

PROGNOSTIC VALUE OF POST-INDUCTION CHEMOTHERAPY VOLUMETRIC PET/CT PARAMETERS FOR STAGE IIIA/B NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING DEFINITIVE CHEMORADIOTHERAPY

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ABSTRACT

Purpose/Objective(s): The aim of this follow-up analysis of the ESPATUE phase-3 trial was to explore the prognostic value of post-induction chemotherapy PET metrics in patients with stage III non-small cell lung cancer (NSCLC) who were assigned to receive definitive chemoradiotherapy.

Materials/Methods: All eligible patients stage IIIA (cN2) and stage IIIB of the trial received induction chemotherapy consisting of 3 cycles of cisplatin/paclitaxel and chemoradiotherapy up to 45 Gy/1.5 Gy per fraction twice-a-day, followed by a radiation-boost with 2 Gy once per day with concurrent cisplatin/vinorelbine. The protocol definition prescribed a total dose of 65-71 Gy. ^{18}F -FDG-PET/CT (PET_{pre}) was performed at study entry and before concurrent chemoradiotherapy (interim-PET; PET_{post}). Interim PET_{post} metrics and known prognostic clinical parameters were correlated in uni- and multivariable survival analyses. Leave-one-out cross-validation was used to show internal validity.

Results: Ninety-two patients who underwent ^{18}F -FDG-PET/CT after induction chemotherapy were enrolled. Median MTV_{post} value was 5.9 ml. Altogether 85 patients completed the whole chemoradiation with the planned total dose of 60–71 Gy. In univariable proportional hazard analysis, each of the parameters MTV_{post}, SUV_{max(post)} and TLG_{max(post)} was associated with overall survival ($p < 0.05$). Multivariable survival analysis, including clinical and post-induction PET parameters, found TLG_{max(post)} (hazard ratio: 1.032 (95%-CI: 1.013–1.052) per 100 ml increase) and total radiation dose (hazard ratio: 0.930 (0.902–0.959) per Gray increase) significantly related with overall survival in the whole group of patients, and also in patients receiving a total dose ≥ 60 Gy. The best leave-one-out cross-validated 2-parameter classifier contained TLG_{max(post)} and total radiation dose. TLG_{max(post)} was associated with time to distant metastases ($p = 0.0018$), and SUV_{max(post)} with time to loco-regional relapse ($p = 0.039$) in multivariable analysis of patients receiving a total dose ≥ 60 Gy.

Conclusion: Post-induction chemotherapy PET parameters demonstrated prognostic significance. Therefore, an interim ^{18}F -FDG-PET/CT is a promising diagnostic modality for guiding individualized treatment intensification.

SHORT RUNNING TITLE: Interim PET for chemoradiation of NSCLC

INTRODUCTION

Induction chemotherapy followed by concurrent chemoradiotherapy is an important commonly applied variant of current regimes of definitive chemoradiotherapy for stage III non-small cell lung cancers (NSCLC). In the recent PACIFIC trial about one-fourth of included patients with locally-advanced stage III NSCLC received induction chemotherapy followed by concurrent chemoradiation and consolidation with durvalumab (1).

In addition, a significant survival benefit was found in meta-analyses on trials comparing surgery with induction chemotherapy and surgery for patients with operable stage III NSCLC patients (2,3). Prognostic factors to guide treatment intensification are needed, as progression-free survival at 18 months of stage III NSCLC is less than 50% after concurrent chemoradiotherapy, even after durvalumab consolidation (1). Randomized and early phase-II trials on radiation dose escalation were conducted for residual metabolic target volumes based on mid-radiation ^{18}F -FDG-PET/CT. Up to now the first results show the feasibility of that approach and promising local tumor control (4,5). Such treatment pathways require that the metabolic volume on mid-treatment PET/CT is a prognostic factor. Limited evidence is available that metabolic tumor volume (MTV) or parameters based on MTV like total lesion glycolysis (TLG), are prognostic for stage III NSCLC patients treated with definitive chemoradiotherapy after induction chemotherapy. Ganem et al. assessed the influence of post-induction chemotherapy TLG on progression-free survival in 50 stage II/III NSCLC patients, and concluded that post-induction ^{18}F -FDG-PET metrics might add value to estimate patients' prognosis (6). Soussan et al. also found a prognostic value of TLG in 33 stage III NSCLC patients, receiving induction chemotherapy and surgery or definitive radio- or chemoradiotherapy (7).

A prognostic value of pretreatment MTV (MTV_{pre}) was not supported by our previous study on patients treated with induction chemotherapy followed by definitive chemoradiotherapy (8). This therapeutic regimen was particularly effective in patients with high tumor burden and large initial MTV_{pre} disease (8).

However, volume based PET parameters MTV_{post} and TLG_{post} after induction chemotherapy might unmask tumor resistance and may have prognostic value.

Hence, the aim of this resulting analysis of the ESPATUE prospective phase-3 trial (9) was to explore the prognostic value of post-induction chemotherapy MTV (MTV_{post}), followed by definitive chemoradiotherapy in patients with stage IIIA/IIIB NSCLC.

MATERIALS AND METHODS

The basis for this analysis was obtained from the large randomized phase-3 trial ESPATUE (9). All patients with pathologically proven stage IIIA/IIIB NSCLC (UICC/TNM-classification, sixth-edition) enrolled in the above-mentioned multicenter trial were evaluated. The ethics committee of the Medical Faculty of the University Duisburg-Essen approved this succeeding analysis. Included patients were treated from 2004 to 2012 at the University Hospital Essen. This site recruited 60% of all patients of the phase-3 trial. PET/CT scans from other institutions were not considered, because of either having recruited less than four patients in total, or the patients' PET/CT scans were no longer available for quantitative analysis. The treatment protocol prescribed an induction chemotherapy consisting of three cycles of cisplatin 50 mg/m² on days 1 and 8 and paclitaxel 175 mg/m² on day 1 every 21 days, and sequential chemoradiotherapy up to 45 Gy given as 1.5 Gy twice a day, with concurrent cisplatin 50 mg/m² and vinorelbine 20 mg/m² on days 2 and 9.

All included patients underwent a PET/CT scan for initial staging before or no longer than nine days after enrolment and three weeks after induction chemotherapy prior to start of radiotherapy. Those patients who underwent a repeated ¹⁸F-FDG-PET/CT examination after induction chemotherapy (interim-PET, PET_{post}), and who were intended for and started with definitive chemoradiotherapy were eligible for this study.

