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Prognostic value of pretherapeutic tumor-to-blood standard uptake ratio (SUR) in patients with esophageal carcinoma.

Short title:

Prognostic value of pretherapeutic SUR

Authors:

Rebecca Bütof[1,2], Frank Hofheinz[3], Klaus Zöphel[2,4,5], Tobias Stadelmann[4], Julia Schmollack[4], Christina Jentsch[1,2], Steffen Löck[2], Jörg Kotzerke[2,4,5], Michael Baumann[1,2,5,6], Jörg van den Hoff[3,4],

First and second author contributed equally.

Institutions:

[1] Department of Radiation Oncology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[2] OncoRay - National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf

[3] Helmholtz-Zentrum Dresden-Rossendorf, PET Center, Institute of Radiopharmaceutical Cancer Research, Dresden, Germany

[4] Department of Nuclear Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[5] German Cancer Consortium (DKTK), Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany

[6] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology, Dresden, Germany

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Corresponding author:

Rebecca Bütof, MD

Department of Radiation Oncology

University Hospital Carl Gustav Carus

Fetscherstraße 74, 01307 Dresden

email: Rebecca.Buetof@uniklinikum-dresden.de

Tel.: +49 (0)351 458-18958

Fax : +49 (0)351 458-5391

ABSTRACT

Despite ongoing efforts to develop new treatment options the prognosis for patients with inoperable esophageal carcinoma is still poor and the reliability of individual therapy outcome prediction based on clinical parameters is not convincing. The aim of this work was to investigate if PET can provide independent prognostic information in such a patient group and if the tumor-to-blood standard uptake ratio (SUR) can improve the prognostic value of tracer uptake values.

Methods: 18F-FDG PET/CT was performed in 130 consecutive patients ((63±11) years, 113 males) with newly diagnosed esophageal cancer prior to definitive radiochemotherapy. In the PET images the metabolic active volume (MTV) of the primary tumor was delineated with an adaptive threshold method. The blood SUV was determined by manually delineating the aorta in the low dose CT. SUR values were computed as ratio of tumor SUV and blood SUV. Uptake values were scan-time corrected to 60min p.i. Univariate Cox regression and Kaplan-Meier analysis with respect to overall survival (OS), distant-metastases-free survival (DM) and locoregional control (LRC) was performed. Additionally, a multivariate Cox regression including clinically relevant parameters was performed.

Results: In multivariate Cox regression with respect to OS, including T-stage, N-stage and smoking state, MTV and SUR based parameters were significant prognostic factors for OS with similar effect size. Multivariate analysis with respect to DM revealed smoking state, MTV and all SUR based parameters as significant prognostic factors. The highest hazard ratios were found for scan-time corrected SUR_{max} (HR=3.9) and SUR_{mean} (HR=4.4). None of the PET parameters was associated with LRC. Univariate Cox regression with respect to LRC revealed only for N-stage>0 a significant effect (P=0.048).

Conclusion: PET provides independent prognostic information for OS and DM but not for LRC in patients with locally advanced esophageal carcinoma treated with definitive radio(chemo)therapy in addition to clinical parameters. Among the investigated uptake based parameters only SUR was an independent prognostic factor for OS and DM. These results suggest that the prognostic value of tracer uptake can be improved when characterized by SUR instead of SUV. Further investigations are required to confirm these preliminary results.

Keywords: PET, esophageal cancer, definitive radiochemotherapy, SUV, SUR

INTRODUCTION

Despite ongoing efforts to develop new treatment options esophageal cancer remains one of the world's most lethal malignancies. In early-stage esophageal carcinoma surgical resection is still the mainstay of therapy. For locally advanced disease several randomized trials have shown the benefit of neoadjuvant chemoradiation followed by surgery compared to surgery alone e.g. (*1*). In case of inoperability due to comorbidities or functional reasons definitive radiochemotherapy is applied. Unfortunately, prognosis for these patients is still poor with an average overall survival of 15% after 5 years (*2*) and the reliability of individual therapy outcome prediction based on clinical parameters alone cannot be considered satisfactory. It would, therefore, be highly desirable to improve prediction of therapy outcome. One promising route is to combine optimized quantitative assessment of the additional functional information provided by ^{18}F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) with proven clinical parameters. Ultimately, this could serve to advance individualized treatment schedules, e.g. use of increased radiation dose in patients with high risk of local recurrence or intensified chemotherapy schedules in case of high risk of distant metastases.

The possible added value of 18F-FDG PET for therapy assessment is well recognized. In fact, it has been demonstrated in several studies that pretherapeutic 18F-FDG PET has the potential to provide prognostic information in addition to clinical parameters (e.g. histology, grading, T-stage and N-stage, age) in patients with esophageal carcinoma (see e.g. (*3*, *4*)). In most of these studies the investigated patient group was treated with neoadjuvant chemoradiation followed by surgery or with surgery alone. Much less has been published regarding patients with inoperable tumors which are thus treated with definitive chemoradiation. We found only four publications where baseline PET-parameters were correlated with survival data in such a patient group. Suzuki et al (*5*) and Atsumi et al (*6*) showed that the maximum standardized uptake value (SUV_{max}) is a prognostic factor for overall survival and relapse free survival. On the other hand in the investigation of Amini et al (*7*) SUV_{max} was not a significant predictor for relapse free survival. Lemarignier et al (*8*) analyzed the prognostic value of several baseline PET parameters: SUV_{max}, SUV_{mean}, the metabolically active tumor volume (MTV), and the product of MTV and SUV_{mean} (total lesion glycolysis, TLG), respectively. In this investigation SUV_{max} was a prognostic factor for disease free survival, but SUV was inferior to MTV and was not predictive for overall survival.

