The value of ^{18}F-FDG PET/CT in assessment of metabolic response in esophageal cancer for prediction of histopathological response and survival after preoperative chemoradiotherapy

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Aim. To evaluate the ability of hybrid ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to predict histopathological response and overall survival (OS) after preoperative neoadjuvant chemoradiotherapy (CRT) in patients with the esophageal carcinoma.

Methods. 73 patients with locally advanced esophageal carcinoma were included in the study. All were treated with CRT and 34 subsequently underwent surgical resection of the esophagus. ^{18}F-FDG PET/CT was carried out prior to (PET/CT1) and 6 weeks after (PET/CT2) completion of the CRT.

Results. PET/CT2-determined complete metabolic response (CMR) was achieved in 6 (17.6%) out of 34 operated patients, the metabolic response was incomplete (NCMR) in 28 (82.4%) patients. A histopathological complete response (CR) to CRT was discovered in 7 patients (20.6%). The median OS in operated patients was 17.1 months, 95% CI:12.9-23.3 months. In a group of 39 non-operated patients, CMR after neoadjuvant CRT was achieved in 12 patients (30.8%), while NCMR was found in 28 (82.4%). The median OS was 13.5 months in this group, 95% CI: 4.4-22.7 months.

Conclusion. No statistically significant correlation was found between the ^{18}F-FDG metabolic response after the neoadjuvant CRT and histopathological response. Presently, the contribution of ^{18}F-FDG PET/CT as a marker of the potential result of CRT cannot be considered definite. Another study with a larger sample of patients and standardized algorithms for the examining protocols would be necessary for reaching definitive conclusions.

Key words: esophageal carcinoma, neoadjuvant chemoradiotherapy, ^{18}F-FDG PET/CT, tumor response

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INTRODUCTION

Esophageal cancer ranks among the 10 most common malignancies worldwide and is associated with high mortality[1,2] – the overall survival of 5 years is only attained in 9-15% patients[3,4]. Carcinomas of the esophagus are a heterogeneous group of tumours with respect to epidemiology, etiology, and histopathology[5]. Squamous cell carcinoma (SCC) occurs most frequently in the upper two thirds of the esophagus. In the lower third of the esophagus and the esophagogastric junction, adenocarcinoma (AC) is more prevalent.

Precise pretherapeutic staging is important when choosing the best available therapy for the patient. It is crucial to be able to differentiate patients with locoregional disease from patients with systemic disease. In systemic disease, there is no curative option and the patients receive palliative treatment[6].

After exclusion of distant metastases, selection of the therapeutic regimen depends on the T stage. Localized tumours (T1/T2) have a high likelihood of R0 resection, and primary esophagectomy represents the most frequent therapeutic procedure. In cases of locally advanced tumours (T3/T4, N+), surgery remains the mainstay of therapy, but evidence is growing that preoperative neoadjuvant chemotherapy or chemoradiotherapy (CRT) improves survival in patients with esophageal cancer[7-9]. The aim of neoadjuvant therapy is to cure potential micrometastatic disease with parallel preoperative tumor downsizing thereby increasing the chance of a more appropriate alternative treatment. Despite conflicting results from randomised trials, concurrent CRT followed by esophagectomy has became the standard option, with about 70% of patients receiving preoperative CRT before undergoing esophagectomy[10-13]. Of resected patients, 11-56% achieve pathologic complete response (CR), and patients who achieve pathologic CR survive longer than those who do not[14-16]. In a recent meta-analysis evaluating the contribution of neoadjuvant CRT for esophageal carcinoma, Gebski et al.[8] reported an absolute 2-year survival

advantage of 7% with neoadjuvant chemotherapy and 13% with neoadjuvant CRT in patients with esophageal carcinomas, compared to those treated by surgery alone. The overall results of this meta-analysis also show that the benefit of neoadjuvant treatment to responders is partially negated by effects in non-responders.

The mortality after esophagectomy continues at around 5-9% (ref.[17]) despite improvements in surgical technology. Furthermore, a recent European trial found that adding surgery to neoadjuvant therapy improves local tumour control but has no overall survival (OS) benefit, particularly for patients who responded to CRT (ref.[18]). This finding, in combination with postoperative mortality rate from esophagectomy, also suggests that surgery may be detrimental for patients who achieved pathologic CR after preoperative CRT (ref.[19]).

Taken together, converging evidence reveals that patients undergoing neoadjuvant treatment and showing an objective tumour response have a better prognosis for survival than those undergoing surgery alone. However, only 40-50% of patients respond to neoadjuvant therapy. As a consequence, the patients who do not respond to therapy may be compromised by toxic side effects and delay caused by ineffective chemotherapy or CRT, and potentially even have biologically more aggressive tumours[6]. Therefore, it is desirable to have a diagnostic test that allows noninvasive prediction of response to neoadjuvant therapy so that responders can be differentiated from non-responders.

