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ORIGINAL ARTICLE

Confirmation of the prognostic value of pretherapeutic tumor SUR and MTV in patients with esophageal squamous cell carcinoma

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Abstract

Purpose 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. In a recent publication, we were able to show that PET can provide independent prognostic information in such a patient group and that the tumor-to-blood standard uptake ratio (SUR) can improve the prognostic value of tracer uptake values. The present investigation addresses the question of whether the distinctly improved prognostic value of SUR can be confirmed in a similar patient group that was examined and treated at a different site.

Methods ^{18}F-FDG PET/CT was performed in 147 consecutive patients (115 male, 32 female, mean age: 62 years) with newly diagnosed esophageal squamous cell carcinoma prior to definitive radiochemotherapy. In the PET images, the metabolic active volume (MTV) of the primary tumor was delineated with an adaptive threshold method. For the resulting ROIs, SUV_{max} and total lesion glycolysis ($TLG = MTV \times SUV_{mean}$) were computed. 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. 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 Univariate Cox regression revealed MTV, TLG, and SUR_{max} as significant prognostic factors for OS. MTV as well as TLG were significant prognostic factors for LRC while SUR_{max} showed only a trend for significance. None of the PET parameters was prognostic for DM. In univariate analysis, SUV_{max} was not prognostic for any of the investigated clinical endpoints. In multivariate analysis (T-stage, N-stage, MTV, and SUR_{max}), MTV was an independent prognostic factor for OS and showed a trend for significance for LRC. SUR_{max} was not an independent predictor for OS or LRC. When including the PET parameters separately in multivariate analysis, MTV as well as SUR_{max} were prognostic factors for OS indicating that SUR_{max} is independent from the clinical parameters but not from MTV. In addition, MTV was an independent prognostic factor for LRC in this separate analysis.

Conclusions Our study revealed a clearly improved prognostic value of tumor SUR compared to tumor SUV and confirms our previously published findings regarding OS. Furthermore, SUR delivers prognostic information beyond that provided by the clinical parameters alone, but does not add prognostic information beyond that provided by MTV in this patient group. Therefore, our results suggest that pretherapeutic MTV is the parameter of choice for PET-based risk stratification in the considered setting but further investigations are necessary to demonstrate that this suggestion is correct.

Keywords PET · Esophageal cancer · Definitive radiochemotherapy · SUV · SUR

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Introduction

Squamous cell carcinoma of the esophagus has an unfavorable prognosis when diagnosed at a locally advanced stage. After definitive radiochemotherapy (RCT), local tumor recurrence is the first site of relapse in about 25%, and

the only site in about 15%, of all patients, which heavily affects the patients' quality of life [1–3]. Due to the considerable rate of local recurrences after definitive RCT, trimodality treatment is usually regarded as the treatment of choice in medically fit patients. These patients undergo radical surgical tumor resection after neoadjuvant RCT, often with somewhat reduced radiation dose in comparison to definitive RCT. The trimodality approach is supported by some recent population-based analyses, which suggest an improvement of overall survival (OS) [4, 5]. Yet, radical esophagectomy is associated with a potential increase of morbidity and a postoperative mortality of up to 7% during the first 3 months after treatment with most of the deaths being caused by surgical complications [6]. Minimally invasive surgery and treatment at high-volume centers may be able to reduce this high rate, but even in this case the in-hospital mortality—which usually underestimates the real rate of surgery-related deaths—still remains as high as 3.8% [7, 8]. Bearing in mind that on the other hand up to one-third of patients present pathological complete remissions already after low-dose preoperative RCT [9], a better patient stratification with respect to tumor radiosensitivity is urgently needed.

Positron-emission-tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) before and/or during RCT is often suggested to guide treatment decision (stop RCT after neoadjuvant dose or continue to higher-dose definitive RCT). Furthermore, in about 8% of the patients, interim-FDG-PET is able to detect interval metastases during treatment, which has a considerable impact on the treatment of these patients [10]. PET parameters might be used to personalize treatment, especially in patients with unfavorable PET parameters: these patients might undergo an additional (PET-based) radiation boost [11] or might also be candidates for the concomitant or sequential addition of novel drugs like checkpoint inhibitors. Additionally, if PET parameters are associated with unfavorable local control rates after definitive RCT, these patients might be offered the trimodality approach with radical surgery following preoperative RCT.