An explanation for this unsatisfactory performance of SUV might be the adverse effects of well known shortcomings of the SUV methodology – especially in the clinical setting – such as scan time dependence of the SUV, inter-study variability of the arterial input function, susceptibility to errors in scanner calibration, etc. (*9–12*) all of which adversely affect the reliability of the SUV as a surrogate of the metabolic rate of glucose consumption (K_m) which in turn can be expected to reduce the prognostic value of SUV. Indeed, in a recent publication we could demonstrate that the standard tumor-to-blood SUV ratio is superior to the (tumor) SUV itself as a surrogate parameter of K_m (*13*) for well standardized uptake periods (i.e. scan start times). In the clinical context, variability of the uptake period is unavoidable which directly translates into a corresponding variability of the measured tracer uptake. But as has been shown recently it is possible to reliably correct SUR (and somewhat less reliably SUV) for variations of the 18F-FDG uptake period (*14*) by converting the measured uptake values to a preselected fixed scan time point. This scan-time normalized SUR removes several of the shortcomings of SUV which leads to a much improved linear correlation between this uptake parameter and the actually targeted quantity, namely the metabolic rate of 18F-FDG. However, so far it has not been investigated whether these principal advantages of SUR translate into an improved prognostic value of this parameter in comparison to SUV.

Therefore, the aim of this exploratory study was to evaluate the prognostic value of pretherapeutic SUR (with and without scan time correction) as well as scan time corrected SUV in comparison to the conventional parameters MTV, TLG and SUV and also considering known clinical prognostic parameters in patients with esophageal carcinoma and definitive chemoradiation treatment regime.

This investigation specifically tests the hypothesis that assessment of the pretherapeutic glucose metabolic rate (as measured by the lesion's SUR) is prognostic for therapy outcome in esophageal carcinoma. By comparing the prognostic value of SUR and SUV it also tests the hypothesis that the more accurate assessment of the lesion's metabolic rate by SUR instead of SUV translates into an improved value of the former parameter in comparison to SUV.

MATERIALS AND METHODS

Patient Characteristics

In the present study 130 consecutive patients with 18F-FDG PET/CT-staged esophageal carcinoma were included retrospectively. Evaluation of the data was approved by the Institutional Ethics Committee and all subjects signed a written informed consent. All cases have been discussed in an interdisciplinary tumor board and either due to locally advanced disease or due to comorbidities/functional inoperability of the patients they received a curative definitive radio(chemo)therapy between September 2005 and October 2013. Inclusion criterions were: > 18 years, histologically confirmed esophageal carcinoma, 18F-FDG PET/CT staging, no distant metastases, curative treatment intention and a minimum follow up of 12 month. All patients had a clinical staging of UICC stage based on PET-imaging and endoscopy/endosonography. The median age of all included patients was 63 years (range 42 to 85) and the majority were male (87%). A summary of patient and tumor characteristics is given in Table 1.

Treatment

All patients were treated with a 3-dimensional CT-planned conformal radiotherapy. Total radiation doses of 60Gy, 66Gy, or 70Gy (cervical tumor localization) were applied in 2Gy per fraction. The GTV was separately delineated in the PET and CT images. Up to 50Gy an elective nodal irradiation of the mediastinum was additionally performed. For boost irradiation margins of 1.5cm in axial and 3.5cm in cranio-caudal direction were used to create the CTV. The chemotherapy schedule consisted of cisplatin (70mg/m^2) and 5-fluorouracil (3000mg/m^2 as an infusion over 96h) in week 1 and 4 of the treatment.

FDG PET/CT Protocol

All patients underwent a hybrid 18F-FDG PET/CT scan prior to treatment. Scans (3D PET acquisition, 3min emission per bed position) were performed with a Biograph 16 (Siemens Medical Solutions Inc., Knoxville, TN, USA). Data acquisition started 77±16 minutes after injection of 212 to 417 MBq 18F-FDG. All patients had fasted for at least 6h prior to 18F-FDG injection. The serum glucose concentration measured prior to injection was 5.8 µmol/ml on average (range: 3.3-9.8). Tomographic images were reconstructed using attenuation

weighted OSEM reconstruction (4 iterations, 8 subsets, 5 mm FWHM Gaussian filter). The resulting image data had a voxel size of $4.1\times4.1\times5\text{mm}^3$.

Data Analysis

ROI definition and ROI analyses was performed using the ROVER software, version 2.1.20 (ABX, Radeberg, Germany). Here and in the following "ROI" is used synonymously for "VOI", for denoting a 3-dimensional volume of interest.

