SUV_{peak}: 1.2-cm diameter fixed sized circle centered around the tumor area with the highest uptake.

SUV_{50}: Average activity concentration in the voxels with an activity concentration>50% of the SUV_{max}.

Methods

Patients & Data

- Data was available from stage-IV NSCLC patients (n=39) recruited in a phase-II trial and first-treated with erlotinib (150mg/day)[3]. 3 PET scans were scheduled (fig. 2). In total 101 observations were made.


Day(-10) till Day 0
Day7
Day42

FDG-PET Baseline
FDG-PET Week 1
FDG-PET Week 6

Staging & enrollment
Pretreatment
Erlotinib 150mg/day
Treated until progression or intolerable adverse events

Fig. 2. Trial Scheme

- A PK/PD model characterizing the SUV of FDG time courses(eq. 1)[5] was used to predict missing data.

$$\frac{dSUV(t)}{dt} = K_P * SUV(t) - K_D * e^{-\lambda * TAD} * Cp(t) * SUV(t)\ ; SUV(0) = BASE \qquad (eq.1)$$

K_P: progression rate constant; SUV(t): SUV at time t; K_D: constant representing the maximum drug effect after the first dose; λ: first-order rate constant for waning of drug effect; TAD: time after the first dose; Cp(t): plasma erlotinib concentration; and BASE: estimated baseline SUV.

Analysis, Model Development & Evaluation

- Non-linear mixed effects modeling was used for analysis (NONMEM 7.3).
- Exponential, Weibull, Gompertz, and log-logistic distributions were tested for development of the parametric survival model.
- Baseline and relative changes of FDG uptakes (SUV_{max}, SUV_{peak}, and SUV_{50}) after 1 and 6 weeks of treatment, demographics, histology, smoking, mutational and performance statuses were tested as OS predictors.
- Bootstrap analyses (1000 samples), visual predictive checks (VPC; 1000 datasets), and residuals based diagnostics were used for evaluation.

Results

Survival Model & Prognostic Factors

- An exponential distribution best described the survival times distribution.
- For all SUV criteria, baseline SUV and relative changes in SUV after 1 week of treatment were statistically significant OS predictors (p<0.05) (eq.2).

$$h(t) = \lambda * e^{(\beta_1 * baseline\ SUV + \beta_2 * \%drop\ in\ SUV)} \qquad (eq.2)$$

h(t): instantaneous hazard of dying at time t; λ: baseline hazard constant; baseline SUV: baseline SUV of FDG, %drop in SUV: % drop in SUV of FDG after 1 week of treatment (expressed as units of 10% drop), and β_1 and β_2 are the respective coefficients.

- For every unit increase in baseline FDG uptake quantified as SUV_{max}, SUV_{peak} or SUV_{50}, the death hazard increased by 16%, 25% and 27%, respectively (the median survival times shortened by 14%, 20%, and 21% respectively), while the hazard decreased for every 10% drop in FDG uptake quantified as SUV_{max}, SUV_{peak} or SUV_{50} after 1 week of treatment by 14%, 16% and 13%, respectively (the median survival times prolonged by 16%, 18%, and 15% respectively).

