Original article

Nuclear Medicine Communications

^{18}F-fluorodeoxyglucose PET/computed tomography and risk stratification after neoadjuvant treatment in esophageal cancer patients

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Objectives **The aim of the study was to evaluate the prognostic value of ^{18}F-fluorodeoxyglucose PET/computed tomography (CT) after neoadjuvant therapy (NAT) in locally advanced esophageal cancer (EC) patients.**

Materials and methods **We recruited 79 EC patients from a sample of 210 who underwent ^{18}F-fluorodeoxyglucose PET/CT after NAT and who did not have evidence or suspicion of distant metastases. All patients were followed up for a median period of 18 months (range: 2–53 months) from nuclear imaging. PET/CT findings were correlated with surgical management and long-term prognosis. The χ^2-test was used for categorical variables and the Student *t*-test for continuous data. Survival curves were computed using the Kaplan–Meier method. A *P* value less than 0.05 was considered statistically significant.**

Results **Twenty patients (25.3%) had negative PET/CT and 59 (74.7%) had positive PET/CT results after NAT. Of the 20 patients with negative PET/CT results, eight underwent radical-intent surgery and 12 did not, whereas of the 59 patients with positive PET/CT 44 were scheduled for surgery and 15 were not ($P<0.05$). On follow-up, 38 patients were seen to be disease free, whereas 23 had relapsed and 15 had died. The overall survival was different between patients with negative PET/CT and those with positive PET/CT scans (98 vs. 40%; $P=0.019$). Event-free survival was higher in patients with negative PET/CT than in those with positive PET/CT after NAT (78 vs. 0%; $P=0.003$). Considering patients with positive PET/CT, in the nonsurgical group only three patients were alive without evidence of disease, whereas in the surgical group 19 patients were disease free (20 vs. 46%; $P<0.001$).**

Conclusion **PET/CT is able to stratify the recurrence risk of EC patients. After a median follow-up period of 18 months, 91% of patients with negative PET/CT scans who did not undergo surgery were seen to be disease free. A positive PET/CT after NAT should be followed by surgery for improving event-free survival. *Nucl Med Commun* 35:160–168 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Nuclear Medicine Communications 2014, **35**:160–168

Keywords: esophageal cancer, ^{18}F-fluorodeoxyglucose PET/computed tomography, prognosis

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Received 3 September 2013 **Revised** 4 October 2013
Accepted 7 October 2013

Introduction

Esophageal cancer (EC) is the third most common type of cancer of the gastrointestinal tract and is characterized by a poor prognosis. It is the seventh deadliest cancer in the world, with a 5-year mortality rate close to 77% [1]. Staging of EC patients has recently been upgraded to include 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET integrated with computed tomography (CT) into the previous algorithm comprising CT and endoscopic ultrasound (EU) [2]. According to data from the literature, ^{18}F-FDG PET seems to be the best available imaging modality for response assessment of neoadjuvant therapy (NAT) in EC [3]. However, for locally advanced EC the outcomes are poor because most of the patients experience recurrence or death within 3 years of diagnosis. The 5-year overall survival (OS) in this latter subset is ~20% [4]. Therefore, it is necessary to find a reliable prognostic tool for locally advanced EC patients that can accurately evaluate the rate of response to NAT and thus indicate the best therapeutic strategy and result in a better prognosis.

Most studies showed that pretreatment ^{18}F-FDG uptake and postneoadjuvant ^{18}F-FDG uptake as absolute values are predictors of survival in univariate analysis [5–10]. Moreover, early decrease (after 14 days) in ^{18}F-FDG uptake during NAT is predictive of response and survival in most studies [10–17]. In the majority of reports, a late maximum standardized uptake value (SUV_{max}) reduction between 50 and 80% was correlated with better disease-free survival/OS [16,18–21]. However, a low SUV after completion of NAT was predictive of response and survival in only one study [22]. The main drawback of late assessment is that it does not allow the therapy to be

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DOI: 10.1097/MNM.0000000000000035

modified for patients not responding to it. Nevertheless, it could correctly guide the surgical approach.