The metabolically active part of the primary tumor was delineated in the PET data by an automatic algorithm based on adaptive thresholding considering the local background (*15*). The resulting delineation was inspected visually by two experienced observers in consensus. Lesions were delineated manually where this was deemed necessary (observers were blinded to patient outcome). This happened in five of 130 cases exhibiting only low diffuse tracer accumulation in the respective lesion. In six further cases the primary tumor was not visible in the PET data and a small ROI (< 1 ml) was manually placed in the esophagus.

For the delineated ROIs SUV_{max}, SUV_{mean}, the metabolic tumor volume (MTV), and the total lesion glycolysis ($TLG=MTV\times SUV_{mean}$) were computed. The arterial blood SUV needed for computation of SUR values was determined by defining a roughly cylindrical aorta ROI in the attenuation CT data which than was transferred to the PET data (Figure 1). To exclude partial volume effects in this evaluation a concentric safety margin was used in the transaxial planes, centering the ROI in the aorta. Planes showing high tracer uptake close to the aorta (pathological or otherwise) were excluded. The minimum volume of the resulting aorta ROI was 5 ml. Blood SUV was computed as the mean SUV in the aorta ROI. Figure 1 shows an example of a delineated aorta ROI. SUR of the lesions was computed as the ratio of lesion SUV and blood SUV.

Additionally, lesion SUV and SUR values were scan time corrected as described in (*14*):

$$SUR^{tc} = \frac{T_0}{T} \times (SUR - V_r) + V_r$$

$$SUV^{tc} = SUV \times \left[\frac{SUR^{tc}}{SUR} \times \left(\frac{T_0}{T}\right)^{-b}\right] \quad (1)$$

where T is the actual scan time p.i. and T_0 is the chosen standard scan time to which the SUV and SUR values are normalized (60min in the present work). V_r is a fixed estimate of the apparent volume of distribution, corresponding to the y-axis intercept of a Patlak Plot in dynamic investigations (we used $V_r = 0.53$ml/ml) and b is a parameter describing the shape and decrease of the arterial input function over time (we used b = 0.313, see (*14*) for details). Corresponding to the four possibilities to quantitatively assess the tracer uptake (conventional SUV, scan time corrected SUV^{tc}, tumor-to-blood uptake ratio SUR, scan-time corrected tumor-to-blood uptake ratio SUR^{tc}), four different measures of maximum tracer uptake, mean tracer uptake, and total lesion glycolysis, respectively were computed and further analyzed.

Clinical Endpoints And Statistical Analysis

The three clinical endpoints of this study were overall survival (OS), locoregional tumor control (LRC), and distant metastases-free survival (DM) measured from the start of radiotherapy to death and/ or event. Patients who did not keep follow-up appointments and for whom information on survival or tumor status was thus unavailable were censored with the date of last follow-up.

The association of OS, LRC, and DM with clinically relevant parameters (gender, age, smoking state, histology, grading, T-stage, and N-stage) as well as quantitative PET parameters was analyzed using univariate Cox proportional hazard regression in which the PET parameters were included as binarized parameters. The cutoffs used for binarization were calculated by performing an univariate Cox regression for each measured value. The value leading to the hazard ratio (HR) with the highest significance was used as cutoff. To avoid too small group sizes only values within the interquartile range were considered as potential cutoff. The cutoff values were separately computed for OS, LRC, and DM. The probability of survival was computed and rendered as Kaplan-Meier curves.

Independence of PET parameters from clinically relevant parameters was analyzed in multivariate Cox regression. Those clinical parameters with at least a trend for significance according to univariate Cox regression ($P < 0.1$) were included.

Correlation was tested by the Spearman's rank correlation method. Statistical significance was assumed at a P-value of less than 0.05. Statistical analysis was performed with the *R language and environment for statistical computing* (*16*) version 3.1.2.

RESULTS

The 2-year, 3-year, and 5-year overall survival rates were 39%, 31% and 16%, respectively. These values are in line with data from current literature (*17*). Overall, 72% of patients died during the observation period (last follow-up October 2014). The median overall survival was 13 months. In our study locoregional tumor control was 46% and freedom from distant metastases was 34% among the survivors at five years.

The values of the investigated PET parameters are summarized in Table 2. Mean blood SUV was 1.7±19% and the scan time correction factor of lesion SUV was 0.89±11% on average. Correlation analysis revealed, as expected, a strong correlation of MTV with the different TLG parameters (Spearman's rho: from 0.94 to 0.95). All TLG parameters as well as all tracer uptake based parameters were strongly correlated as well (Spearman's rho: 0.98 to 1 and 0.81 to 0.98, respectively). Correlation of MTV and uptake parameters ranged from 0.44 to 0.6 and correlation of TLG and uptake parameters ranged from 0.62 to 0.79. All correlations were significant.

Overall Survival

Overall survival was significantly associated with all PET parameters with the exception of SUV_{mean}^{tc}. The HRs ranged from 1.6 to 2.5. HRs >2 were found for MTV, SUR_{max}, SUV_{mean}^{tc}, SUR_{mean}, and SUR_{mean}^{tc} (Table 3). Kaplan-Meier curves with respect to OS are shown in Figure 2.