Conventional structure-based imaging technology, such as computed tomography (CT), endoscopy and endoscopic ultrasonography (EUS), are generally considered inaccurate in predicting response to neoadjuvant treatment, in particular due to their inability to differentiate between a viable tumor and inflammation, edema or fibrosis[20,21]. The functional modality which can detect changes in tissue metabolism which usually precede structural changes, consists of 2-[fluorin-18] fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography (^{18}F-FDG PET) (ref.[22,23]). Current evidence suggest that this method can identify patients who achieve a pathologic response to neoadjuvant treatment prior to surgical resection, as well as being able to predict long-term survival[24-26]. Song et al.[27] previously showed that the pathologic response of initially highly metabolic tumour after preoperative CRT could correlate with the metabolic response. It has not, however, been unequivocally demonstrated whether a complete metabolic response (CMR), evaluated by means of ^{18}F-FDG PET, always reflects a histopathological complete response (CR). SCC and AC of the esophagus demonstrate a characteristically high accumulation of FDG (ref.[28-30]). A number of studies have demonstrated the contribution of ^{18}F-FDG PET in the primary staging of esophageal carcinoma particularly in the detection of distant metastasis[28,31-34]. The potential of this functional method in detecting response to neoadjuvant treatment in a group of patients with upper gastrointestinal malignancy was first published in 1998 (ref.[35]). Subsequent studies on the ability of ^{18}F-FDG PET to identify histopathological responders reached conflicting conclusions[23-27,36-39]. Several others found a correlation between significant reduction of ^{18}F-FDG accumulation in a primary lesions and a significant histopathological tumor reduction[24,25,37,39] in patients with SCC of the esophagus.

The aim of our study was to evaluate the potential of ^{18}F-FDG PET/CT examination carried out both prior to and after neoadjuvant chemoradiotherapy (CRT) for detecting therapeutic response in patients with esophageal carcinoma, to assess whether the level of metabolic response to chemoradiotherapy can predict a complete histopathological response and survival of these patients.

MATERIAL AND METHODS

From August 2006 to January 2010, 82 consecutive patients with biopsy-proven locally advanced squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the middle and distal esophagus were included in the study. As part of staging, all patients underwent endoscopy, EUS, CT and hybrid 2-[fluorin-18] fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography combined with multislice computed tomography (^{18}F-FDG PET/CT). After these diagnostic procedures, all patients underwent neoadjuvant chemoradiotherapy (CRT). Endoscopy and ^{18}F-FDG PET/CT were once again carried out after completion of CRT.

Of the 82 patients who underwent ^{18}F-FDG PET/CT before and after CRT, 39 did not undergo esophagectomy due to patient refusal, poor general condition, disease progression or advanced age. The esophagectomy was performed in 43 patients.

^{18}F-FDG PET/CT

All patients fasted for at least 6 h and the blood glucose levels were measured. If the glucose concentration did not exceed 130 mg/dL, 400 MBq of ^{18}F-FDG per 70 kg of weight were administered intravenously, with the activity applied being recalculated based on the actual weight. Sixty minutes after the administration of ^{18}F-FDG and oral administration of a contrast medium, the PET/CT examination using Siemens Biograph 16 HI-REZ scanner was initiated. Contrast-enhanced multislice CT scans were carried out typically from the skull base to the upper third of the thighs with arms upwards. The lung region was scanned with patients holding their breath in expiration. This was followed by caudocranial PET scanning with iterative reconstruction of the images. Transmission attenuation correction was carried out by CT. For semiquantitative analysis of each lesion showing increased ^{18}F-FDG uptake in the esophagus, the maximal standardized uptake value normalized to the body surface area (SUV_{bsa}max) was computed on the most intense uptake area (graded colour-scaled parametric analysis applied in reconstructed coronal PET image) in accordance with standard formulas.

Neoadjuvant chemoradiotherapy

Neoadjuvant CRT consisted of early radiation with a linear accelerator in the area of the primary tumour and catchment nodes; total radiation was 50 Gy and was applied in 25 fractions of 2 Gy over the course of 5 weeks. 2 cycles of chemotherapy, composed of cisplatinum and fluorouracil, were applied along with radiotherapy; the third cycle of chemotherapy was applied three weeks after completion of radiotherapy. Cisplatinum was applied once a week during the period of radiotherapy in patients with a worse overall state and with SCC. Restaging (endoscopy with biopsy and PET/CT2) was carried out after completion of CRT.

^{18}F-FDG PET/CT assessment of response to neoadjuvant chemoradiotherapy

All FDG-PET/CT images were reviewed and interpreted by two experienced nuclear physicians. The presence of a normal distribution of ^{18}F-FDG at the site of the original pathological FDG-PET finding and even in the case of an abnormal CT finding in an identical localization was considered as a complete metabolic response (CMR). The finding of focal uptake of ^{18}F-FDG was considered as a non-complete metabolic response (NCMR). A diffuse increased uptake of ^{18}F-FDG in the esophagus in the area of radiotherapy was viewed as benign esophagitis. The visual evaluation was always accompanied by a semi-quantitative [SUV_{bsa}max] evaluation. In cases of a negative FDG-PET finding on the pre-operative FDG-PET scans, SUV was uniformly designated as 0.5 of the baseline or background FDG uptake level[19].

Operation and assessment of histopathological response to neoadjuvant chemoradiotherapy

After restaging, all patients underwent esophagectomy. Trans-hiatal laparoscopic exstirpation of the esophagus with gastroplasty and cervical anastomosis from laparotomy and cervical incision were carried out in patients with distal esophageal carcinoma. A lymphadenectomy and pyloromyotomy were part of the surgery. A right-sided thoracoscopic or thoracotomic exstirpation of the esophagus with passage renewal in the same fashion as described in the distal esophagus was performed for carcinomas located in the middle esophagus to an endoscopic tumour distance of 30 cm from the incisors. A classic approach (thoracotomy) was chosen for large tumours with a suspicion of infiltration of surrounding structures.

In each case the histopathological examination of the entire resection specimens were examined for degree of local tumour spread and lymph node metastases. Patients with no residual viable tumour cells in the surgical specimen (pT0N0M0) were classified as having achieved pathologic CR. Patients with macroscopic or microscopic foci of residual tumours were considered to have pathologic RD. A semi-quantitative evaluation was not used.