The aim of our study was to evaluate whether ^{18}F-FDG PET/CT performed after NAT in locally advanced EC patients, independently from surgery, may provide reliable prognostic information.

Materials and methods

Design and study population

From January 2008 to June 2012, 210 patients with locally advanced EC underwent PET/CT at our center for the evaluation of response to NAT. Out of 210 patients, 131 had distant progression of disease during NAT. Therefore, from this sample we retrospectively reviewed PET/CT scans of 79 patients. The median time between the end of NAT and PET/CT was 2.4±1.9 months. Some patients in this report ($n = 29$) had already been included in our previous study, which had assessed the impact of ^{18}F-FDG PET/CT on the staging and prognosis of EC patients [23]. The patients' characteristics are reported in Table 1.

^{18}F-fluorodeoxyglucose PET/computed tomography

The enrolled patients fasted for at least 6 h before undergoing the PET/CT examination. After the evaluation of blood glucose levels, measured with a dedicated stick (acceptable value $\leq$ 130 mg/dl), 3 MBq of ^{18}F-FDG per kilogram of body weight was injected. Patients rested in a comfortable room and images were acquired 60 min after administration of tracer. Whole-body ^{18}F-FDG PET/CT was performed using a dedicated PET/CT scanner (Biograph 16; Siemens Medical Solutions, Chicago, Illinois, USA). The PET component is a high-resolution scanner with a spatial resolution of 4.7 mm and has no septa, thus allowing only three-dimensional acquisitions. The CT portion of the scanner is the Somatom Sensation 16 slices (Siemens Medical Solutions). Together with the PET system, the CT scanner is used both for attenuation correction of PET data and for anatomical localization of ^{18}F-FDG uptake in PET images. Transmission images were performed using the followed parameters: 100 kV, 80 mA, 1.35 : 1 pitch, 0.5-s rotation, and a detector configuration of 8×1.25 mm. Emission images ranging from the proximal femur to the base of the skull were acquired for 2–3 min (based on the body weight) per acquisition field of view. Acquired images were reconstructed using the attenuation weighted-ordered subset expectation maximization iterative reconstruction, with two iterations and eight subsets. The Gaussian filter was applied to the images after reconstruction along the axial and transaxial directions. The data were reconstructed over a 128×128 matrix with 5.25 mm pixel size and 2 mm slice thickness. The images were displayed on three planes (coronal, transverse, and sagittal).

Table 1 Characteristics of the patient population

Characteristics	*N*
Age (mean±SD) (years)	61±10
Sex [*n* (%)]	
Male	61 (77.2)
Female	18 (22.8)
Histology [*n* (%)]	
SCC	41 (51.9)
Adenocarcinoma	35 (44.3)
Others	3 (3.8)
Surgery [*n* (%)]	
No	27 (34)
Yes	52 (66)
Complete response to NAT [*n* (%)]	
No	54 (68)
Yes	25 (32)
ypTNM [*n* (%)]	
ypT0N0M0	12 (15)
ypT + N0M0	18 (23)
ypT + N + M0	17 (22)
ypT + N + M +	5 (6)
NA	27 (34)
NAT regimen [*n* (%)]	
CHT	21 (27)
CHT + RT	58 (73)
Type of NAT regimen [*n* (%)]	
Cisplatinum + FU	56 (70)
Cispatinum + paclitaxel	5 (6)
ECF	9 (11)
Folfox + cetuximab	1 (1)
TCF	8 (10)

CHT, chemotherapy; ECF, epirubicin, cisplatinum, and continuous infusion of 5-fluorouracil; FU, fluorouracil; NA, not available; NAT, neoadjuvant therapy; RT, radiation therapy; SCC, squamous cell carcinoma; TCF, taxol + cisplatinum + fluorouracil.