The clinical parameters T-stage, N-stage, UICC-stage, and smoking state were significant prognostic factors for OS according to univariate Cox regression (HR=1.7, P=0.026 / HR=1.71, P=0.016 / HR=1.61, P=0.027 / HR=1.85, P=0.016). These four parameters and the PET parameters were included in the multivariate Cox regression. Only MTV, SUR_{max}, SUR_{max}^{tc}, SUR^{tc} and SUR_{mean} were multivariate significant prognostic factors for OS with similar effect size. TLG, TLG_{SUR}, TLG_{SUR}^{tc}, SUV_{max} and SUR_{mean}^{tc} showed a trend for significance (Table 4). The P-value for all other investigated PET parameters was larger than 0.1.

Distant Metastases Free Survival

For TLG, TLG^{tc} and TLG^{tc}_{SUR} no significant effect was found. All other PET parameters were significant prognostic factors for DM with HRs ranging from 2.1 to 4.5 (Table 3). The highest HRs were found for SUR^{tc}_{max} (HR=4.1) and SUR^{tc}_{mean} (HR=4.5). For SUV_{max} and SUV_{mean} the HRs were distinctly lower (HR=2.2 and HR=3.3, respectively). Kaplan-Meier curves with respect to DM are shown in Figure 3.

Among the investigated clinical parameters only smoking state was prognostic for DM in univariate (HR=3.35, P=0.026) and multivariate analysis (HR=3.1, P=0.04). The results of multivariate Cox regression including this parameter and the PET parameters are shown in Table 5. MTV and all SUR based parameters were prognostic for DM, $SUV_{max/mean}$ showed a trend for significance. The P-value for all other investigated PET parameters was larger than 0.1. The highest hazard ratios were found for SUR^{tc}_{max} (HR=3.9, P=0.014) and SUR^{tc}_{mean} (HR=4.4, P=0.007).

Locoregional Tumor Control

Univariate Cox regression with respect to LRC revealed only for N-stage>0 a significant effect (P=0.048). For patient age>61 years a trend for significance was found (P=0.052). The P-value for all other investigated parameters was larger than 0.1. Therefore, this clinical endpoint was not further analyzed.

DISCUSSION

In this exploratory study we investigated the prognostic value of pretherapeutic SUR (with and without scan time correction) and scan time corrected SUV in comparison to MTV, TLG, and SUV under consideration of known clinical prognostic parameters in patients with locally advanced esophageal carcinoma treated with definitive chemoradiotherapy.

Our main result is that scan time correction of lesion SUV and, more pronouncedly, normalization of (scan time corrected) lesion SUV to blood SUV (i.e. the use of SUR instead of SUV) increases the prognostic value of the thus quantified tracer uptake that serves as a surrogate of the lesion's glucose consumption. A second result is that 18F-FDG PET parameters in general provide independent prognostic information for OS and DM but not for LRC in this patient group. The only clinical parameter remaining significant in multivariate analysis performed together with the PET parameters was smoking status of the patients.

For OS, multivariate analyses revealed significant correlations only for MTV, SUR_{max}, SUR^{tc}_{max} and SUR_{mean}. TLG and $SUV_{max/mean}$ did not show a significant effect. This result is in agreement with a recent publication by Lemarignier et al (*8*) were MTV was prognostic for OS, while SUV_{max} was not prognostic. Normalization to blood SUV and scan time correction of SUV improved the prognostic value in our patient group, which led to comparable HRs and levels of significance for MTV and SUR values. For DM, SUV_{max} and SUV_{mean} were significant predictors according to multivariate Cox regression. However, the HR of scan time corrected SUR was notably larger than that of MTV or SUV: e.g., the hazard ratio of SUR^{tc}_{max} with respect to DM was HR=3.9 compared to HR=2.2 for SUV_{max}. This suggests that SUR may have more potential than the other PET parameters to predict occurrence of DM after therapy.

The largest hazard ratio with respect to DM was found for SUR^{tc}_{mean}, the scan time corrected mean SUR (Table 5). Surprisingly, this did not lead to a prognostic value of TLG^{tc}_{SUR}, which was not significantly correlated with DM. A plausible explanation would be that the prognostic value of TLG is dominated by MTV (strongly suggested by the pronounced linear correlation between TLG and MTV) while the influence of the tracer uptake on variations of TLG is less pronounced.

As our results demonstrate, both, MTV and SUR provide prognostic information for overall survival and development of distant metastases which add to clinical parameters. It should be noted, however, that MTV in the present study was determined by using an essentially fully automated delineation algorithm. Although several viable automated algorithms have been published (*18–27*), in many institutions MTV is presently still determined by manual delineation. Manual delineation is known to be prone to intra-and interobserver variability as well as to potentially gross size and background dependent bias if fixed absolute or relative thresholds are used. Therefore, the prognostic value of MTV may potentially be less convincing when the lesions are delineated manually. In contrast, SUR^{tc}_{max} and SUV_{max} have the clear advantage that they are independent of the details of the delineation and, can always be determined unambiguously.

In our study scan time correction of SUV did generally not improve the prognostic value of SUV. This indicates that in our patient group the improved prognostic value of SUR is caused mainly by the beneficial influence of normalization to blood SUV rather than by scan time correction since the variability of the blood SUV (19%) is larger than that of the scan time correction factor (11%).