Imaging

All patients received an ^{18}F -FDG-PET/CT scan at two time points, t1 and t2. The first one was performed at initial diagnosis and the second one after three cycles of induction chemotherapy (follow-up before concurrent chemoradiotherapy). The baseline and follow-up ^{18}F -FDG-PET/CT scans were both performed at the same center. PET/CT scans were acquired with a Biograph mCT-machine (Siemens-Healthcare, Erlangen, Germany) or a Siemens Biograph Duo-scanner. Details about PET/CT acquisition and ^{18}F -FDG administration have been reported previously (10).

For determination of the MTV measurement, this study utilized a combination of a hybrid based approach, visual interpretation and delineation, and an auto-segmentation procedure analogous to the method used in the Radiation Therapy Oncology Group/American College of Radiology Imaging Network RTOG 1106/ACRIN6697 trial (11). The RTOG 1106 method uses a fixed source/background ratio in combination with CT anatomy-based manual editing to exclude mediastinal normal tissues. The initial and current CT-morphology is mandatory information. For shrinking tumors, we limited the MTV_{post} to the initial MTV_{pre} . Normal tissues like large vessels as well as tumor extension were manually defined in a detailed examination done by two expert radiation-oncologists in consensus. The activity within the post-induction MTV_{post} was evaluated against the background of normal tissue. For the background definition, the mean activity in 1 cm^3 of blood pool within the aortic arch was determined. MTV_{post} had to be above 1.5 times of the background activity and was limited by the tumor borders on CT (12). For auto-contouring, the Eclipse treatment planning system Version15.5 was used (Varian Medical Systems, Palo Alto, CA, US) (13-15). The MTV_{post} and maximal tracer activity value within the tumor volume (Bq/ml ; $\text{SUV}_{\text{max}(\text{post})}$) were measured. Total lesion glycolysis ($\text{TLG}_{\text{max}(\text{post})}$) after induction chemotherapy was calculated here as the product of MTV_{post} and $\text{SUV}_{\text{max}(\text{post})}$. Since the SUV_{max} and SUV_{mean} values of the lesion highly correlate with correlation coefficients above 0.93 in many studies, the determination of SUV_{mean} was dispensed (16-18).

Statistics

Overall survival, time to progression as well as time to loco-regional progression as a component of the first recurrence or distant progression alone, were used for primary endpoints.

Event times were defined as the time interval between patient's registration to the study and the time of event. PET metrics combined with other known prognostic factors were analyzed for prediction of treatment outcome.

A prognostic n -parameter classifier ($n = 1-4$) was built from the parameters of the post-induction chemotherapy PET/CT. A score-selection method for proportional hazard regression with leave-one-out cross-validation (LOO-CV) was applied (13,19). The LOO-CV approach was performed using the SAS-macro described by Rushing et al. (20). The selection of the variables for the best n -parameter model was done based on the highest chi-square (χ^2) score for the proportional hazard model in comparison to all other n -parameter models. Classifier calibration was performed on a training dataset, leaving out the i -th patient. Endpoint was overall survival. The i -th patient was then classified as high-risk or low-risk depending on its predictive risk score according to the classifier from the training dataset. This procedure was repeated for each patient. Patients with a cross-validated predictive index greater than the median in the respective training dataset were classified as high-risk and the other ones as low-risk.

Kaplan-Meier survival curves for the high-risk and low-risk groups were compared with the nonparametric log-rank test. In addition, overall survival in the high-risk and low-risk groups was compared using the Cox proportional hazard-model and the corresponding hazard ratios were reported along with their 95%-confidence intervals (CI).

As measures of relative inter-patient heterogeneity, the classical coefficient of variation (CV) and the quartile-coefficient of dispersion (QCD) were used, the latter calculated according to $QCD = \frac{Q_3 - Q_1}{Q_1 + Q_3}$, where Q_1 and Q_3 represent the first and third quartile of the distribution, respectively (21).

The proportional hazard analysis and receiver operator characteristic (ROC) analysis were performed using the procedure PHREG in SAS statistical software, SAS/STAT-version-14.3 (13). The validity of the proportional hazards assumption was assessed by a Kolmogorov-type supremum test (procedure PHREG, SAS).

RESULTS

Altogether 92 patients from the ESPATUE trial fulfilled the inclusion criteria of this study. All patients were enrolled at the University Hospital Essen in the period from 2004 to 2012 (9,10). Median follow-up of living patients is 94.8 months (range: 67.1–159.9 months). Patients' and tumors' characteristics are shown in Table 1. The interim PET/CT at time point t2 was performed within a median interval of 8 days (10th–90th percentile: 5–15 days) before the start of radiotherapy. In total, 62 patients relapsed. Among them, 32 had a loco-regional relapse as a component of the first recurrence and 30 relapsed at distant sites alone. There was a significantly positive Spearman correlation coefficient between MTV_{post} and $SUV_{max(post)}$ ($r_s = 0.74$; $p < 0.0001$), between MTV_{post} and $TLG_{max(post)}$ ($r_s = 0.98$; $p < 0.0001$) as well as between $SUV_{max(post)}$ and $TLG_{max(post)}$ ($r_s = 0.83$; $p < 0.0001$). $TLG_{max(post)}$ revealed the greatest inter-tumor heterogeneity of the parameters, characterized by a CV of 370.5% and a QCD of 94.7%, followed by MTV_{post} with a CV of 245.5% and a QCD of 87.4% (Table 1). For comparison, inter-tumor heterogeneity of $TLG_{max(pre)}$ and MTV_{pre} was smaller in pretreatment PET/CT, with the CV of 164.2% and 109.8% and the QCD of 63.0% and 57.2%, respectively. Analysing also the ratios between $TLG_{max(post)}$ and MTV_{post} and their respective initial values in the first PET/CT, the variations of the ratios were also smaller according to their CVs of 185.2% and 117.1%, respectively, than those of the respective parameters from the interim-PET/CT .

Univariable analysis of the post-induction chemotherapy PET/CT parameters using proportional hazard analysis revealed that for all three parameters, MTV_{post} , $SUV_{max(post)}$ and $TLG_{max(post)}$, the hazards ratios for an increase of one unit of the variables were greater than 1.

The unit for MTV_{post} was 10 ml, for $TLG_{max(post)}$ 100 ml and for $SUV_{max(post)}$ a value of 10. The p -values for the association with survival became smaller with increasing coefficients of variation of the parameters. No deviations from the proportional hazards or the functional form of the covariate were observed for any of these parameters (Kolmogorov supremum test; $p > 0.05$).