However, data on the prognostic value of pretreatment FDG-PET parameters are very inconclusive. Conventional tumor PET parameters, notably the standardized uptake value (SUV), can probably not be used for treatment guidance, as they are not reproducibly correlated with tumor response and patient outcome [12–16]. One cause for insufficient performance could be the well-known shortcomings of SUV quantification, e.g., uptake time dependence of the SUV, interstudy variability of the arterial input function (AIF), and susceptibility to errors in scanner calibration [17–19], which adversely affect the reliability of the SUV as a surrogate of the metabolic rate of glucose consumption. In recent publications, we were able to show that the uptake time normalized tumor-to-blood SUV ratio (standardized uptake ratio, SUR) essentially removes most of these shortcomings, which leads to improved correlation with the metabolic uptake rate [20–22], improved test–retest stability [23], and significantly better prognostic value compared to tumor SUV [24–26].

The present investigation addresses the question of whether the distinctly improved prognostic value of SUR reported in [24] for patients with esophageal cancer treated with definitive RCT can be confirmed in a similar patient group that was examined and treated at a different site. Furthermore, we investigated if the optimal cutoff values for discrimination of high- and low-risk patients found in [24] are also suitable for risk stratification in the current patient group.

Methods

Patient characteristics

A total of 147 consecutive patients (115 male, 32 female, mean age, 62 years, range, 42–90) with esophageal squamous cell carcinoma were analyzed retrospectively. A summary of patient and tumor characteristics is given in Table 1. All patients received curative intended definitive radiochemotherapy (RCT) between May 2009 and October 2013. The analyzed patients are a subgroup of a published cohort [27] with updated follow-up and matching the following inclusion criteria: age > 18 years, histologically confirmed esophageal squamous cell carcinoma, whole-body ^{18}F-FDG PET/CT before RCT, no evidence of distant metastases at initial PET/CT, and prescription of definitive RCT or high-dose radiotherapy with curative intent. These criteria resulted in exclusion of 13/160 patients in the group analyzed in [27]. Evaluation of the data was approved by the Human Research Ethics Sub-committee of Ethics Committee of the first affiliated hospital of Xiamen University (EA2/122/17). All patients signed a written informed consent.

Treatment and follow-up

Patients were treated with RCT or radiotherapy with either 1.8 or 2 Gray (Gy) single dose per fraction. Treatment planning and delineation was described in detail previously [27, 28]. Briefly, gross tumor volume (GTV) was delineated using information from high-resolution contrast enhanced computed tomography (CT) and ^{18}F-FDG PET and clinical information (especially from endoscopy). Clinical target volume (CTV) of the primary tumor was calculated by enlarging the primary GTV volume 4 cm along the esophageal wall and 0.5 cm in radial extension excluding

Table 1 Patient and tumor characteristics

Characteristics	Value (%)
Age (years)	
Mean ± SD	62±10
Median	61
Gender	
Male	115 (78)
Female	32 (22)
Grade	
x	14 (10)
1	16 (11)
2	94 (64)
3	21 (14)
4	2 (1)
T stage	
1	2 (1)
2	7 (5)
3	43 (29)
4	95 (65)
N stage	
0	58 (39)
1	56 (38)
2	32 (22)
3	1 (1)
UICC stage	
I	5 (3)
II	23 (16)
III	119 (81)
Chemotherapy	
None	57 (39)
Cisplatin + 5-FU	48 (33)
Cisplatin + paclitaxel	42 (29)

Clinical staging was determined according to the Chinese Clinical Staging Criteria for the Non-Surgical Treatment of Esophageal Cancer [39]. Grading was based on the international recommendations for esophageal cancer with G1 representing a well-differentiated tumor and G4 representing an undifferentiated tumor [40].