Another possible explanation is that scan time correction of SUV requires stronger assumptions than that of SUR. In the latter case, it has only to be assumed that the arterial input function (AIF) can be described by some power law starting early after bolus passage which empirically is fulfilled to a very good degree (*14*). For scan time correction of SUV it is necessary to assume that all AIFs can be described with the same power law, i.e. the exponent b in Equation 1 is identical for all AIFs and its value directly enters the correction formula Equation 1. Any inter-individual residual variability of b would adversely affect the accuracy of the SUV scan time correction and might thus explain the failure to improve the prognostic value of the SUV. Further investigations will be necessary to settle this question.

Regarding the superior performance of SUR in the present study it should be emphasized that in comparison to SUV its determination additionally requires the thorough delineation of an aorta ROI to derive the blood SUV. Principally, this introduces a further potential source of error including intra-and interobserver variability effects. But fortunately, the aorta (and its boundaries) can be quite easily and unambiguously identified in the CT data and it is also easy to observe the safety margin (and to possibly exclude aorta sections affected by high tracer uptake in immediately adjascent structures) as illustrated in Figure 1 in order to obtain unbiased blood SUV values. Overall, if the necessary care is taken during the aorta delineation the reproducibility of the blood SUV (and reproducability of the resulting SUR) is very high.

The fact that only N-stage as clinical parameter and none of the PET parameters in our patient cohort was significantly correlated with LRC is somewhat surprising. However, in contrast to overall and disease-free survival local control after primary radiochemotherapy of esophageal cancer is scarcely reported in the literature, and we are only aware of two studies correlating this endpoint with PET-derived parameters (*6*, *7*). The majority of our patients suffered from T3 and N1 tumors and represent therefore a comparably narrow range of tumor burden undergoing homogeneous treatment, making it difficult to identify prognostic factors in the sample size reported here. Statistical power is further diminished by the fact that the locoregional control rate in our study was 46% after 5 years, i.e. the number of events for this endpoint was considerably less than the number of events for distant metastases or death. In addition almost all of the patients were deemed as suffering from unresectable tumors or unfit for surgery by the multidisciplinary cancer team so that life-expectancy may be impacted not only by distant metastases but also by co-morbidity. Both of these

confounders may have interfered with detection of recurrent tumors after radical radio(chemo)therapy in our study.

A general limitation of our study is its retrospective explorative character, i.e. our findings have to be considered as hypothesis generating and preliminary. Therefore our results need validation in further studies with independent patient groups before final conclusions on the prognostic value of the described parameters can be drawn. In case that the prognostic value will be confirmed, the predictive value of the described PET parameters needs to be addressed in prospective stratification or intervention studies.

CONCLUSION

PET provides independent prognostic information for OS and DM but not for LRC in patients with locally advanced esophageal carcinoma treated with definitive radio(chemo)therapy in addition to clinical parameters. Among the investigated uptake based parameters only SUR was an independent prognostic factor for OS and DM. These results suggest that the prognostic value of tracer uptake can be improved when characterized by SUR instead of SUV. Further investigations are required to confirm these preliminary hypothesis generating results.