Multivariable proportional hazards analysis of all covariates shown in Table 1, revealed total radiation dose positively and $TLG_{max(post)}$ negatively related to longer survival, using forward selection at $\alpha = 0.05$. All patients were intended to receive a total dose of 65-71 Gy as per protocol. Our per-protocol definition prescribes a total dose of at least 60 Gy. Seven patients have received a total dose less than 60 Gy. Two of these seven died during radiotherapy. Because reasons for early stopping the radiotherapy were or might be directly related to survival, we also performed a second analysis to look for the effect of total dose on survival in the per-protocol group of 85 patients. Again, total radiation dose and $TLG_{max(post)}$ remained significant prognostic factors for survival (Table 2). The internal validity of the prognostic value of the parameters from the post-induction chemotherapy PET/CT was assessed using leave-one-out cross-validation. The best 2- to 4-parameter signatures were consistently included and exposed the $TLG_{max(post)}$ in 99% or more of the leave-one-out training dataset as the most important parameter from post-induction chemotherapy PET/CT to predict survival, provided the prescribed radiation dose was applied. The generalizability of the 2-parameter signature to the held-out training dataset was better than that of the 3- or 4-parameter signature as indicated by the lowest p -value for the differences between cross-validated survival curves for the high and low-risk groups at $\alpha = 0.05$ (Table 3).

Figure 1a shows the split of the cross-validated survival curves in the high and low-risk group of all included patients [$n = 92$] according to $TLG_{max(post)}$ of the respective leave-one-out observation being greater than the median (group 2) or less than or equal to the median of the training dataset (group 1).

Figure 1b shows the split of the survival curves for the 85 patients treated as per protocol with total radiation doses of at least 60 Gy, in accordance with the best 2-parameter classifier analysis consisting of total dose and $TLG_{\max(\text{post})}$ in 99% and total dose and $SUV_{\max(\text{post})}$ in 1% of the cross-validation loops (Table 3, Figure 1b).

In an exploratory manner, we determined the optimal cut-point for MTV_{post} and $TLG_{\max(\text{post})}$ to divide patients into high-risk and low-risk groups by a time-dependent ROC analysis according to the criterion of maximum sum of sensitivity and specificity (Youden's J statistic). For survival at 60 months, the areas under the ROC-curve (AUC) for MTV_{post} and $TLG_{\max(\text{post})}$ were 0.634 (95%-CI: 0.528–0.7445) and 0.643 (95%-CI: 0.532–0.755), respectively. The corresponding cut-points for MTV_{post} and $TLG_{\max(\text{post})}$ were 2.9 ml and 11.3, respectively. This is close to the cut-point of maximum separation of the high-risk and low-risk groups according to the log-rank test (Supplement Figures 1a/1b), which is at 2.3 ml for MTV_{post} and 9 for $TLG_{\max(\text{post})}$. There is a second cut-point for MTV_{post} and $TLG_{\max(\text{post})}$ at higher values 20 ml and 75, resulting in a second local maximum separation of the high-risk and low-risk groups at reversed group sizes. This emphasizes that the MTV_{post} and $TLG_{\max(\text{post})}$ are continuous risk parameters with a constant hazard ratio per unit increase. The respective survival curves separated according to $TLG_{\max(\text{post})}$ cut-points of 11.3 and 75 are shown in supplementary Figures 1a/1b.

Figure 2 shows a patient with complete remission of the central lung cancer on PET imaging and with a curative outcome after induction chemotherapy and definitive chemoradiation.

As parameters related to MTV from post-induction PET/CT were significantly related to overall survival, we also analysed the relation of the endpoint to the pattern of relapse, i.e. time to progression, time to loco-regional progression as a component of the first relapse analysis and time to distant progression alone. $TLG_{\max(\text{post})}$ was a significant prognostic factor for the time to progression and time to distant metastases endpoints using multivariable proportional hazard analysis combined with forward selection (Table 2). For the time to loco-regional progression as a component of the first relapse endpoint, $SUV_{\max(\text{post})}$ was the single important factor from PET/CT.

DISCUSSION

There is a current need to find a valid diagnostic procedure to predict therapy response in lung cancer. For systemic therapies like chemotherapy or immune checkpoint blockade in lung cancer, PERCIST_1.0 (Positron Emission Tomography Response Criteria in Solid Tumors) proved to be a valuable tool to calculate treatment outcome (22,23).

In this ensuing analysis of a large randomized phase-3 trial, we aimed to evaluate known prognostic clinical parameters combined with volumetric PET/CT metrics after induction chemotherapy. Complete data to long term follow-up and sites of relapses are available in this study.

MTV_{post} , $SUV_{max(post)}$ and $TLG_{max(post)}$ are associated with prognosis in univariable analysis for all stage III NSCLC patients of this trial, who started with definitive chemoradiotherapy after induction chemotherapy and who did not receive surgery. $TLG_{max(post)}$ was the most prognostic factor agglomerating the prognostic information of both MTV_{post} and $SUV_{max(post)}$. We have previously shown that the percentage decrease of SUV_{max} obtained from the pre- and post-induction chemotherapy PET/CT has a prognostic relevance in the entire group of randomized patients treated with definitive chemoradiotherapy or trimodality treatment following induction chemotherapy (10), and have demonstrated with this study that the post-induction chemotherapy PET/CT provides important prognostic information.

However, MTV_{pre} obtained from the pre-therapeutic PET/CT did not show prognostic value for patients intended for definitive chemoradiotherapy in this trial (8). Extending the analysis by MTV-based factors from the post-induction chemotherapy PET/CT on this cohort of patients who were not treated with surgery, the present results reinforce the prognostic value of the post-induction chemotherapy PET/CT (Figure 1-3). From all patients' and PET derived factors, $TLG_{max(post)}$ demonstrated the greatest association with overall survival. This finding showed

internal validity since $TLG_{\max(\text{post})}$ was consistently selected as the best 2- or 4-parameter classifier in 99% of leave-one-out validation loops for the total radiation dose given.

In addition, we performed a subgroup analysis excluding patients who received a total radiation dose of less than 60 Gy and again the same parameters remained significant. Prospective trials did not find any important influence of total radiation dose on survival (24). In this trial, the radiation dose was escalated with dose volume limits of the entire lung, so that mean lung dose could not exceed 19 Gy. As total dose was not randomized, there might be some hidden factors acting on both selection total radiation dose and prognosis. However, the analysis in this trial showed that the total dose remains an important factor, either in the per protocol group of patients receiving a total dose of at least 60 Gy, or together with the most significant tumor dependent factors, i.e. $TLG_{\max(\text{post})}$.