Statistical analysis

Survival probability analyses were performed using the Kaplan–Meier method. Survival was calculated from the beginning of neoadjuvant chemoradiotherapy (CRT) to the date of death or most recent follow-up. Statistical significance was assessed by the log-rank test. Receiver-operating-characteristic (ROC) analysis was performed to determine an optimal cut-off value of SUVmax reduction from PET/CT1 to PET/CT2 in predicting overall survival [OS]. Variables age, sex, maximum SUV of primary tumour and pre- and post-CRT SUV change were used in Cox regression analyses. Data analysis was performed with the SPSS version 15.0 (SPSS, Chicago, IL). Statistical significance was defined as $P<0.05$.

RESULTS

Forty-three of the total 82 patients with esophageal carcinoma underwent esophagectomy. Nine died as a result of early post-operation complications and were removed from the analyses.

Statistical analyses were carried out on a group of 73 patients (62 men, 11 women, median 58 years, range 34 – 84 years), 24 patients (32.9%) with AC and 49 (67.1%) with SCC of the esophagus.

The median time interval from completion of the neoadjuvant CRT to the PET/CT2 was 42 days (range 21– 56 days).

In the 34 operated patients, 3 (8.8%) were in stage I, 17 (50.0%) in stage II, 11 (32.4%) in stage III and 3 patients (8.8%) in stage IV. Distribution according to histopathological grading in this group was: grade 1 in 16 patients (29.4%), grade 2 in 8 patients (23.5%) and grade 3 in 16 patients (47.1%).

In the 39 non-operated patients, 5 (13.2%) were in stage II, 25 (65.8%) in stage III and 8 patients (21.1%) in stage IV. Histopathological grade 1 was found in 14 patients 36.8%), grade 2 in 7 (18.4%) and grade 3 in 17 (44.7%) patients.

The groups differed significantly in distribution according to stage; the non-operated group were patients with a higher disease stage (P=0.0004, Fisher's exact test) but the difference for histopathological grade was not statistically significant (P=0.825, Fisher's exact test) (table 1).

Operated group

The 34 operated patients consisted of 30 men and 4 women (median 57 years, range 34 - 74 years), 17 (50.0 %) patients had AC and 17 (50%) SCC. The median time interval from completion of neoadjuvant CRT to operation was 43 days (range 8 – 114 days). The mean follow-up was 12.3±6.0 (range 4.4-25.8) months.

A complete metabolic response (CMR) to neoadjuvant CRT was found in 6 patients (17.6%) in a PET/CT2 examination; a complete metabolic response (NCMR) was not achieved in 28 (82.4%) patients.

The median of the SUVmax (SUVmax1) in PET/CT1 examination was 11.3 (range 5.1 – 33.0), in PET/CT2 (SUVmax2) 4.6 (range 2.1 – 10.6).

The median percentage decrease between SUVmax1 and SUVmax2 prior to and after neoadjuvant CRT was -58.4% (range -83.0 to -6.3%).

Table 1. Baseline demographic and clinical characteristics of the entire group of patients with esophageal cancer, groups of operated and non-operated patients (N = 73).

	Whole group	Operated	Non-operated
N	73	34 (46.6%)	39 (53.4%)
Sex			
F	11 (15.1%)	4 (11.8%)	7 (17.9%)
M	62 (84.9%)	30 (88.2%)	32 (82.1%)
Age [yrs]			
median (range)	58.1 (34.0-84.3)	57.0 (34.0-73.8)	60.7 (42.5-84.3)
Type of cancer			
AC[1]	24 (32.9%)	17 (50.0%)	7 (17.9%)
SCC[2]	49 (67.1%)	17 (50.0%)	32 (82.1%)
Pathologic staging			
Stage I	3 (4.1%)	3 (8.8%)	0
Stage II	22 (30.1%)	17 (50.0%)	5 (13.2%)
Stage III	36 (49.3%)	11 (32.4%)	25 (65.8%)
Stage IV	5 (6.8%)	0	5 (13.2%)
Stage IVA	7 (9.6%)	3 (8.8%)	4 (7.8%)
Histopathologic grading of cancer			
G1	24 (33.3%)	10 (29.4%)	14 (36.8%)
G2	15 (20.8%)	8 (23.5%)	7 (18.4%)
G3	34 (45.9%)	16 (47.1%)	18 (44.8%)

[1]AC = adenocarcinoma, [2]SCC=squamous cell carcinoma

Table 2. ^{18}F-FDG PET/CT and histopathologic response.

	Operated	Non-operated
N	34	39
Time from CRT[1] to PET/CT2[2] median (range) [d]	42 (21-56)	36 (23-50)
PET/CT2		
CMR[3]	6 (17.6%)	12 (30.8%)
NCMR[4]	28 (82.4%)	27 (69.2%)
SUVmax1[5] median (range)	11.3 (5.1-33.0)	12.0 (4.5 – 25.0
SUVmax2[6] median (range)	4.6 (2.1-10.6)	3.4 (1.4 -16.3)
ΔSUVmax [%][7] median (range)	-58.4 (-83.0 - -6.3)	-65.8 (-92.9- +15.4)
Histopathol. response		
CR[8]	7 (20.6%)	
RD[9]	27 (79.4%)	

[1]CRT = chemoradiotherapy; [2]PET/CT2 = ^{18}F-FDG PET/CT before CRT;
[3]CMR = complete metabolic response; [4]NCMR = non-complete metabolic response;
[5]SUVmax1 = maximal standardised uptake value in PET/CT examination before CRT;
[6]SUVmax2 = maximal standardised uptake value in PET/CT2 examination after CRT
[7]ΔSUVmax [%] = percentual change SUVmax from SUVmax1 to SUVmax2;
[8]CR = complete histopathologic response; [9]RD = histopathologic residual disease

The median OS for operated patients from initiating neoadjuvant CRT was 17.1 months, 95%CI: 12.9 – 21.3 months.