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FIGURES

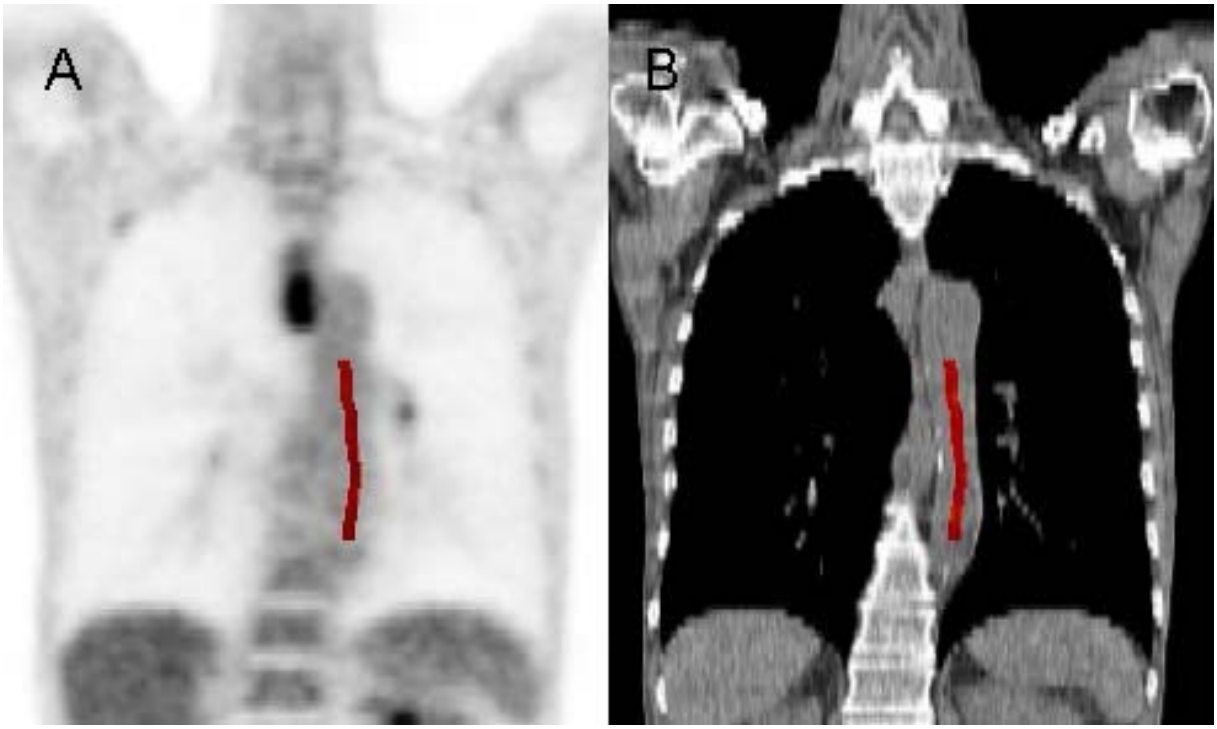

FIGURE 1 Illustration of the delineation of the aorta. The actual delineation was performed on the attenuation CT (B, marked in red). The resulting ROI was then transferred to the PET image (A). The high tracer uptake of the lesion close to the aorta will cause spillover into the neighboring aorta which could adversely affect the blood SUV determination. Therefore, this part of the aorta is excluded from the ROI delineation.

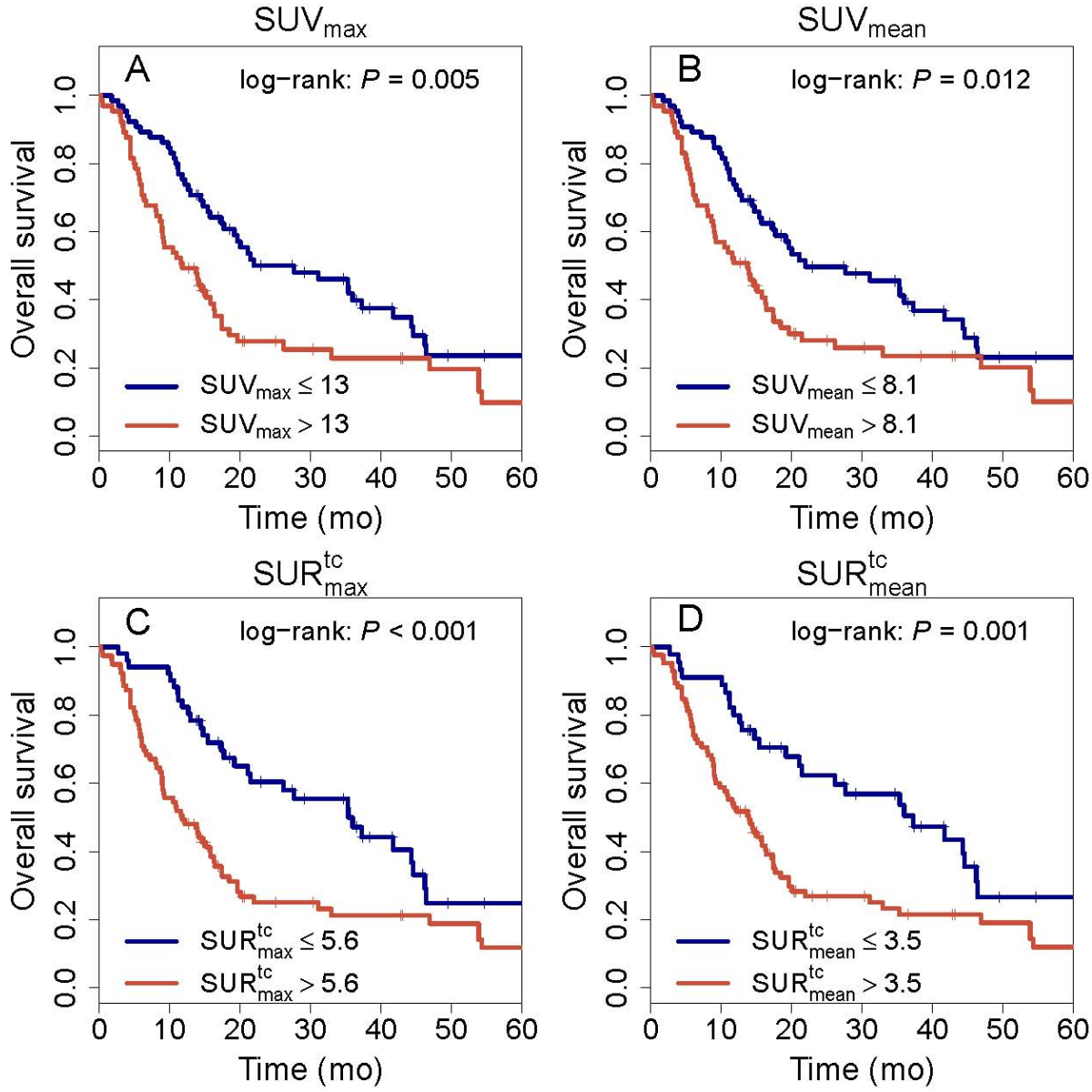

FIGURE 2 Kaplan-Meier curves with respect to OS.