Studies revealing that MTV_{post} or $TLG_{\max(\text{post})}$ can have a high prognostic value after induction chemotherapy originate from oesophageal cancer (25,26) and squamous cell carcinomas of the head and neck region (27,28), but data from NSCLC are scant (6,7). This analysis considerably adds to the evidence of the prognostic relevance of the $TLG_{\max(\text{post})}$ after induction chemotherapy for patients who were consecutively treated with definitive chemoradiotherapy.

With respect to potential implications for therapy intensification based on PET prognostic parameters the site of treatment failure is important. In the analysis of the additional endpoints 'distant progression alone' and 'loco-regional progression' as a component of the first relapse, $TLG_{\max(\text{post})}$ was more strongly related to distant progression, while $SUV_{\max(\text{post})}$ was more strongly related to loco-regional progression. The latter may indicate that tumor heterogeneity and the most resistant subvolumes are of importance for local control after definitive chemoradiotherapy (29). Whether a larger set of PET/CT based radiomics features along with a deep-learning approach will result in a better prognostication from post-induction chemotherapy PET/CTs, remains an open question for further studies (30).

There are some limitations in the interpretation of these results. This is not a confirmatory but an initial exploratory study. An interim PET/CT is not yet a standard diagnostic procedure. Potential ways to adapt treatment to a poor PET-response in the future include delivering a dose-escalated boost to a residual MTV, intensifying concurrent chemoradiotherapy with e.g., simultaneous immune checkpoint inhibitors or enhancing consolidation therapies. A further potential limitation of the applicability of these results is that the induction chemotherapy is performed before definitive chemoradiotherapy only in a minority of centers. Thus, 26.8% of patients in the PACIFIC trial received induction chemotherapy (1). However, there is a high current interest in combining induction chemotherapy followed by definitive chemoradiotherapy with immunotherapy and consolidation therapy with a checkpoint inhibitor (PACIFIC BRAZIL trial ClinicalTrials.gov identifier: NCT04230408; ESPADURVA trial: NCT04202809). The ESPADURVA trial compares induction chemotherapy and chemoradiotherapy followed by surgery or a radiotherapy boost with and without immunotherapy. The ADMIRAL trial (NCT04372927) avoids mediastinal irradiation in patients with complete response after 3–4 cycles of chemoimmunotherapy and radiotherapy of the primary tumor. Validated response-dependent prognostic parameters during treatment are of high importance for such schedules of adaptive treatment intensification.

CONCLUSION

In summary, a post-induction chemotherapy interim PET/CT confers important prognostic information before definitive chemoradiotherapy in patients with locally advanced NSCLC and should be taken into consideration as a standard for radiotherapy treatment planning after induction chemotherapy.

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KEY POINTS

QUESTION: Can post-induction PET metrics direct chemoradiation in locally advanced non-small cell lung cancer?

PERTINENT FINDINGS: The results are based on the ***ESPA TUE phase-3 trial***. MTV_{post} , $SUV_{max(post)}$ and $TLG_{max(post)}$ together with total radiation dose have the power to predict local and systemic control, as well as overall survival.

IMPLICATIONS FOR PATIENT CARE: Post-induction chemotherapy interim PET/CT confers important prognostic information prior to definitive chemoradiotherapy. An interim ^{18}F -FDG-PET/CT is a promising diagnostic modality for guiding individualized treatment intensification for patients with non-small cell lung cancer in curative intent.

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FIGURES

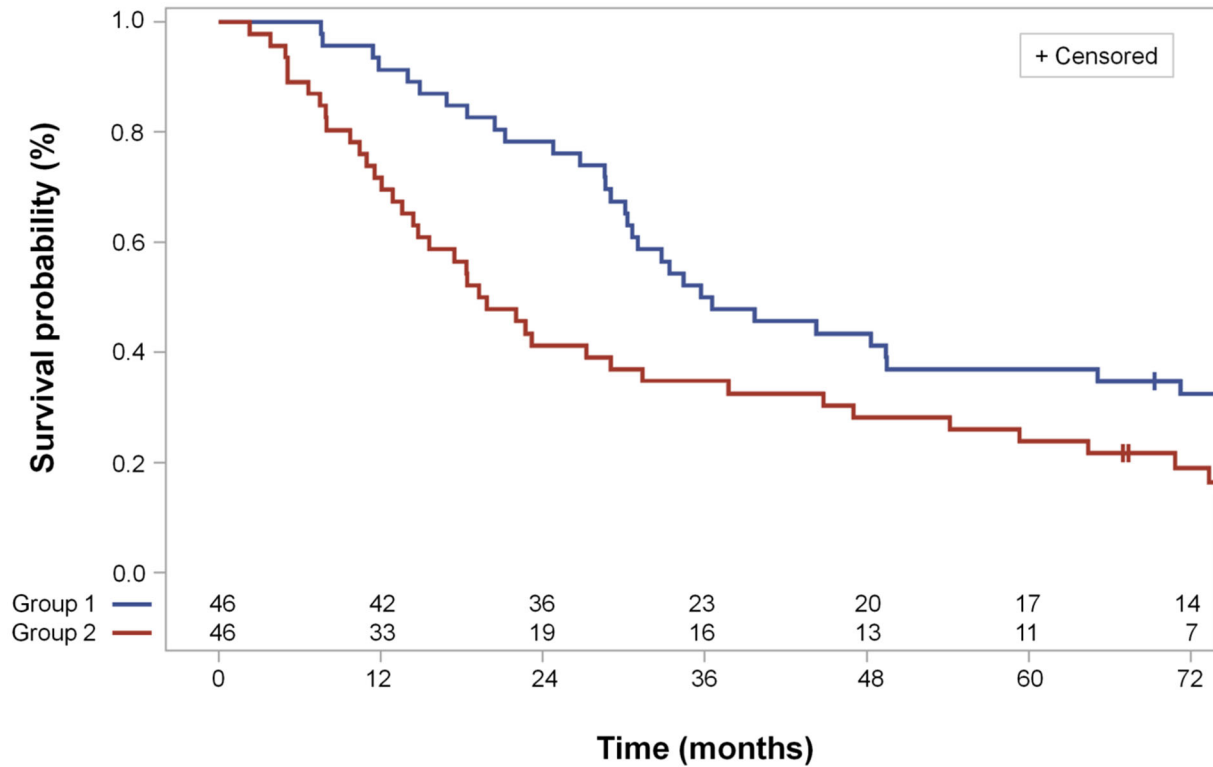


FIGURE 1A: Cross-validated Kaplan-Meier survival curves for the high-risk and low-risk groups of all eligible patients according to median $TLG_{max(post)}$ in the training dataset. Differences between survival curves: $p = 0.036$, log-rank test [$n=92$]