A histopathological complete response (CR) to CRT was found in 7 operated patients (20.6%), while RD was determined in 27 patients (79.4%).

The correspondence of findings with PET/CT2 examination (CMR/NCMR) and histopathological examination (CR/RD) was average (coefficient AC1 = 0.532). The sensitivity, specificity, accuracy, PPV and NPV for predicting CR by means of the CMR finding on PET/CT2 examination was 14.3%, 81.5%, 67.6%, 16.7% and 78.6%.

The median decrease in SUVmax in patients with histopathological CR was -64.5% (range -21.9% to -79.7%) while the median decrease in SUVmax in patients with RD was -57.8% (range -6.3% to -83.0%). The difference was not statistically significant (Mann-Whitney test, *P*=0.383).

According to the Cox regression analysis, change in SUVmax in % (RR=1.080) was a significant predictor of survival and exitus in operated patients. Decrease in SUV by less than 1% was connected with increased risk of exitus by 1.08x, 95%CI: 1.044 – 1.116.

The ROC analysis yielded an optimal cut-off value of 62.4% for SUVmax reduction from PET/CT1 to PET/CT2 in predicting OS. In the case of SUVmax2 reduction ≥ 62.4%, the overall survival could be predicted with a sensitivity, specificity, accuracy, and a positive and negative predictive value of 66.7%, 60.7%, 61.8%, 26.7% and 84.5%, respectively. The Kaplan–Meier survival analyses showed a significantly longer median overall survival in patients with SUVmax2 reduction ≥ 62.4% (log-rank test, *P*=0.0002, Fig. 1).

The average OS for operated patients with esophageal carcinoma histopathological grade 1 was 22.1 months, 95% CI: 18.6–25.5 months, the median survival was 21.0 months, 95% CI: 17.5–24.5 months. The average OS of operated patients with grade 2 was 16.4 months, 95% CI: 14.4-18.5 months, the median survival was 15.2 months, 95%CI: 15.1-15.3 months and the mean OS of operated patients with grade 3 was 7.0 months, 95% CI: 6.0 - 8.1 months, the median survival was 6.2 months, 95% CI: 5.2-7.3 months. There was a highly significant difference in OS for different histopathological grades (log-rank test, *P*<0.0001, Fig. 2).

Non-operated group

The 39 non-operated patients consisted of 32 men, 7 women (median age 61 years, range 43 - 84 years), 7 (17.9 %) had AC and 32 (82.1%) had SCC. The mean follow-up period was 14.8±8.9 (range 3.6-41.0) months.

The complete metabolic response (CMR) after neoadjuvant CRT was found in 12 cases (30.8%) in the PET/CT2 examination while the metabolic response was incomplete (NCMR) in 27 patients (69.2%).

On PET/CT1 examination, the median of SUVmax1 was 12.0 (range 4.5 – 25.0), SUVmax2 3.4 (range 1.4 – 16.3).

The median change in SUVmax1 and SUVmax2 prior to and after neoadjuvant CRT was 65.8% (range -92.0 to + 15.9%).

The median OS was 13.5 months, 95% CI: 4.4 – 22.7 months.

According to Cox´s regression analysis, PET/CT2 (RR=4.377) and gender of the patient (RR=3.089) were significant predictors of OS and exitus. The results of PET/CT2 = NCMR increased the risk of exitus by 4.38x, 95% CI: 1.48 – 12.92. The risk of exitus of non-operated women was 3.09 x higher than of non-operated men, 95% CI: 1.03 – 9.24.

The average OS in non-operated patients with grade 1 was 31.2 months, 95% CI: 25.6 – 36.8 months (the median survival cannot be estimated). The mean OS of patients with grade 2 was 13.1 months, 95% CI: 12.3-13.9 months, the median survival was 13.0 months, 95% CI: 11.5 – 14.6 months. The mean OS of non-operated patients with grade 3 was 8.6 months, 95% CI: 7.2 – 10.1 months, the median survival was 8.2 months, 95% CI: 7.3 – 9.1 months. The OS of non-operated patients was significantly different in relation to histopathological grading (log-rank test, *P*<0.0001, Fig. 3).

A comparison of some parameters of the groups of operated and non-operated patients

The period of OS in operated and non-operated patients in the evaluated group of 73 patients did not differ statistically significantly (log-rank test *P*=0.595, Kaplan-Meier analysis, Fig. 4). The average period of OS in non-operated patients with CMR was 27.9 months, 95% CI: 19.6 -36.1 months, median survival was 22.3. The average period of OS in operated patients with CMR was 18.7 months, 95%CI: 11.8 – 25.6 months, the median survival was 15.2 months, 95% CI: 15.1-15.3 months. The difference in survival of both groups was not statistically significant (log-rank test, *P*=0.473. Fig. 5).

A significant dependence (Fisher's exact test, *P*=0,009) was determined between the histopathological grade of esophageal carcinoma and the metabolic response (^{18}F-FDG-PET/CT). Significantly more metabolical respondents were in the group of patients with grade 2 (46.7%) in comparison with the group of patients with grade 3 (9.1%). The results are summarized in Table 2.