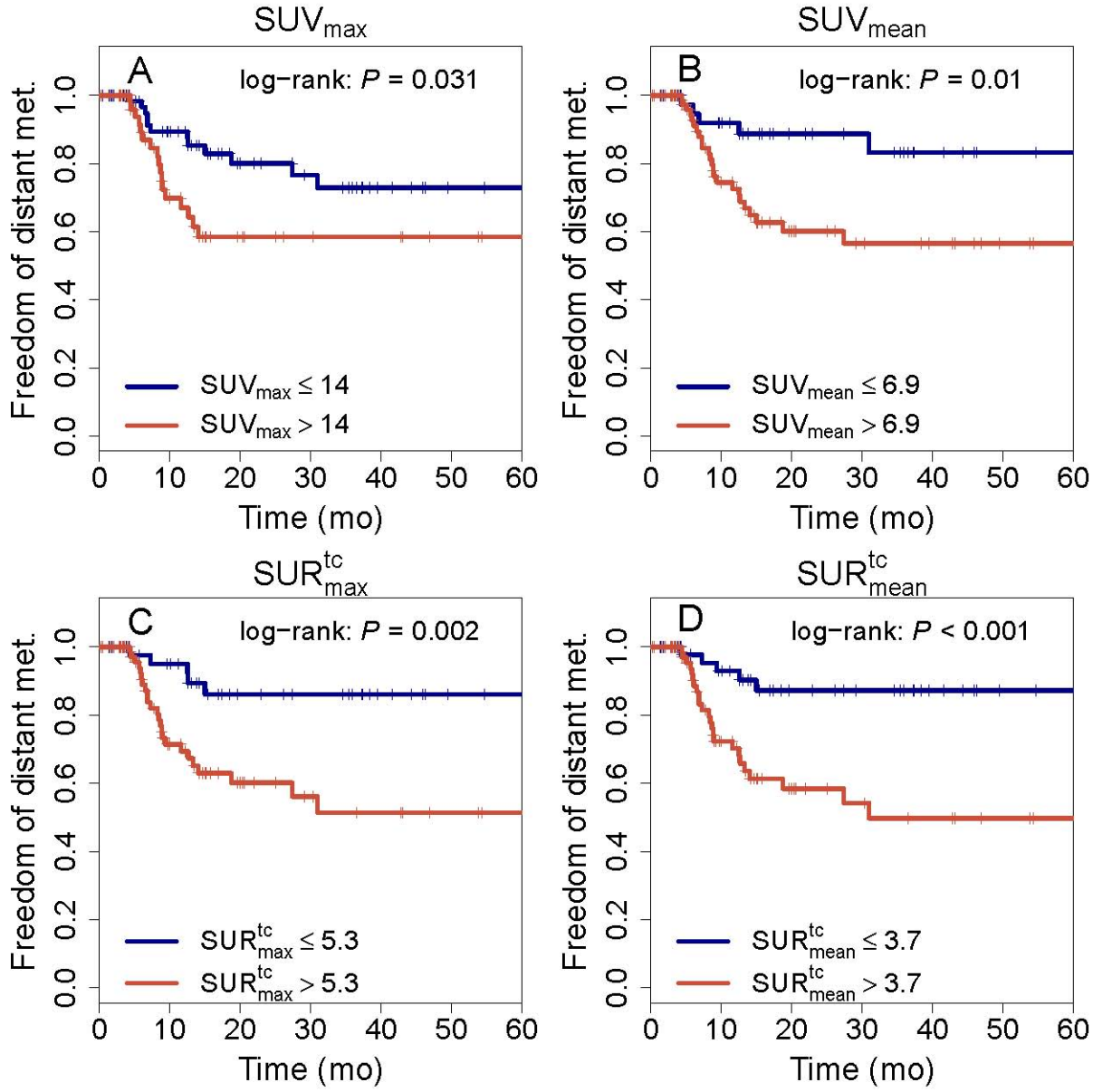

FIGURE 3 Kaplan-Meier curves with respect to DM.

TABLES

TABLE 1 Patient and tumor characteristics.

Characteristics	Value
Age (years)	
Mean ± SD	63±11
Median	65
Gender	
Male	113 (87)
Female	17 (13)
Histology	
Squamous cell carcinoma (SCC)	106 (82)
Adenocarcinoma (ADC)	21 (16)
Other	3 (2)
T-stage	
T1	7 (5)
T2	23 (18)
T3	82 (63)
T4	13 (10)
Tx	5 (4)
N stage	
N0	41 (32)
N1	74 (57)
N2	7 (5)
N3	2 (1)
Nx	6 (5)
UICC-stage	
I	15 (11)
II	35 (27)
III	80 (62)

All data are specified as percentage values except where indicated otherwise.

TABLE 2 Summary of investigated PET parameters.

Parameter	Mean±SD	Range
Metabolic active volume		
MTV (ml)	21.5±26.8	1.32–162
Total lesion glycolysis		
TLG (ml)	218±299	6.4–1610
TLG^{tc} (ml)	197±281	6.14–1500
TLG_{SUR} (ml)	132±177	3.82–910
TLG^{tc}_{SUR} (ml)	112±159	3.28–809
Maximum tracer uptake		
SUV_{max}	14.2±7.2	2.09–34.9
SUV^{tc}_{max}	12.4±6.43	1.98–34.6
SUR_{max}	8.69±4.53	1.53–23.2
SUR^{tc}_{max}	7.06±3.69	1.28–21.2
Mean tracer uptake		
SUV_{mean}	8.8±4.03	1.88–21.8
SUV^{tc}_{mean}	7.78±3.61	1.8–21.7
SUR_{mean}	5.41±2.54	1.38–13.4
SUR^{tc}_{mean}	4.43±2.1	1.16–13.3

TABLE 3 Univariate Cox regression with respect to OS and DM.