- Group 1, low-risk group: $TLG_{max(post)}$ below or at the median of the $TLG_{max(post)}$ values in the respective leave-one-out training dataset
- Group 2, high-risk group: $TLG_{max(post)}$ above the median in the respective leave-one-out training dataset

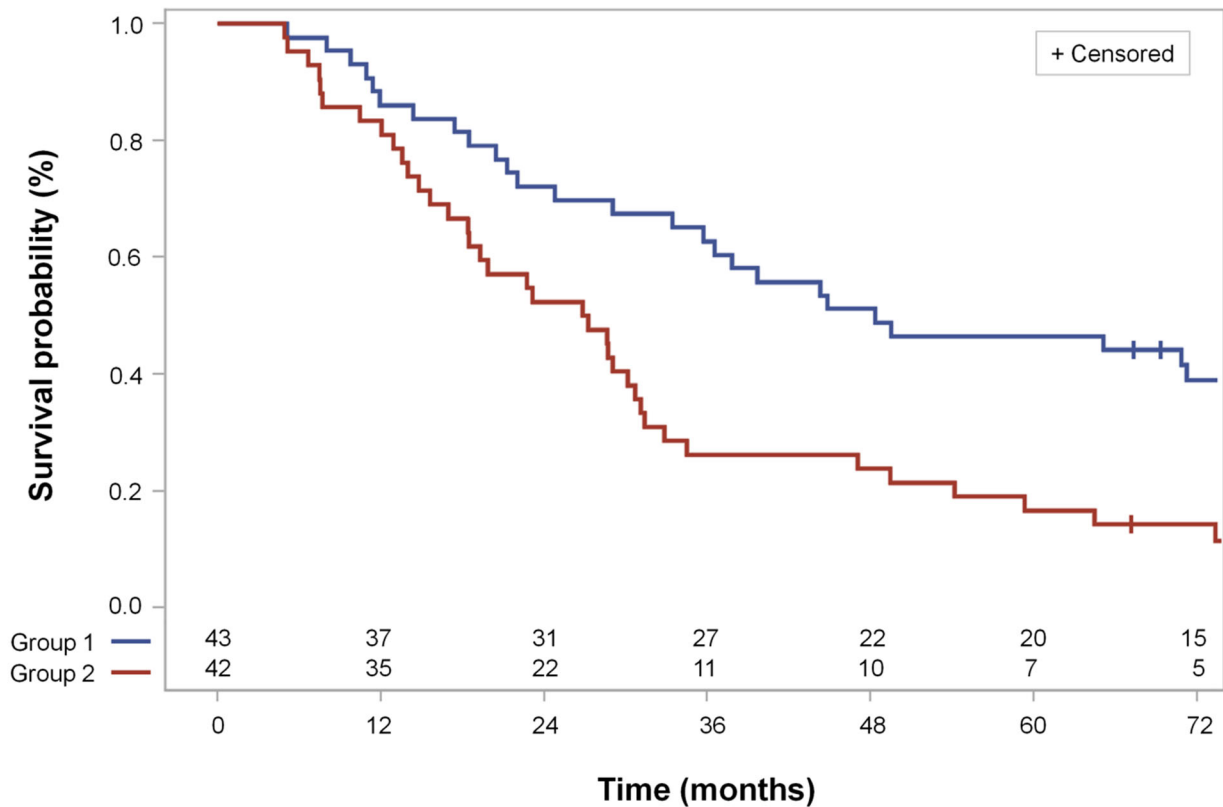


FIGURE 1B: Cross-validated Kaplan-Meier survival curves for patients who received chemoradiotherapy up to a total dose of at least 60 Gy as per protocol according to the best 2-parameter classifier:

Best leave-one-out cross-validated 2-parameter classifier: The best classifier contained in 99% of the leave-one-out loops the parameters total dose and $TLG_{max(post)}$ and in 1% of the leave-one-out loops the parameters total dose and $SUV_{max(post)}$.

Differences between survival curves: $p = 0.0026$, log-rank test [$n=85$]

- Group 1, low-risk group: Patients with a linear predictor built from the complementary leave-one-out training dataset below or at the median of values in the training dataset
- Group 2, high-risk group: Linear predictor above the median