bones, lungs, and large vessels. Planning treatment volume 50 Gy (PTV 50 Gy) comprised CTV with an additional 0.5 cm margin. After application of 50 Gy, a sequential radiation boost of 2 − 18 Gy (average, 57.2 Gy) was prescribed to a reduced treatment volume compromising only GTV with reduced safety margins (PTV boost). Radiation treatment was mostly delivered as intensity modulated radiotherapy (61%). Patients who received concomitant chemotherapy were either treated with two cycles of cisplatin (25 mg/m^2/day, days 1-3 and days 29-31) or with paclitaxel (135 mg/m^2/day, day 1 and day 29) always in combination with 5-fluorouracil (500 mg/m^2/day, days 1-5 and days 29-33). Details about chemotherapy regimes are shown in Table 1. Follow-up consisted of an ^{18}F-FDG PET/CT 1 month after completing radio(chemo)therapy and clinical examination and CT scans of the thorax and abdomen every 3–6 months thereafter. Additional diagnostic procedures including endoscopic examinations were performed as indicated at the discretion of the treating physician.

FDG PET/CT protocol

All patients underwent a hybrid ^{18}F-FDG PET/CT scan prior to therapy. Scans (3D PET acquisition, 90 s per bed position) were performed with a Discovery STE (General Electric Medical Systems, Milwaukee, WI, USA). Data acquisition started 71±23 min (range, 50–140 min) after injection of 121 to 548 MBq ^{18}F-FDG. Tomographic images were reconstructed using CT-based attenuation-weighted OSEM reconstruction (two iterations, 20 subsets, 6-mm FWHM Gaussian filter).

Data analysis

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 [29, 30]. The resulting region of interest (ROI) delineation was inspected visually by an experienced observer (who was blinded to patient outcome) and manually corrected when this was deemed necessary. This was the case in five out of 147 patients, which exhibited only low diffuse tracer accumulation in the respective lesion. For the delineated ROIs, the parameters SUV_{max}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG = $MTV \times SUV_{mean}$) were computed.

The arterial blood SUV (BSUV) needed for computation of SUR values was determined by defining a roughly cylindrical aorta ROI in the attenuation CT data, which then was transferred to the PET data. To reduce partial volume effects, a concentric safety margin of about 8 mm was used in the transaxial planes, centering the ROI in the aorta. Planes showing high tracer uptake close to the aorta (pathological or otherwise, e.g., high myocardial FDG uptake) or showing obvious attenuation correction artifacts (e.g., near the diaphragm) were excluded. The aorta ROI was positioned in the descending aorta and the minimum volume was 5 ml. BSUV was computed as the mean SUV in the aorta ROI.

Lesion SUR_{max} was computed as the uptake time corrected ratio of lesion SUV_{max} and BSUV. Uptake time correction to $T_0 = 60$ min p.i. was performed as described in [21]. A value of zero for the apparent volume of

distribution was assumed (i.e., $V_r = 0$ was used in the correction formula) for the reasons discussed in [22]. The uptake time corrected SUR is then given by

$$\mathrm{SUR}_{\max} = \frac{T_0}{T} \times \frac{\text{lesion } SUV_{\max}}{\mathrm{BSUV}} \quad (1)$$

where T is the actual time of measurement in the respective scan. In the following we omit the index "max" from lesion SUV and SUR since only maximum values of these quantities were considered.

ROI definition and analysis was performed using the ROVER software, version 3.0.36 (ABX, Radeberg, Germany).

Statistical analysis

The same clinical endpoints as in the previous publication [24] were investigated, namely overall survival (OS), locoregional tumor control (LRC), and distant metastases-free survival (DM) measured from the start of radio(chemo)therapy 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 (age, gender, grade, T-stage, N-stage, and UICC stage) as well as quantitative PET parameters was analyzed using univariate Cox proportional hazard regression in which the PET parameters were included as metric parameters. PET parameters showing a significant effect or a trend for significance ($P < 0.1$) in this analysis were further analyzed in univariate Cox regression using binarized PET parameters. The cutoff values used for binarization were calculated by performing an univariate Cox regression for each measured value. The values leading to the hazard ratio (HR) with the highest significance were 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. Cutoff values leading to $P < 0.05$ were further investigated for stability by determining the full range of cutoff values around the optimal cutoff for which a significant effect remained in univariate Cox regression. The probability of survival was computed and rendered as Kaplan–Meier curves. Independence of parameters was analyzed by multivariate Cox regression.

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* [31] version 3.4.4.