PET/computed tomography imaging analysis

PET/CT images were first analyzed visually. The scan was considered negative when no pathological ^{18}F-FDG uptake in any of the explored body sites was present, whereas it was classified as positive if a pathological uptake at the esophageal level and/or at locoregional lymph nodes was recognized. Second, a semiquantitative analysis was performed in the case of a positive scan for each lesion site. Maximum/average/minimum SUV and total lesion glycolysis (TLG) were computed. SUV and TLG were calculated according to the following formulas:

$$K\,(\mathrm{SUV}) = K\left(\mathrm{Bq/cm^3}\right) \times [\mathrm{Weight\,(kg)/dose\,(Bq)}] \times 1000\mathrm{cm^3/kg}$$

where K (Bq/cm^3) is the volume pixels calibrated and scaled; dose (Bq) the injected dose in becquerels and corrected for the decay time.

$$\mathrm{TLG} = \left(\mathrm{SUV_{avg}}\right) \times (\mathrm{volume})$$

For the semiquantitative assessment of pathological findings we used a region of interest manually drawn using an $\mathrm{SUV_{max}}$ cutoff of 2.0 or higher. Two nuclear medicine specialists independently performed the analysis of PET/CT images, and in the case of discordance a third nuclear medicine specialist gave the consensus. All metabolic evaluations were blindly made from previous conventional imaging (CI) studies, such as diagnostic CT. To reduce errors in SUV measurements, standard calibration as recommended by the vendor was performed: germanium-68 phantom cylinder calibration daily uniformity/reference

scan, two-dimension and three-dimension normalization, single-attenuation calibration, and monthly detector calibrations.

PET/computed tomography assessment of neoadjuvant therapy

On the basis of PET/CT results, patients were considered metabolic responders (MRs) in the case of a negative scan and as nonmetabolic responders (NMRs) in the case of a positive scan [24]. The metabolic PET/CT assessment of response therapy (mTNM) was compared both with the clinical staging obtained on CI (ycTNM) and with the histopathologic response obtained from the surgical specimen (ypTNM) or biopsy from the EU, according to the seventh edition of the American Joint Committee on Cancer (AJCC).

Pathological response to treatment

The scoring system applied to evaluate the evidence of histopathological response was the Mandard Tumour Regression Grade (TRG) of surgical specimens. Patients with a TRG score of 1 or 2 were considered as having a significant response; patients with all other TRG scores (scores 3–5) were considered as nonresponders, including those with progression and stable disease.

Follow-up

The follow-up data of enrolled patients were obtained by telephone interviews conducted from 1 to 13 December 2012 by a researcher blinded to the imaging results. The information was confirmed by consulting medical archives. To determine follow-up time, the date of the last examination or consultation was used. Defined events included all-cause death and recurrence of disease. All-cause death was confirmed by review of the death certificate, hospital chart, or physician's records.

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical data as percentage. Differences between groups were assessed using the unpaired Student *t*-test for continuous data and the χ^2-test or Fisher test for proportions, as appropriate. Event-free survival (EFS) and OS were defined as the length of time from the date of PET/CT scan to relapse or death and to death alone from any cause, respectively. Survival curves were generated using the Kaplan–Meier method and compared using the log rank test. Univariate and multivariate Cox proportional hazard regression analyses were adopted to identify independent predictors of events and OS [25,26]. Variables were selected with entry and retention set at a significance level of 0.2. Incremental value of ^{18}F-FDG PET/CT over clinical and therapeutic parameters in the prediction of events was evaluated with a Cox proportional hazard model in a stepwise manner. The incremental prognostic value was assessed by considering, in hierarchical order, clinical and therapeutic parameters (age, male sex, histology, surgery, and response to therapy), visual PET/CT assessment (normal and abnormal scan), and semiquantitative PET/CT data (SUV_{max}, SUV_{min}, SUV_{avg}, and others).