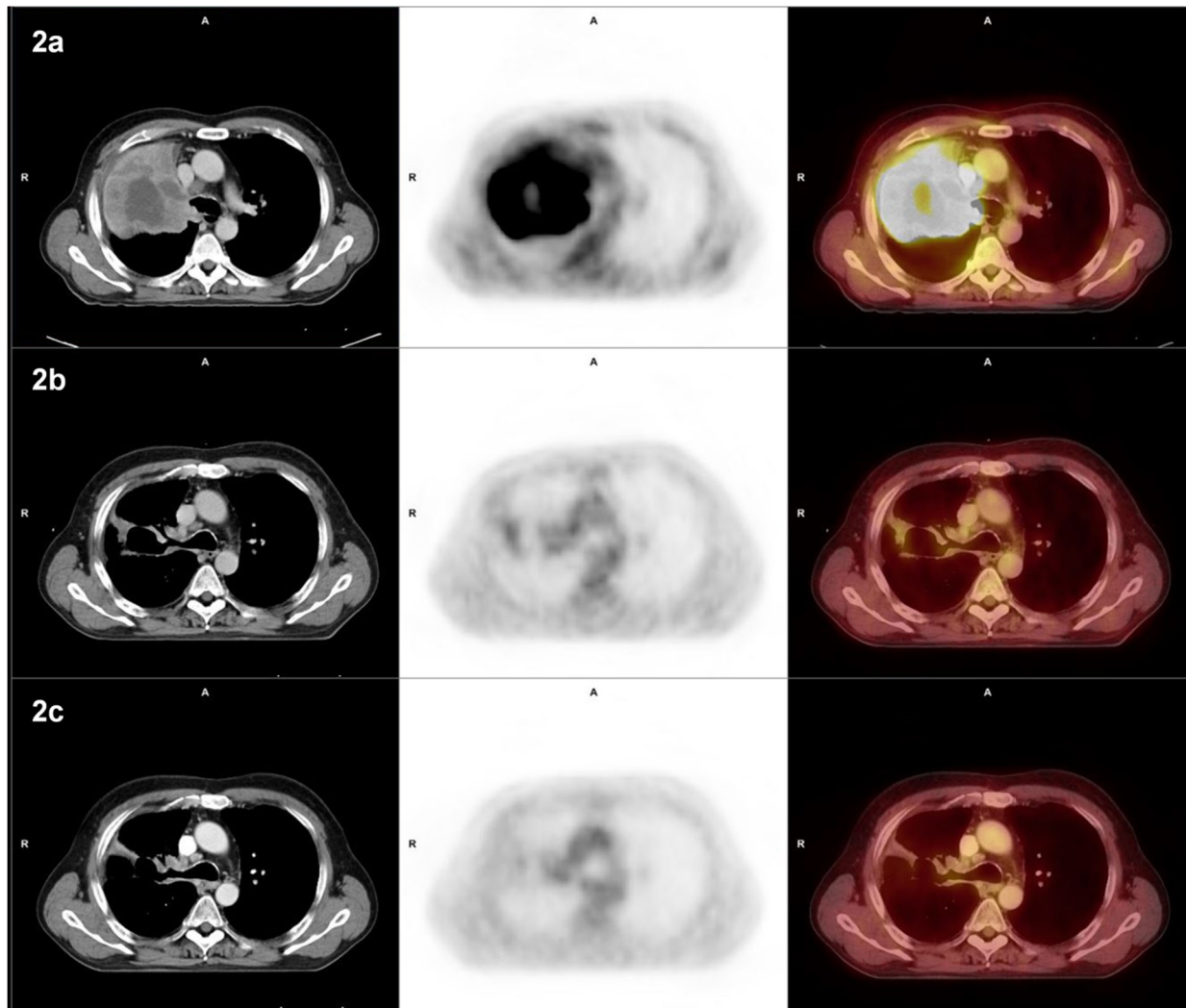


FIGURE 2: Initial (2a), interim (2b) and follow-up (2c) ^{18}F -FDG PET/CT in a patient with poorly differentiated non-small cell lung cancer with complete remission after induction chemotherapy with cisplatin/paclitaxel and definitive chemoradiation with cisplatin/vinorelbine and a total dose of 71 Gy, overall survival time > 60 months.

2a: Vivid ^{18}F -FDG uptake before start of treatment (MTV_{pre} 480.1 ml).

2b: Response after 3 cycles of chemotherapy (7 days before start of chemoradiation), complete PET-response with $\text{SUV}_{\text{max}(\text{post})}$ below 1.5 times of the background activity (central 1 cm^3 of the blood pool within the aortic arch), low-risk group with MTV_{post} below the defined cut-point ($\text{MTV}_{\text{post}} \leq 2.9\text{ ml}$)

2c: Complete fading of metabolic activity after induction chemotherapy and completion of concurrent chemoradiation during follow-up (10.9 months after start of radiotherapy).

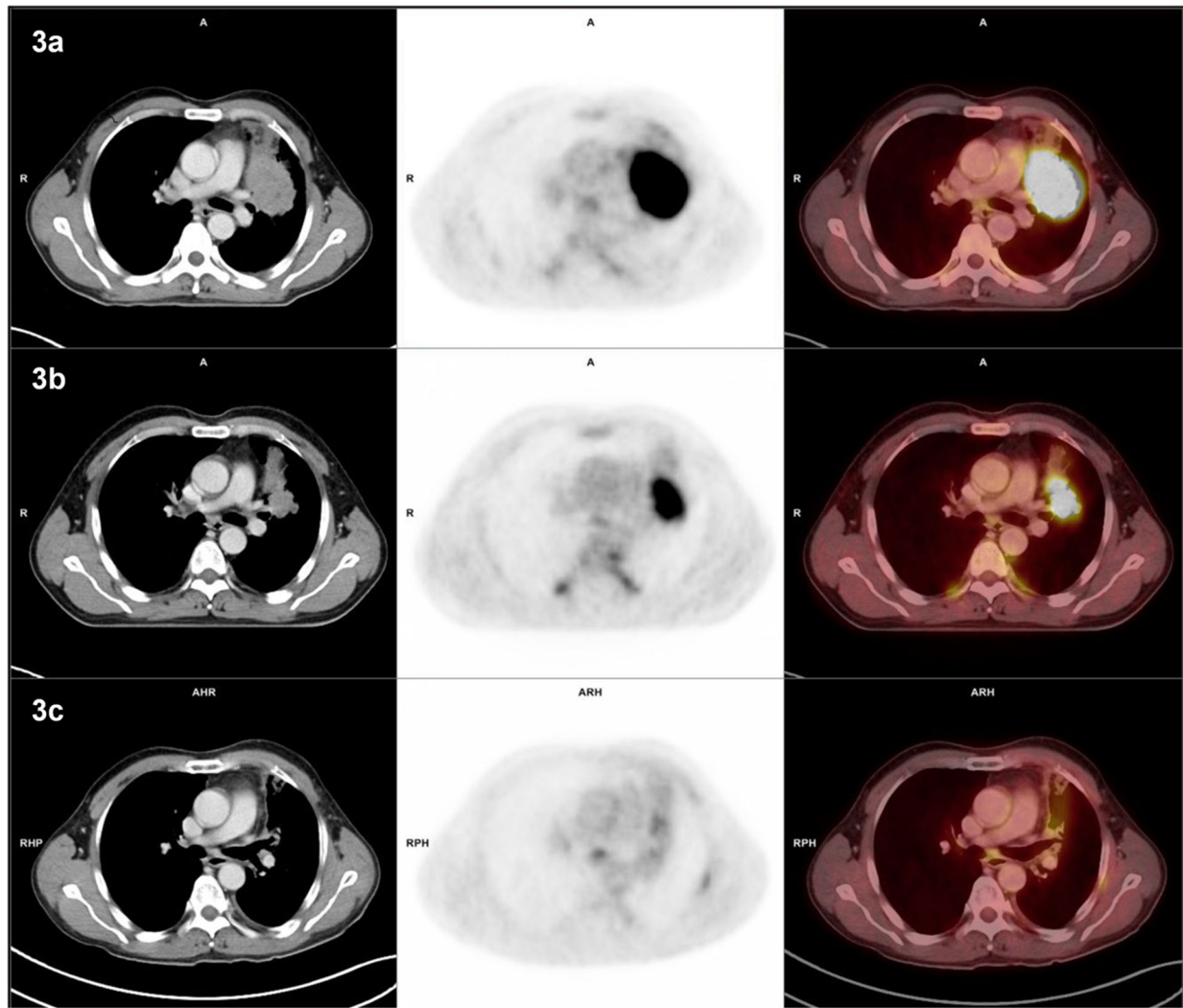


FIGURE 3: Initial (3a), interim (3b) and follow-up (3c) ^{18}F -FDG PET/CT in a patient with poorly differentiated non-small cell lung cancer with partial remission after induction chemotherapy with cisplatin/paclitaxel before definitive chemoradiation with cisplatin/vinorelbine and a total dose of 71 Gy: overall survival (21 months)

3a: Vivid ^{18}F -FDG uptake before start of treatment (MTV_{pre} 72.8 ml).