DISCUSSION

We evaluated the ^{18}F-FDG PET/CT-determined metabolic response after neoadjuvant CRT as a marker of prediction of histopathological response and survival period in a group of 34 patients with operable esophageal carcinoma (17 SCC and 17 AC). The median time interval after completion of CRT to PET/CT2 was 42 days (range of 21– 56 days).

The level of correspondence of the findings with PET/CT2 examination (CMR/NCMR) and histopathological examination (CR/RD) was average (coefficient AC1 = 0.532). No statistically significant difference in the per-

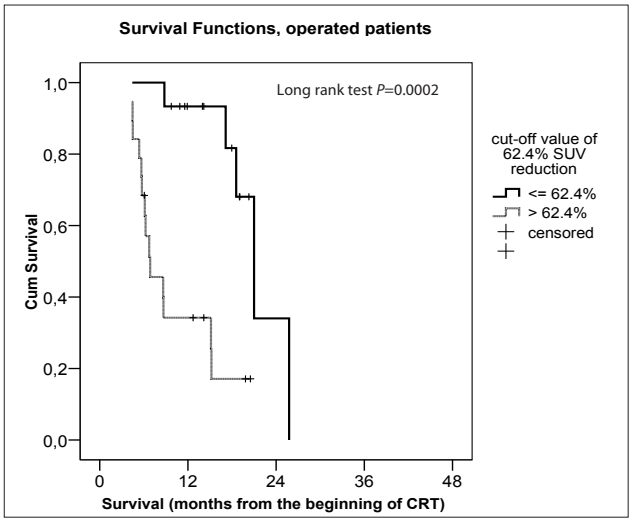

Fig. 1. The Kaplan–Meier survival probability analysis shows significantly longer median OS in the group of operated patients (N = 34) with SUVmax reduction > 62.4% (log-rank test, *P*=0.0002).

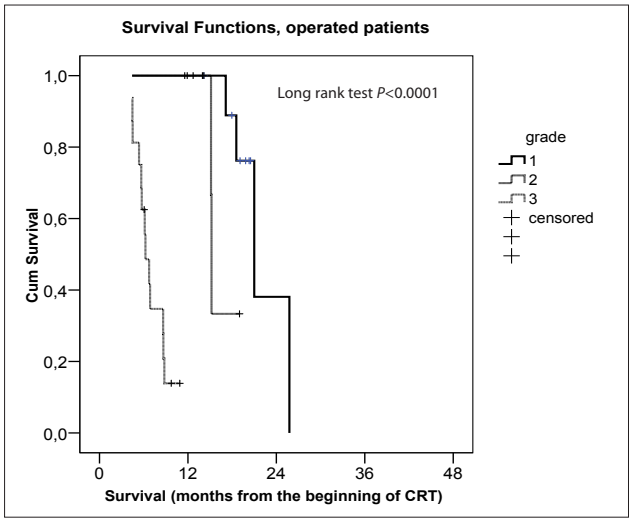

Fig. 2. The Kaplan–Meier survival probability analysis shows a significant difference in OS in the group of operated patients (N = 34) in relation to histopathological grading (log-rank test, *P*<0.0001).

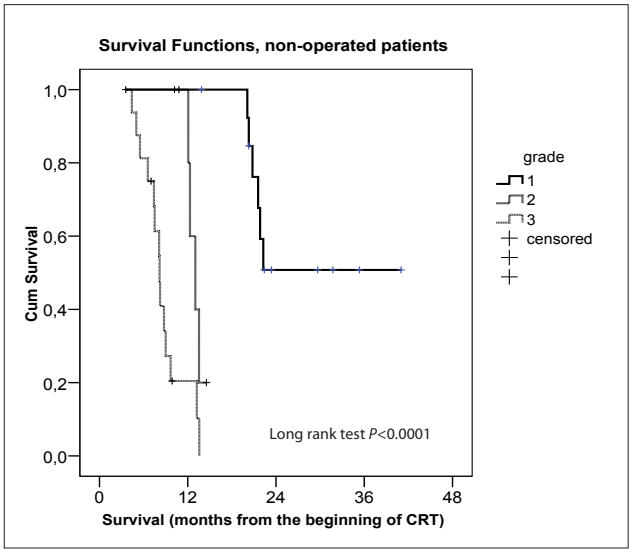

Fig. 3. The Kaplan–Meier survival probability analysis shows a statistically significant difference in OS in the group of non-operated patients (N = 39) in relation to histological grading (log-rank test, *P*<0.0001).

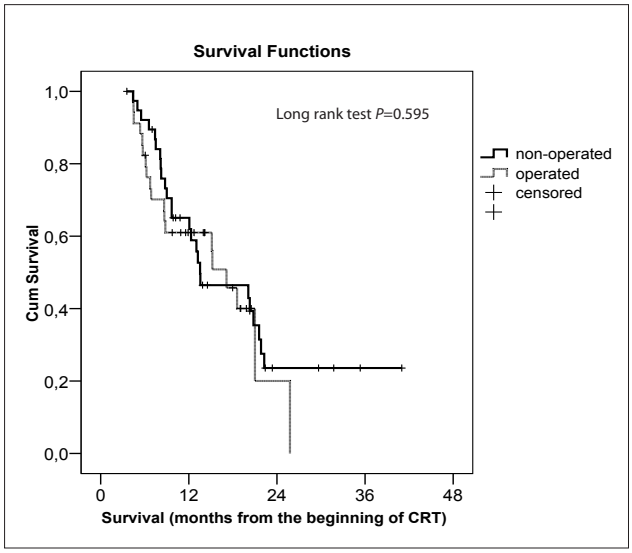

Fig. 4. OS of operated and non-operated patients (N = 73) did not significantly differ (Kaplan-Meier survival probability analysis, log-rank test, *P*=0.595).

centage decrease of SUVmax2 after chemoradiotherapy (Mann-Whitney test, *P*=0.383) was discovered between patients with a histopathological CR and RD.