	OS				DM			
Parameter	Risk	HR	CI	P-value	Risk	HR	CI	P-value
Clinical parameters								
Gender	male	1.05	0.56–1.97	0.88	male	4.53	0.62–33.27	0.14
Age	>61 (years)	1.15	0.75–1.76	0.51	>61 (years)	1.43	0.66–3.09	0.36
T-stage	> 2	1.7	1.06–2.71	0.026	> 2	1.61	0.71–3.64	0.25
N-stage	> 0	1.71	1.11–2.65	0.016	> 0	1.31	0.62–2.77	0.49
UICC-stage	> II	1.61	1.06–2.46	0.027	> II	1.53	0.72–3.26	0.27
Grading	>2	1.02	0.65–1.6	0.92	>2	1.57	0.71–3.44	0.26
Histology	SCC	1	0.58–1.72	1	SCC	0.93	0.35–2.44	0.88
smoker	yes	1.85	1.12–3.05	0.016	yes	3.35	1.15–9.75	0.026
Metabolic active volume								
MTV	>8.5 (ml)	2.04	1.32–3.14	0.001	>7.43 (ml)	2.34	1.03–5.33	0.042
Total lesion glycolysis								
TLG	>124 (ml)	1.73	1.15–2.6	0.0085	>47.1 (ml)	1.95	0.86–4.41	0.11
TLG^{tc}	>143 (ml)	1.68	1.11–2.56	0.015	>41.8 (ml)	1.95	0.86–4.41	0.11
TLG_{SUR}	>75.5 (ml)	1.88	1.25–2.82	0.003	>75.5 (ml)	2.12	1.02–4.43	0.045
TLG^{tc}_{SUR}	>29.1 (ml)	1.77	1.15–2.73	0.0091	>38.1 (ml)	2.08	0.96–4.5	0.063
Maximum tracer uptake								
SUV_{max}	>12.8	1.78	1.18–2.69	0.0056	>13.6	2.22	1.06–4.65	0.035
SUV^{tc}_{max}	>10.5	1.57	1.02–2.4	0.039	>10.5	2.38	1.05–5.39	0.037
SUR_{max}	>6.17	2.48	1.56–3.94	< 0.001	>10.2	3.06	1.46–6.4	0.003
SUR^{tc}_{max}	>5.56	2.18	1.4–3.37	< 0.001	>5.26	4.07	1.55–10.71	0.004
Mean tracer uptake								
SUV_{mean}	>8.14	1.68	1.12–2.52	0.013	>6.86	3.29	1.25–8.64	0.016
SUV^{tc}_{mean}	>6.09	1.4	0.9–2.16	0.13	>6.09	2.5	1.02–6.14	0.046
SUR_{mean}	>4.46	2.27	1.46–3.53	< 0.001	>4.9	4.05	1.72–9.52	0.001
SUR^{tc}_{mean}	>3.52	2.11	1.34–3.33	0.001	>3.75	4.49	1.71–11.79	0.002

TABLE 4 Multivariate Cox regression with respect to OS.

Parameter	HR	CI	P-value
Clinical parameters			
T-stage	1.5	0.75–2.8	0.27
N-stage	1.3	0.71–2.5	0.38
UICC-stage	0.84	0.41–1.7	0.64
smoker	1.7	1–2.8	0.045
PET parameters			
MTV	1.8	1.1–2.9	0.019
TLG	1.5	0.94–2.4	0.086
TLG_{SUR}	1.6	0.95–2.7	0.083
TLG^{tc}_{SUR}	1.6	0.94–2.8	0.084
SUV_{max}	1.6	0.99–2.7	0.056
SUR_{max}	2	1.2–3.6	0.012
SUR^{tc}_{max}	1.9	1.1–3.2	0.019
SUR_{mean}	2.1	1.2–3.7	0.01
SUR^{tc}_{mean}	1.7	0.95–3.1	0.071

Each PET parameter was analyzed separately together with the clinical parameters which were significant prognostic factors (or exhibited a trend for significance) in univariate Cox regression. Note that the HRs and the P-values of the clinical parameters were averaged over all analyses.

TABLE 5 Multivariate Cox regression with respect to DM.

Parameter	HR	CI	P-value
Clinical parameters			
smoker	1.7	0.95–3.1	0.071
PET parameters			
MTV	2.5	1–6	0.039
SUV_{max}	2.2	0.99–4.7	0.052
SUR_{max}	3.1	1.4–6.7	0.005
SUR^{tc}_{max}	3.9	1.3–11	0.014
SUV_{mean}	2.5	0.94–6.7	0.065
SUR_{mean}	3.3	1.4–7.9	0.007
SUR^{tc}_{mean}	4.4	1.5–13	0.007

Each PET parameter was analyzed separately together with the clinical parameters which were significant prognostic factors (or exhibited a trend for significance) in univariate Cox regression. Note that the HRs and the P-values of the clinical parameters were averaged over all analyses.