3b: Residual ^{18}F -FDG uptake after 3 cycles of chemotherapy prior to definitive chemoradiation, high-risk group with MTV_{post} above the defined cut-point (MTV_{post} > 2.9 ml)

3c: Follow-up PET/CT (10.5 months after start of radiotherapy).

Note: Progression in-field starting 12 months after primary treatment

TABLES

TABLE 1

Patients' and tumors' characteristics. Clinical risk factors, all patients received pre- and post-induction chemotherapy PET/CT and were treated with definitive chemoradiotherapy

Characteristics	Values
Sex (women/men)*	22/70
ECOG Performance-status (0/1/2)	57/34/1
Age (years), median (range)	58.5 (41.0–74.0)
cT1-2/cT3/cT4-category	28/7/57
cN0-N1/cN2-N3-category	32/60
Squamous-Cell-Carcinoma/ Adenocarcinoma/ Other	39/36/17
MTV _{post} (ml) Median (range) Interquartile-range (Q1-Q3) [†] Coefficient-of-variation	5.9 (0.0–540.8) 1.6–23.8 245.5%
SUV _{max(post)} Median (range) Interquartile-range (Q1-Q3) [†] Coefficient-of-variation	3.6 (<1.0–38.4) 2.6–6.6 99.9%
TLG _{max(post)} Median(range) Interquartile-range (Q1-Q3) [†] Coefficient-of-variation	20.8 (0.0–10058) 3.5–128.9 370.5%
Total radiation dose Median (range) Interquartile-range (Q1-Q3) [†]	71.0 (3.0–72) 66.0–71.0

* All patients who started with definitive chemoradiotherapy [n=92]

[†]Q1, Q3: first and third quartile of the distribution

TABLE 2

Univariable and multivariable proportional hazard analysis of parameters from the post-induction chemotherapy PET/CT using forward parameter selection at alpha = 0.05

Prognostic variables*	Hazard ratio†	95%-Confidence interval	p-value: χ^2 -test
(A) Univariable survival analysis – all eligible patients who started with definitive chemoradiotherapy (n=92)			
MTV _{post}	1.042	1.007–1.079	0.017
SUV _{max(post)}	1.486	1.062–2.080	0.043
TLG _{max(post)}	1.028	1.009–1.048	0.0044
(B) Multivariable survival analysis – all eligible patients (n=92)			
Total radiation dose	0.930	0.902–0.959	< 0.0001
TLG _{max(post)}	1.032	1.013–1.052	0.0002
(C) Multivariable survival analysis – all patients who received at least 60 Gy total dose (n=85)			
Total radiation dose	0.891	0.813–0.977	0.0142
TLG _{max(post)}	1.034	1.014–1.054	0.0008
(D) Multivariable time to progression analysis – all patients who received at least 60 Gy total dose (n=85)			
TLG _{max(post)}	1.038	1.018–1.058	0.0001
Total radiation dose	0.848	0.770–0.934	0.0008
(E) Multivariable time to distant progression alone analysis – all patients who received at least 60 Gy total dose (n=85)			
TLG _{max(post)}	1.037	1.014–1.061	0.0018
(F) Multivariable time to loco-regional progression as a component of the first relapse analysis – all patients who received at least 60 Gy total dose (n=85)			
Total radiation dose	0.807	0.705–0.924	0.0019
cT3 tumor category	3.605	1.326–9.800	0.012
SUV _{max(post)}	1.070	1.003–1.141	0.039

*All clinical and PET parameters listed in Table-1 were included in the analysis.

†Hazard ratios are given per 10 ml increase in MTV, or per SUV_{max} increase of 10, or per TLG increase of 100 ml.

TABLE 3

Leave-one-out cross validated 1- to 4-parameter classifiers for separating high-risk and low-risk groups by the median predictive-index according to the parameters shown in Table 1. Endpoint is overall survival.

Clinical parameters	Parameters selected	Percentages of LOO-CV loops*	p-value: High-risk vs. low-risk group, log-rank test	Hazard ratio with 95% CI: High-risk vs. low-risk group
(A) 1-parameter classifier, all 92 eligible patients who started with definitive chemoradiotherapy†				
Best classifier	Total dose TLG _{max(post)}	99 1	0.036	1.62 (1.03-2.55)
TLG _{max(post)} classifier	TLG _{max(post)}	100	0.036	1.60 (1.03-2.51)
(B) 2-parameter classifier, all 92 eligible patients‡				
Best classifier	Total dose TLG _{max(post)}	100 99	0.0006	2.17 (1.38-3.42)
(C) 3-parameter classifier, all eligible 92 patients§				
Best classifier	Total dose TLG _{max(post)} cT4	100 99 88	0.0069	1.84 (1.17-2.89)
(D) 4-parameter classifier, all 92 eligible patients 				
Best classifier	Total dose TLG _{max(post)} cT4 cN2/N3	100 99 95 93	0.017	1.73 (1.10-2.71)
(E) 2-parameter classifier, all 85 patients who received at least 60Gy total dose¶				
Best classifier	Total dose TLG _{max(post)}	100 99	0.0026	2.05 (1.27-3.30)

*Percentages of leave-one-out (LOO) cross-validation (CV) loops: these percentages indicate the consistency with which a parameter is selected into the best *n*-parameter model across all LOO iteration loops.