Smithers et al.[40] also failed to find a correlation between ^{18}F-FDG PET findings after neoadjuvant chemotherapy and CRT and a histopathological response in a group of 45 patients with AC of the esophagus. A correlation was only determined when evaluating an entire group of patients treated with neoadjuvant therapy, but not, however, when evaluating chemotherapy and CRT individually. The authors pointed out the possible connection between this result and the histological type of esophageal carcinoma, as studies with groups of patients with SCC of the esophagus had a significant correlation between the histopathological response and the determined metabolic (^{18}F-FDG PET) response. Brücher et al.[24] have published results on 27 patients with SCC of the esophagus. A threshold of 52% mean SUV divided the histopathological responders from nonresponders with a sensitivity of 100% and specificity of 55%. Flamen et al.[25] showed in a study of 36 patients with esophageal cancer (27 cases of SCC and 9 of adenocarcinoma) that a decrease of more than 80% in the tumour-to-liver uptake ratio 3-4 wk after completion of neoadjuvant chemoradiotherapy predicted a histopatological response with a sensitivity of 71% and a specificity of 82%. Kim et al.[19] published results of 62 patients with SCC. A complete metabolic response (reduction of maximum SUV > 80%)

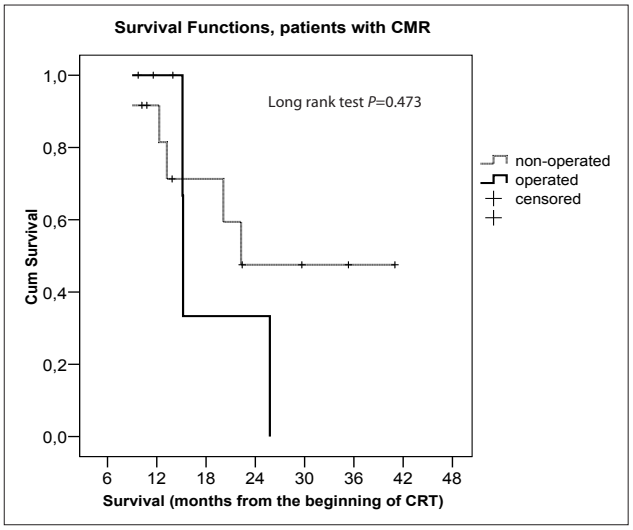

Fig. 5. The Kaplan–Meier survival probability analysis did not indicate a statistically significant difference in OS in patients with complete metabolic response (CMR) in the group of non-operated (N = 12) and operated (N = 6) – log-rang test, *P*=0.473.

after completion of therapy correlated significantly with a histopathological response. However, in another study, by Cerfolio et al.[41], with a prevalence of patients with AC of the esophagus (41 cases of adenocarcinoma and 7 of SCC) ^{18}F-FDG PET/CT predicted a complete histopatological response with a sensitivity of 87%, specificity of 88%, and an accuracy of 88%. The correlation between the ^{18}F-FDG PET response after neoadjuvant chemoradiotherapy and the histopathological response was, however, also not determined in additional studies[23,33,38].

The authors Port et al.[42] determined the ability of ^{18}F-FDG PET to predict a clinical and pathological response and survival in a group of 62 patients with esophageal carcinoma (51 AC, 11 SCC). Apart from determination of a significantly improved prediction of disease-free survival in patients with a decrease in SUVmax by 50%, they also discovered that the complete absence of residual uptake of ^{18}F-FDG need not necessarily be connected with a complete histopathological response. Swisher et al.[23] in a group 103 patients (90 AC, 13 SCC) demonstrated that ^{18}F-FDG PET failed to rule out residual microscopic disease, because ^{18}F-FDG uptake in the tumour bed did not differ between patients with no residual viable tumour cells and patients with up to 10% viable tumour cells. A range of similar studies[23,25,36,40,43] employed the semi-quantiative Mandard's or Becker's classifications and their modifications[44,45] for histopathological evaluation of response to neoadjuvant therapy, where the complete histopathological response was considered either the complete absence or presence of less than 10% viable tumour cells in the resection specimens. In our study, we employed qualitative evaluation of the resected specimens where only complete absence of viable tumour cells was considered a complete histopathological response (CR) and residual disease (RD) was every histopathological finding containing viable tumour cells in any amount including smaller than 10%. It cannot thereby be fully ruled out that a less significant correlation between ^{18}F-FDG PET metabolic and histopathological response to CRT in our study could also have been influenced by this fact. A negative factor preventing the formulation of definitive conclusions in connection with the majority of the above-cited works could also be the limited number of patients in the groups.