Separate models were created for all-cause mortality and events. At each step increment in information of the model (increase in global χ^2) was considered significant when the log likelihood difference adjusted for differences in degrees of freedom associated with each model had a P value less than 0.05. Statistical analyses were performed using Advanced Models 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Evaluation of response to treatment

All 79 recruited patients at the end of NAT were restaged by a multidisciplinary team with CI and with PET/CT for assessing the indication to a radical surgical treatment. On the basis of both clinical status and conventional staging, the medical staff scheduled 52/79 (67.1%) patients for surgery, but not the remaining 27 (32.9%). According to PET/CT findings (that is, mTNM) 20 patients were classified as MRs (25.3%) and 59 patients as NMRs (74.7%). Twelve out of 20 MR patients (60%) who showed a cervical and superior thoracic primary tumor were not scheduled for surgery. In contrast, 44 NMR patients (74%) underwent radical surgery. Histopathologic tumor response and PET/CT findings were significantly different between surgical and nonsurgical patients (all $P < 0.05$). The data are shown in Table 2. Moreover, as illustrated, SUV_{max}, SUV_{min}, and SUV_{avg} were significantly higher in the surgical group compared with the nonsurgical group (6.41 ± 5.38 vs. 3.97 ± 4.85, 2.28 ± 1.09 vs. 1.60 ± 1.52, and 3.19 ± 1.70 vs. 2.19 ± 2.22, respectively; all $P < 0.05$).

In accordance with histopathologic tumor response, only 12/52 (23%) patients undergoing surgery showed a complete response (ypT0N0), whereas 40/52 (78%) did not. In the residual patients who were not scheduled for surgery ($n = 27$), the response to treatment was based on the bioptic results of samples obtained from the EU. Out of 27 patients, 14 showed complete response, whereas 13 had persistence of disease (52 vs. 48%). Moreover, PET/CT was falsely positive in six out of 12 patients (50%) with a complete histopathologic response and falsely negative in two out of 40 (5%) patients without any response (χ^2-test; $P < 0.001$). False-positive results were probably related to inflammation processes after radiation therapy, whereas false-negative findings could have been due to microscopic residual disease.

Follow-up data and prognosis

Follow-up data were obtained in 96% of patients (three were lost) and the length of follow-up was 20 ± 13 months (median: 18 months, range: 2 – 53 months). At the end of this period, 38 patients (48.1%) were disease free, 23

Table 2 Characteristics of the study population according to surgical management

	No surgery ($n=27$)	Surgery ($n=52$)	*P* value
Histology [*n* (%)]			
SCC	21 (76.9)	20 (39.6)	0.001
Adenocarcinoma	5 (19.2)	30 (56.6)	
Others	1 (3.9)	2 (3.8)	
Sex [*n* (%)]			
Male	20 (74)	41 (79)	0.631
Female	7 (26)	11 (21)	
Follow-up status [*n* (%)]			
Free	13 (50)	25 (50)	0.996
Relapse	8 (31)	15 (30)	
Death	5 (19)	10 (20)	
Lost at follow-up	1 (4)	2 (4)	
Events [*n* (%)]			
No	13 (48)	25 (48)	1
Yes	13 (48)	25 (48)	
Lost at follow-up	1 (4)	2 (4)	
Survival status [*n* (%)]			
Alive	21 (78)	40 (77)	0.936
Dead	5 (19)	10 (19)	
Lost at follow-up	1 (4)	2 (4)	
Complete response to NAT [*n* (%)]			
No	13 (48)	41 (79)	0.005
Yes	14 (52)	11 (21)	
ypTNM [*n* (%)]			
ypT0N0M0	–	12 (23)	
ypT+N0M0	–	18 (35)	–
ypT+N+M0	–	17 (33)	
ypT+N+M+	–	5 (9)	
PET results [*n* (%)]			
Negative	12 (44)	8 (15)	0.005
Positive	15 (56)	44 (85)	
Response to NAT at CT [*n* (%)]			
Negative	13 (48)	11 (21)	0.022
Positive	10 (37)	29 (56)	
NA	4 (15)	12 (23)	
Age	60.74±9.78	60.87±10.53	0.959
Time between PET and follow-up	21.19±14.60	18.54±12.14	0.403
Metabolic volume	10.02±33.74	24±84.71	0.385
X size	13.06±15.69	28.24±24.31	0.004
Y size	14.29±20.53	28.329±23.33	0.010
Z size	17.70±25.15	40.30±34.69	0.004
SUV_{max}	3.97±4.85	6.41±5.38	0.050
SUV_{min}	1.60±1.52	2.28±1.09	0.025
SUV_{avg}	2.19±2.22	3.19±1.70	0.030
TLG	56.78±211.94	115.374±489.34	0.555
Time between PET and the end of NAT	2.96±2.50	2.15±1.67	0.109