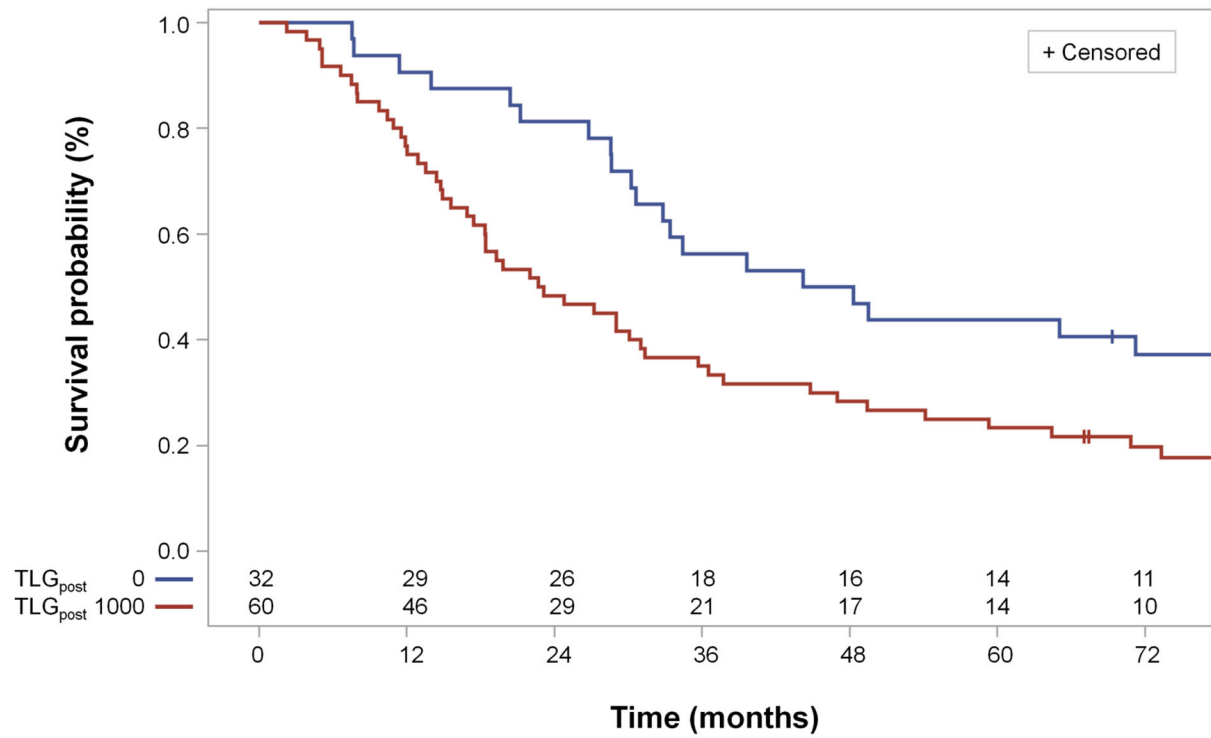
†(A): Best 1-parameter classifier, all 92 eligible patients: Total dose

‡(B): Best 2-parameter classifier, all 92 eligible patients: Total dose, TLG_{max(post)}

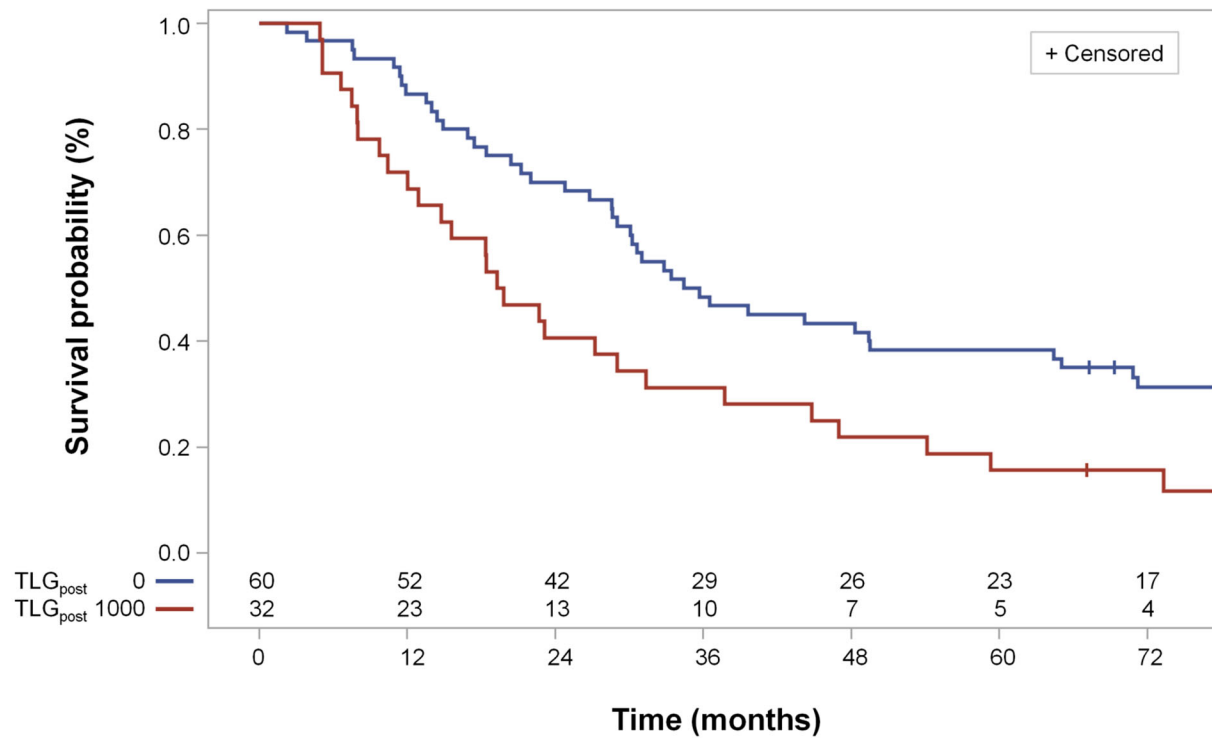
§(C): Best 3-parameter classifier, all 92 eligible patients: Total dose, TLG_{max(post)}, cT4-category (clinical tumor stage-4 as per TNM classification)

|| (D): Best 4-parameter classifier, all 92 eligible patients: Total dose, TLG_{max(post)}, cT4-category (clinical tumor stage-4 as per TNM classification), cN2/N3-category (lymph node stage-2/3 as per TNM classification)

¶(E): Best 2-parameter classifier, all eligible 85 patients who received a total dose ≥ 60 Gy, Total dose, TLG_{max(post)}



SUPPLEMENT FIGURE 1A: Exploration of Kaplan-Meier survival curves for the high-risk and low-risk groups of all eligible patients according to a $TLG_{\max(\text{post})}$ at a cut-point of 11.3 by Youden's criterion from the time dependent ROC-curves at 60 months ($p = 0.014$, log-rank test).



SUPPLEMENT FIGURE 1B: Kaplan-Meier survival curves for the high-risk and low-risk groups of all eligible patients according to a $TLG_{\max(\text{post})}$ cut-point of 75 separating into groups with reversed sizes compared to Supplement Fig1a ($p = 0.008$, log-rank test).