Results

The 2-year, 3-year, and 5-year overall survival rates were 39, 31, and 23%, respectively. Overall, 78% of the patients died during the observation period. Median follow-up time of the survivors was 60 months (range, 49.6 to 97.9 months). The rates for LRC and freedom from DM at 5 years were 32 and 69%, respectively.

Univariate Cox regression using the metric PET parameters revealed MTV, TLG, and SUR as significant prognostic

Table 2 Univariate Cox regression with respect to OS, LRC, and DM. PET parameters were included as metric parameters

	OS			LRC			DM		
Parameter	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Clinical parameters									
Gender male	1.31	0.83 – 2.06	0.24	0.94	0.56 – 1.59	0.81	0.95	0.4 – 2.26	0.91
Age	0.999	0.98 – 1.019	0.91	0.993	0.97 – 1.018	0.59	1.01	0.97 – 1.05	0.58
Grade > 2	0.74	0.44 – 1.25	0.26	1.02	0.57 – 1.84	0.94	1.14	0.46 – 2.83	0.78
T-stage > 3	1.6	1.18 – 2.18	**0.002**	1.25	0.9 – 1.73	0.18	1.26	0.73 – 2.18	0.41
N-stage > 0	1.51	1.2 – 1.89	< **0.001**	1.5	1.13 – 2.01	**0.0057**	1.88	1.17 – 3.02	**0.009**
UICC stage > II	1.68	1.1 – 2.56	**0.017**	1.35	0.86 – 2.11	0.19	1.21	0.59 – 2.49	0.6
Chemotherapy no	1.56	1.07 – 2.27	**0.02**	1.19	0.73 – 1.94	0.48	1.56	0.72 – 3.4	0.26
PET parameters									
MTV	1.03	1.02 – 1.04	< **0.001**	1.03	1.01 – 1.05	**0.001**	1.02	0.99 – 1.05	0.15
TLG	1.003	1.002 – 1.004	< **0.001**	1.002	1 – 1.004	**0.025**	1.002	0.999 – 1.004	0.21
SUV	1.009	0.982 – 1.038	0.51	1.01	0.98 – 1.04	0.52	0.997	0.939 – 1.06	0.93
SUR	1.1	1.04 – 1.16	**0.002**	1.07	1 – 1.15	**0.067**	1.05	0.93 – 1.18	0.47

The bold entries indicate a significant result ($p < 0.05$)

Table 3 Univariate Cox regression with respect to OS and LRC

Parameter	Risk	HR	95% CI	*p* value
OS				
MTV	> 22.3 ml	2.3	1.53 – 3.48	< **0.001**
TLG	> 46 ml	2.84	1.75 – 4.63	< **0.001**
SUR	> 6.75	2.26	1.43 – 3.56	< **0.001**
OS (previously published cutoff values)				
MTV	> 8.5 ml	2.14	1.41 – 3.24	< **0.001**
TLG	> 124 ml	1.6	1.1 – 2.31	**0.013**
SUR	> 5.56	1.99	1.19 – 3.34	**0.0092**
LRC				
MTV	> 14.9 ml	1.72	1.07 – 2.74	**0.024**
TLG	> 46 ml	2.19	1.28 – 3.75	**0.004**
SUR	> 6.87	2.76	1.59 – 4.79	< **0.001**

PET parameters were included as binarized parameters

The bold entries indicate a significant result ($p < 0.05$)

factors for OS. MTV as well as TLG were significant prognostic factors for LRC while SUR showed only a trend for significance. None of the PET parameters was prognostic for DM. In univariate analysis, SUV was not prognostic for any of the investigated clinical endpoints ($p > 0.5$ in all cases, see Table 2).

MTV, TLG, and SUR were binarized as described above. In univariate Cox regression, all three binarized parameters were prognostic factors for OS (HR > 2 and $p < 0.001$). Univariate analysis using the previously published cutoff values [24] also led to a significant effect for all three parameters (see Table 3). Corresponding Kaplan–Meier curves are shown in Fig. 1. Univariate Cox regression with respect to LRC revealed binarized MTV, TLG, and SUR as prognostic factors (see Table 3 and Fig. 2). For both clinical endpoints, the respective cutoff value exhibits adequate stability as demonstrated by the range of cutoff values for which a significant effect remains (see Table 4).