CT, computed tomography; NA, not available; NAT, neoadjuvant therapy; SCC, squamous cell carcinoma; SUV, standardized uptake value; TLG, total lesion glycolysis.

(29.1%) had recurrence, and 15 (19.1%) had died. On the basis of mTNM, out of 59 NMR patients, 22 were disease free, 21 presented recurrence of disease, and 14 died. Among the MR patients, 16 were disease free, two presented relapse, and one died ($P < 0.005$).

On Kaplan–Meier analysis, MR patients showed a better prognosis compared with NMRs after 60 months (78 vs. 0%; $P = 0.003$, and 98 vs. 40%; $P = 0.019$, respectively; Fig. 1a), independently from surgery. Among NMR patients, 46 and 20% of patients in the surgical and nonsurgical group, respectively, were disease free. In contrast, 91% of MR patients who did not undergo surgery were disease free. Moreover, as shown in Fig. 1, PET/CT demonstrated superior prognostic power compared with CI. In contrast, a similar trend for OS both for ypTNM and mTNM was found (both $P < 0.05$). The differences in OS and EFS in the surgical groups based on PET/CT imaging are shown in Fig. 2. As illustrated, in the group of nonsurgical patients, a negative PET/CT scan was associated with a good prognosis after a long-term follow-up.

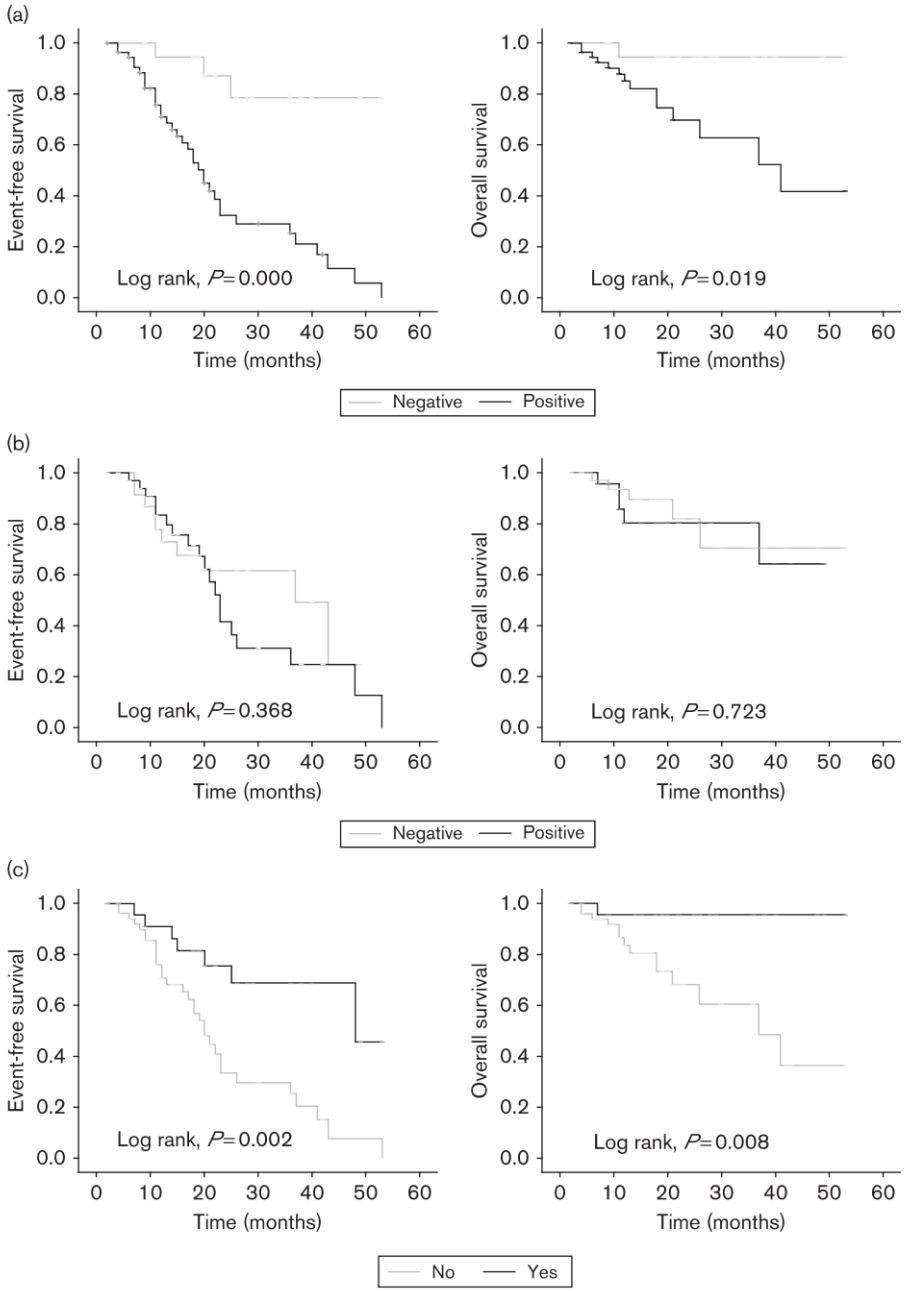
Semiquantitative evaluation of metabolic findings