Krause et al.[6] in their review work evaluating the importance of ^{18}F-FDG PET and ^{18}F-FDG PET/CT examinations for evaluation of response to treatment of esophageal carcinoma state that most studies assessing a late response to neoadjuvant therapy for esophageal cancer (3-6 weeks after completion of neoadjuvant therapy) have shown that ^{18}F-FDG PET signal after neoadjuvant therapy correlates with histopathological response and long term prognosis. However, the main drawback of late assessment is that it does not allow therapy modification for patients not responding to it. One might speculate whether patients benefit from a change in therapy after a late response assessment. The authors emphasize that clinical trials are necessary to answer the question of whether further neoadjuvant or adjuvant chemotherapy or chemoradiation for ^{18}F-FDG PET non-responders improves clinical outcome. Therefore, an early assessment of response to therapy by ^{18}F-FDG PET has been proposed as a surrogate marker for predicting response and potentially allowing therapy modification, although is not yet established in clinical routine practice. Weber et al.[36] reported a histopathological response prediction with a sensitivity of 93% and a specificity of 95% in 40 patients with AC of the esophagogastric junction undergoing neoadjuvant chemotherapy. ^{18}F-FDG PET images were performed pre-treatment and 14 days after commencement of neoadjuvant treatment in contrast to the preoperative ^{18}F-FDG PET performed some weeks after the conclusion of treatment. Thus the timing of the scan may be critical, with earlier scans during therapy providing a clinical guide in patients with esophageal cancer. Similar results with early (2 weeks) assessment of pathologic response to neoadjuvant chemotherapy of locally advanced adenocarcinoma of the esophagus and esophagogastric junction has been reported in the prospective unicenter MUNICON study[46].

According to the results of Cox's regression analysis the parameter of change in SUVmax in % (RR=1.080) and the histopathological grade of the tumour (log-rank test, $P<0.0001$) were significant predictors of survival in our group of 34 operated patients. Tumour grading was also a significant predictor of the overall survival in the group of 39 non-operated patients (log-rank test, $P<0.0001$).

In predicting OS, a ROC analysis yielded an optimal cutoff value of 62.4% SUVmax reduction from PET/CT1 to PET/CT2. Kaplan–Meier survival probability analyses showed significantly longer median survival time in patients with SUVmax reduction ≥ 62.4% (log- rank test, $P=0.0002$). These results are in accordance with the majority of similarly designed studies[19,23-25,39,42,47].

The survival of operated (34) and non-operated (39) patients in our set of 73 patients did not differ signifi-

cantly. Despite the fact that the median of OS patients with CMR in both groups was relatively different on average, the difference is not significant in light of the small number of patients (log-rank test, P=0,473).

CONCLUSION

In conclusion, it can be stated that in our group of a mixed population of operated patients with SCC and AC of the esophagus we did not find, in contrast to several similar studies, a robust correlation between ^{18}F-FDG metabolic response after neoadjuvant CRT and histopathological response, and the contribution ^{18}F-FDG PET/CT as a marker of the potential result of CRT cannot at present be considered unequivocal. In light of the non-homogenous character of the examining protocols, the varied regimens of neoadjuvant chemotherapy and finally the small number of treated patients in the compared groups, further studies with a larger number of patients and with standardized algorithms of protocols will be necessary in order to reach definitive conclusions. In the group of operated patients, ^{18}F-FDG PET/CT examination predicted a significantly longer period of survival in patients with a reduction of SUVmax ≥ 62.4%. This result is in accordance with the majority of published works. Surprisingly, a statistically significant difference in overall survival between operated and non-operated patients was not demonstrated.

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REFERENCES

1. Parkin DM. International variation. Oncogene 2004;23:6329-40.
2. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10-30.
3. Reis L, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK, eds. SEER Cancer Statistic Review, 1973-97. Bethesda, MD: National Cancer Institute, 2000.
4. Berrino F, Capocaccia R, Esteve J, Gatta G, Hakulinen T, Micheli A, Sant M., Verdacchia A, eds. Survival of Cancer Patients in Europe: the EUROCARE–2 Study. IARC Scientific Publications No.51, Lyon: IARC, 1999.
5. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.
6. Krause BJ, Herrmann K, Wieder H, zum Buschenfelde CM. ^{18}F-FDG PET and ^{18}F-FDG PET/CT for Assessing Response to Therapy in Esophageal Cancer. J Nucl Med 2009;50:89S-96S.
7. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727-34.
8. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 2007;8:226-34.
9. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
10. Walsh TN, Noonan M, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462-7.
11. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161-7.
12. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patiens with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305-13.
13. Lee JL, Park SI, Kim SB, Jung HY, Lee GH, Kim JH, Song HY, Cho KJ, Kim WK, Lee JS, Kim SH, Min YI. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol 2004;15:947-54.
14. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, Wang H, Goldberg M. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 2005;23:4330-7.
15. Kim SB, Park SI, Kim JH. A phase II trial of preoperative one cycle of induction chemotherapy [capecitabine(CAP), CDDP] followed by concurrent chemoradiation (CRT) in patients with resectable esophageal cancer. J Clin Oncol 2005;23:4063[abstract].
16. Heath EI, Burtness BA, Heitmiller RF, Salem R, Kleinberg L, Knisely JP, Yang SC, Talamini MA, Kaufman HS, Canto MI, Topazian M, Wu TT, Olukayode K, Forastiere AA. Phase II evaluation of preoperative chemoradiation and postoperative adjuvant chemotherapy for squamous cell and adenocarcinoma of the esophagus. J Clin Oncol 2000;18:868-76.
17. Ponsner MC, Forastiere AA, Minsky BD. Cancer of the esophagus. In: Devuta TV, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 7th ed. Philadelphia (PA): Lippincot Williams and Wilkins 2005, p.861-909.
18. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310-7.
19. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Park SI, Kim YH, Song HY, Shin JH, Jung HY, Lee GH, Choi KD, Cho KJ, Kim JH. Value of complete metabolic response by ^{18}F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer 2007;43:1385-91.
20. Jones DR, Parker LA, Detterberk FC, Egan TM. Inadequacy of computed tomography in assessing patients with esophageal carcinoma after induction chemoradiotherapy. Cancer 1999;85:1026-32.
21. Beseth BD, Bedford R, Isacoff WH, Holmes EC, Cameron RB. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. Am Surg 2000;66:827-31.
22. Rigo P, Paulus P, Kaschten BJ, Hustinx R, Bury T, Jerusalem G, Benoit T, Foidart-Willems J. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. Eur J Nucl Med 1996;23:1641-74.
23. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, Komaki R, Macapinlac H, Munden RF, Putnam JB, Rice D, Smythe WR, Vaporciyan AA, Walsh GL, Wu TT, Roth JA. Utility of PET, CT and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg 2004;78:1152-60.
24. Brücher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233:300-9.
25. Flamen P, Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, De Leyn P, Van Raemdonck D, De Wever W, Ectors N, Maes A, Mortelmans L. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 2002;13:361-8.
26. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, Melin SA, Lovato J, Oaks T, Blackstock AW. Predictive value of 18-fluoro-deoxy-

glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg 2006;243:472-8.
27. Song SY, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, Song HY, Cho KJ, Ahn SD, Lee SW, Shin SS, Choi EK. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys 2005;63:1053-9 .
28. Mc Ateer D, Wallis F, Couper GW, Norton M, Welch A, Bruce D, Park K, Nicolson M, Gilbert FJ, Sharp P. Evaluation of 18F-FDG positron emission tomography in gastric and oesophageal cancer. Br J Radiol 1999;72:529.
29. Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Sundaresan SR, Patterson GA, Cooper JD. Staging of esophageal cancer with 18F-fluorodeogyglucose positron emission tomography. Am J Roenthenol 1997;168:417-24.
30. Cook G, Taylor H, Mason R, Rankin S, Fogelman I. A comparison of 18FDG PET and CT in the staging of oesophageal carcinoma. J Nucl Med 1997;38(Suppl):247. Abstract 1043.
31. Block MI, Patterson GA, Sundaresan RS, Bailey MS, Flanagan FL, Dehdashti F, Siegel BA, Cooper JD. Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thoracic Surg 1997;64:776-7.
32. Luketich JD, Friedman DM, Weigel TL, Methan MA, Keenan RJ, Townsend DW, Meltzer CC. Evaluation of distant metastases in oesophageal cancer: 100 consecutive positron emission tomography scans. Ann Thoracic Surg 1999;68:1133-6.
33. Flamen P, Lerut A, Van Cutsen E. Utility of positron emission tomography for staging of patiens with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202-10.
34. Kneist W, Schreckenberger M, Bartenstein P, Menzel C, Oberholzer K, Junginger T. Prospective evaluation of positron emission tomography in the preoperative staging of esophageal carcinoma. Arch Surg 2004;139:1043-9.
35. Couper GW, McAteer D, Wallis F, Norton M, Welch A, Nicolson M, Park KG. The detection of response to chemotherapy using positron emission tomography in patients with oesophageal and gastric cancer. Br J Surg 1998;85:1403-6.
36. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschläger G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2002;19:3058-65.
37. Kato H, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Masuda N, Fukuchi M, Manda R, Tsukada K, Oriuchi N, Endo K. Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. Am J Surg 2002;184:279-83.
38. Brink I, Hentschel M, Bley TA, Walch A, Mix M, Kleimaier M, Moser E, Imdahl A. Effects of neoadjuvant radio-chemotherapy on 18F-FDG PET in esophageal carcinoma. EJSO 2004;30:544-50.
39. Downey RJ, Akhurst T, Ilson D, Ginsberg R, Bains MS, Gonen M, Koong H, Gollub M, Minsky BD, Zakowski M, Turnbull A, Larson SM, Rusch V.khurst T, Ilson D. Whole body 18FDG-PET and response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003;21:428-32.
40. Smithers BM, Couper GC, Thomas JM, Wong D, Gotley DC, Martin I, Harvey JA, Thomson DB, Walpole ET, Watts N, Burmeister BH. Positron emission tomography and pathological evidence of response to neoadjuvant therapy in adenocarcinoma of the esophagus. Deseases of the Esophagus 2008;21:151-8.
41. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle asporation, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1241-2.
42. Port JL, Lee PC, Korst RJ, Liss Y, Meherally D, Christos P, Mazumdar M, Altorki NK. Positron emission tomographic scanning predicts survival after induction chemotherapy for esophageal carcinoma. Ann Thorac Surg 2007;84:393-400.
43. Ott K, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, Wieder H, Fink U, Schwaiger M, Siewert JR. Metabolic imaging predicts response, survival and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol 2006;24:4692-8.
44. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumour regression after preoperative chemoradiotherapy of esophageal carcinoma: clinicopathologiocal correlations. Cancer 1994;73:2580-686.
45. Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 2003;98:1521-30.
46. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the esopgagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8:797-805.
47. Higuchi I, Yasuda T, Yano M, Doki Y, Miyata H, Tatsumi M, Fukunaga H, Takiguchi S, Fujiwara Y, Hatazawa J, Monden M. Lack of fludeoxygflucose F18 uptake on posttreatment positron emission tomography as a signifiant predictor of survival after subsequens surgery in multimodality treatment for patients with locally advanced esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg 2008;136:205-12.