Multivariate Cox regression included T-stage, N-stage, chemotherapy (yes/no), MTV, and SUR (using metric PET parameters). In this analysis, MTV was an independent prognostic factor for OS and for LRC. SUR was not an independent predictor for OS or LRC (see Table 5). When including the PET parameters separately in multivariate analysis, MTV as well as SUR were prognostic factors for OS ($p < 0.001$ and $p = 0.018$, respectively) indicating that SUR is independent from the clinical parameters but not from MTV.

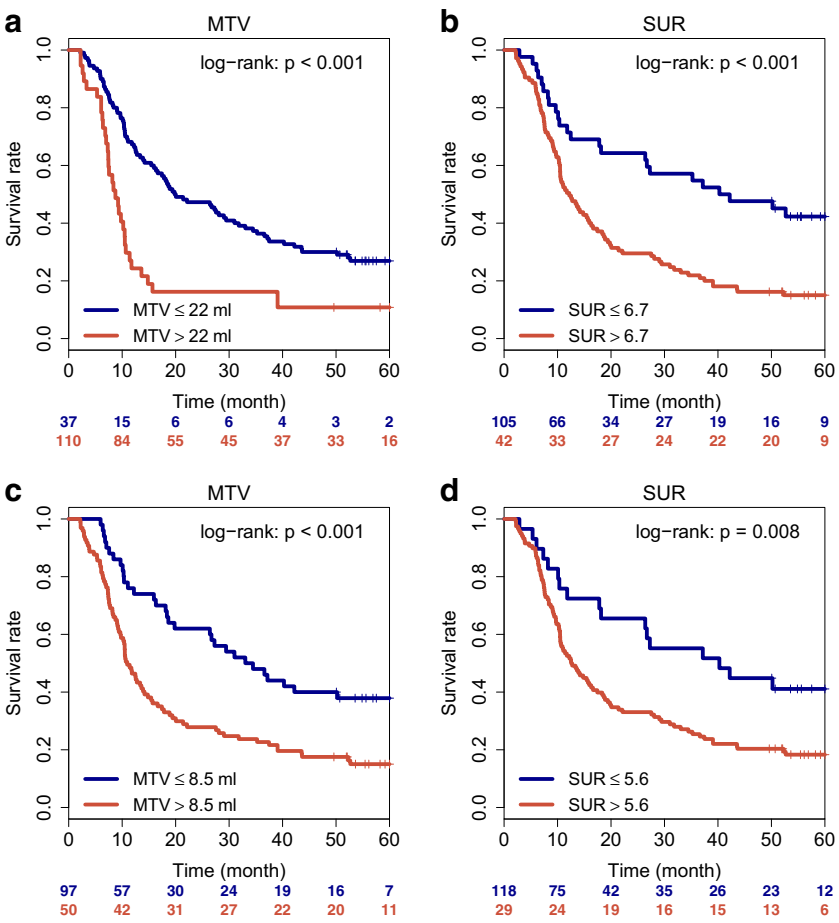

Fig. 1 Kaplan-Meier curves for MTV (**a**, **c**) and SUR (**b**, **d**) with respect to OS. Shown are the results for the cutoff values optimized for the current patient group (top) and for the cutoff values published in [24] (below)