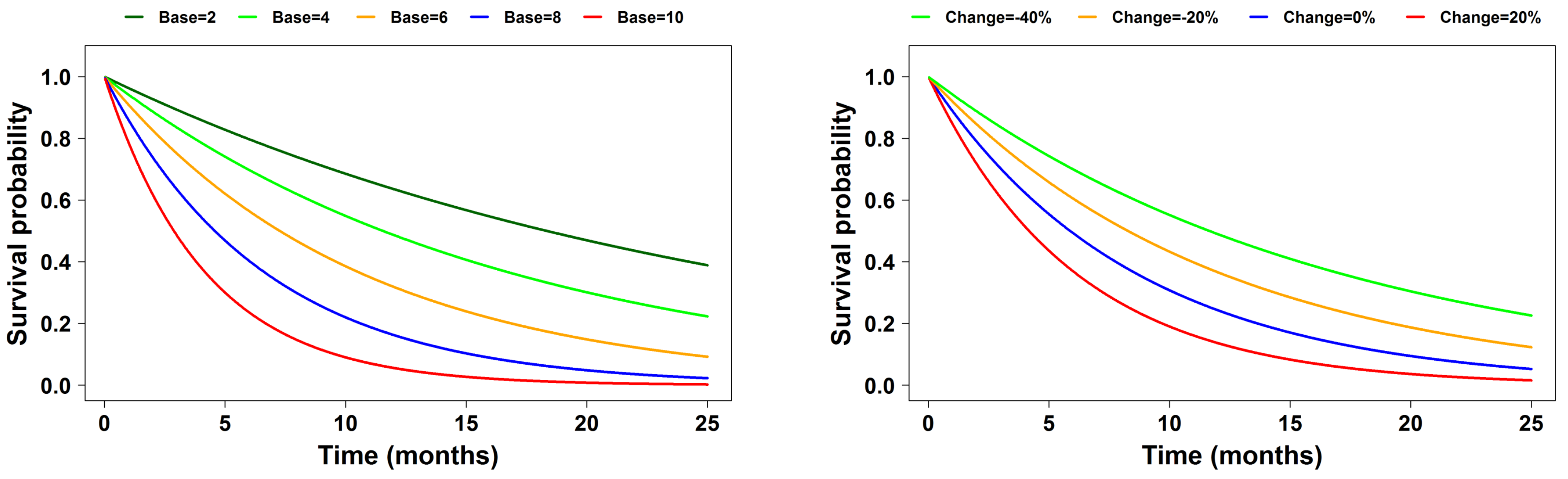


Fig. 3. *Left*: survival plots showing how different baseline SUV_{peak} can affect survival; the plots are normalized to the median drop in SUV_{peak} at week 1 (-8.36%); *right*: survival plots showing how different relative changes in SUV_{peak} after 1 week of treatment with erlotinib can affect survival; the plots are normalized to the median baseline SUV_{peak} (6.3).

Model Evaluation

- Model parameters were estimated with low bias and adequate precision as evaluated in the bootstrap analyses (table 1).

Parameter	SUV_{max}	SUV_{peak}	SUV_{50}
λ; hazard constant (day^{-1})	0.00338 (0.00248-0.00501)	0.00398 (0.00298-0.00551)	0.00365 (0.00272-0.00533)
HR for every unit increase in baseline SUV	1.16 (1.07-1.31); p-value=0.0013	1.25 (1.14-1.4); p-value=0.0004	1.27 (1.12-1.5); p-value=0.0009
HR for every 10% drop in the SUV after 1 week of treatment	0.863 (0.786-0.94); p-value=0.0147	0.845 (0.713-0.911); p-value=0.0065	0.866 (0.754-0.931); p-value=0.0104

Table 1. Parameter estimates and their 95% confidence intervals based on bootstrap analyses for the survival models incorporating SUV_{max}, SUV_{peak}, and SUV_{50} parameters.

- The VPC (fig. 4a) demonstrated the predictive power of the model. Cox-Snell and Martingale residual plots (fig. 4b & 4c) raised no critical concerns.

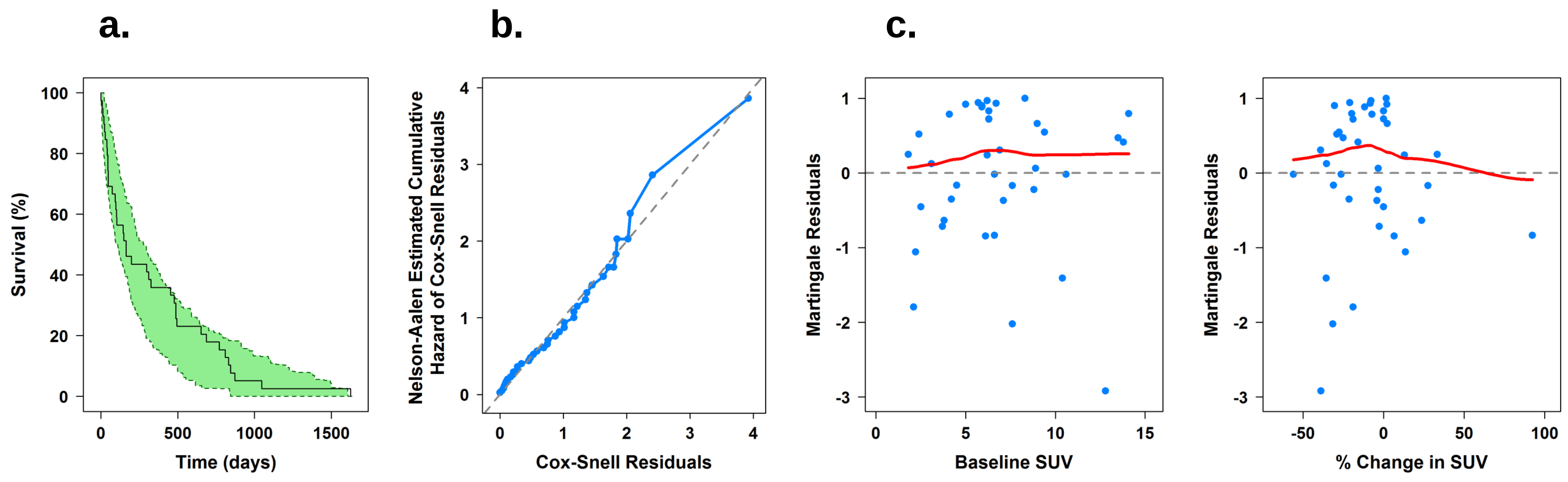


Fig. 4. a) Kaplan-Meier visual predictive check, b) Cox-Snell residual plot, c) Martingale residual plots.

Conclusion

- Regardless of the SUV quantification criteria, FDG-PET can be used as an early OS predictor for advanced NSCLC patients treated with erlotinib.

References
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4. Boellaard R et al. Eur J Nucl Med Mol Imaging (2010) 37:181-200
5. Suleiman et al. Submitted.