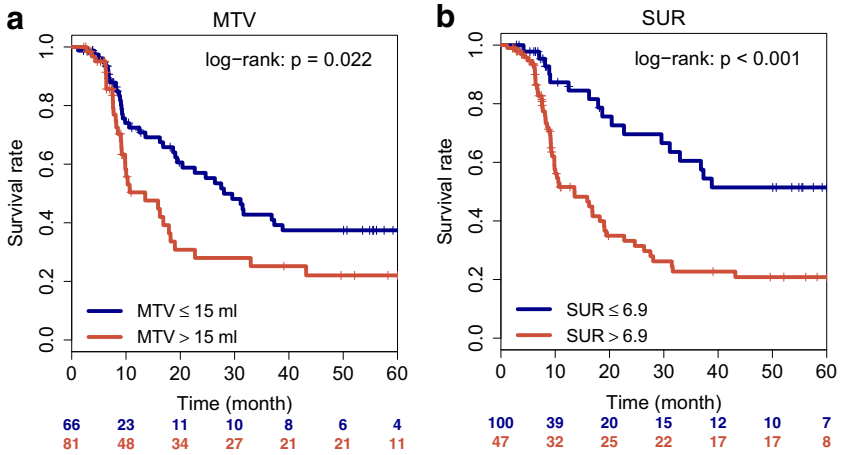

Fig. 2 Kaplan–Meier curves for MTV (**a**) and SUR (**b**) with respect to LRC

Discussion

In this study, we investigated the prognostic value of pretherapeutic SUR in patients with esophageal cancer and compared the results with conventional PET parameters as well as with previously published results on SUR. In the present investigation, too, SUR clearly outperformed SUV: SUV showed no significant effect for any of the investigated clinical endpoints, while SUR was a significant predictor for OS and LRC. This confirms our previous finding that the improved correlation of SUR with the metabolic uptake rate (i.e., improved quantification of tumor metabolism) translates directly into an improved prognostic value of SUR compared to SUV. However, multivariate analysis revealed a prognostic value of SUR that was independent from clinical parameters only for OS. Furthermore, SUR was not independent from MTV with respect to OS and LRC, respectively. On the other hand, MTV provides independent prognostic value for both endpoints. Therefore, a second important result of the present investigation is that MTV adds prognostic information to the clinical parameters. SUR does not add further information to the combination of clinical parameters and MTV. It would therefore be principally interesting to evaluate if PET is dispensable and CT-derived gross tumor volume alone might bear sufficient prognostic value. However, delineation on CT is much more observer dependent then semi-automatic delineation of PET images and the morphological volume might not coincide with MTV, anyway. Additionally, small tumor lesions might be hard to identify on CT. This is especially true for the current cohort of patients for which diagnostic CT was not available.

Table 4 Cutoff stability test

Parameter	min. cutoff	HR	max. cutoff	HR
OS				
MTV	4.69 ml	2.3	28.2 ml	2.29
TLG	31.1 ml	2.62	147 ml	1.45
SUR	5.23	2.28	8.9	1.44
LRC				
MTV	9.39 ml	1.6	17.8 ml	1.61
TLG	31.1 ml	2.9	79.6 ml	1.54
SUR	5.23	2.07	8.02	1.56

Shown is the range of cutoff values still leading to a significant effect

A direct comparison of our results with the results presented by Bütof et al in [24] reveals concordance only regarding OS. For this endpoint, the optimal SUR cutoff value from [24] leads to a significant discrimination of high- and low-risk groups in the present data as well. The previously published MTV and TLG cutoff values could be confirmed, too (see Table 3). On the other hand, the significant effect of MTV, TLG, and SUR with respect to DM found in [24] was absent in the current patient group while the significant effect with respect to LRC found here was not present in the patient group investigated in [24]. These discrepancies might be caused by the different number of events in the two patient groups. In [24], the number of LRC events was considerable lower than the number of events for DM or OS. In the current group, the situation is the opposite: only 26 patients developed distant metastases while 72 patients suffered from locoregional treatment failure. The notable differences in follow-up time are another potential explanation. While the median follow-up time in the present data was 60 months (minimum 50 months), the median follow-up time was only 32 months (minimum 12 months) in [24]. A further explanation might be the different histologies in the two patient groups. In the current group, all tumors were SCC, while in [24] only 82% of the tumors were SCC. Since this is still the distinct majority of the tumors included in that study, it can be expected that the remaining small fraction of other

Table 5 Multivariate Cox regression with respect to OS and LRC

	OS			LRC		
Parameter	HR	95% CI	*p* value	HR	95% CI	*p* value
Chemotherapy no	2.24	1.5–3.34	< **0.001**		–	
T-stage > 3	1.71	1.11–2.63	**0.016**		–	
N-stage > 0	1.99	1.32–3.02	**0.001**	1.64	0.996–2.71	0.052
MTV	1.03	1.01–1.04	< **0.001**	1.02	1–1.04	**0.037**
SUR	1.04	0.967–1.11	0.3	1.01	0.926–1.1	0.83

PET parameters were included as metric parameters

The bold entries indicate a significant result ($p < 0.05$)

histologies does not have much impact on the survival analyses.

A remarkable result of the present investigation is the good stability of the cutoff values: MTV, TLG, and SUR turned out to be prognostic factors for OS and LRC over a wide range of cutoff values (see Table 4). Regarding individualized therapy planning, a wide range of applicable cutoff values provides the opportunity to adjust the cutoff value to the given therapy options; e.g., if therapy deescalation is an option, the false-negative rate might be optimized by selecting a rather high cutoff value. Selecting a rather low cutoff instead optimizes the false-positive rate, which would be desirable in the context of therapy intensification. This observation seems especially relevant since there is no consensus on the total radiation dose for the definitive treatment of esophageal cancer. The prematurely terminated INT 0123/RTOG 94-05 trial randomized patients to RCT with a total dose of 50.4 Gy (standard arm) or dose escalated treatment with 64.8 Gy. There was no survival benefit observed by dose escalation. However, the interpretation of this study is hampered by the fact that there was an excess mortality of patients in the dose escalation group that was not attributable to increased dose [32]. Given these inconsistencies and in view of the fact that modern radiation treatment approaches are able to deliver high radiation doses within the thorax without excessive morbidity, a unanimous recommendation regarding dose prescription for definitive RCT of esophageal cancer is lacking; 50.4 Gy is considered the standard dose in many centers, especially in the US. There exists preliminary evidence (although not reaching statistically significance) from one prospective trial and some retrospective evaluations [32–34] that higher radiation doses are associated with a lower risk of loco-regional recurrence. Higher doses also seem to be associated with improved OS in a recent meta-analysis of mainly Asian patients [35]. It therefore seems beneficial to prescribe relatively high radiation doses if possible. Currently, there is a dose corridor between 50 and 70 Gy that is commonly prescribed in definitive RCT. One large caveat of higher radiation dose is increased late effects of radiotherapy. Especially, esophageal stricture seems to be more frequent after high-dose radiotherapy [36]. This can heavily affect patients' long-time quality of life. PET-based imaging biomarkers may therefore help to individually tailor radiation dose as has already been suggested in one retrospective study [37]. This is especially important for loco-regional control. However, pretherapeutic PET parameters may not be sufficient in their ability to predict loco-regional control (as suggested by our previous publications and others), but distant metastasis-free survival and overall survival may be improved by PET-adapted (additional or concomitant) systemic therapy as suggested by another retrospective analysis [38]. Importantly, both of the above-mentioned retrospective studies analyzed response by re-staging PET and adapted therapy accordingly. The results of our study and the validation by external data indicate that pretreatment PET, too, bears important prognostic information. This would potentially enable earlier treatment individualization.

A strength of our study is the external validation of previously published cutoff values. This is noteworthy as the validation cohort consisted of Asian patients with potential differences regarding etiology, prognosis, and treatment response. The applicability of cutoff values obtained in a European cohort of patients and the wide range of cutoff values for which a significant effect is manifest demonstrate robustness of the identified PET parameters.

Of course, a general limitation of our study is its retrospective character, thus our findings have to be considered as preliminary. They need validation in further studies in a prospective multicenter setting before final conclusions on the prognostic value of the described parameters can be drawn. A further limitation of this study is that not exactly the same clinical parameters as in [24] could be analyzed. In particular, the smoking status of the patients was not recorded for the current patient group and could thus not be included in the analysis.

Conclusions

Our study revealed a clearly improved prognostic value of tumor SUR compared to tumor SUV and confirms our previously published findings regarding OS. Furthermore, SUR delivers prognostic information beyond that provided by the clinical parameters alone, but does not add prognostic information beyond that provided by MTV in this patient group. Therefore, our results suggest that pretherapeutic MTV is the parameter of choice for PET-based risk stratification in the considered setting but further investigations are necessary to demonstrate that this suggestion is correct.

Author Contributions FH and SZ provided ideas for the study. FH, YL, JVDH and SZ performed the analysis and drafted the manuscript. FH and IS designed the figures and calculated the underlying statistics. YL, QL, CL, and WH were responsible for treatment, imaging, collection of patient data, and follow-up. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of interests None.

Ethical approval The study was approved by the Institutional Ethics Committees.

Informed Consent All patients provided signed written informed consent.

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