On univariate and multivariate analysis, SUV_{max} and SUV_{avg} revealed themselves as independent prognostic factors of EFS [hazard ratio (HR) = 0.712 (95% confidence interval: 0.531–0.954); $P = 0.023$, and HR = 7.368 (95% confidence interval: 1.901–28.549); $P = 0.004$, respectively], whereas only SUV_{avg} was seen as an independent predictor of OS [HR = 5.087 (95% confidence interval: 0.950–27.230); $P = 0.050$]. In contrast, none of the sizing parameters were seen as independent predictors of disease recurrence and death (Table 3). The global χ^2 of the multivariable Cox proportional hazard model for prediction of adverse events and OS increased significantly from 13.872 to 42.229 ($P < 0.0001$) and from 8.990 to 22.582 ($P = 0.050$), respectively, after addition of visual and semiquantitative PET/CT data to the clinical variables (Fig. 3).

Discussion

Only histopathologic response to NAT was a strong predictor of survival on univariate analysis as compared with metabolic response, according to the results of the MUNICON II study [12]. We showed that metabolic evaluation by ^{18}F-FDG PET/CT after NAT was able to stratify the recurrence risk of EC patients. In particular, our data suggested that the demonstration of cancer persistence and the recognition of small residuals on metabolic imaging after NAT have a consequence on survival, independently from surgery. In fact, we observed a better EFS and OS in MR patients. As seen from our results, 100% of MR patients who did not undergo surgery remained alive and 91% of them were disease free after 5 years of follow-up. This group of patients avoided the risks related to surgery as demonstrated by Kim *et al.* [20], who showed that postoperative mortality rate from esophagectomy may be detrimental for patients who achieved pathologic complete response after preoperative chemoradiation therapy. As reported by Stahl *et al.* [27], surgery improves local tumor control but not OS benefit, particularly for patients who respond to chemoradiation therapy. In our experience, a complete metabolic response to NAT could support the surgeon in postponing radical surgery especially if primary tumor was pinpointed in the cervical and/or upper thoracic tracts. Eight out of 11 (73%) MR patients who were not scheduled for surgery had a squamous cell carcinoma (SCC) and were disease free after 5 years of follow-up.

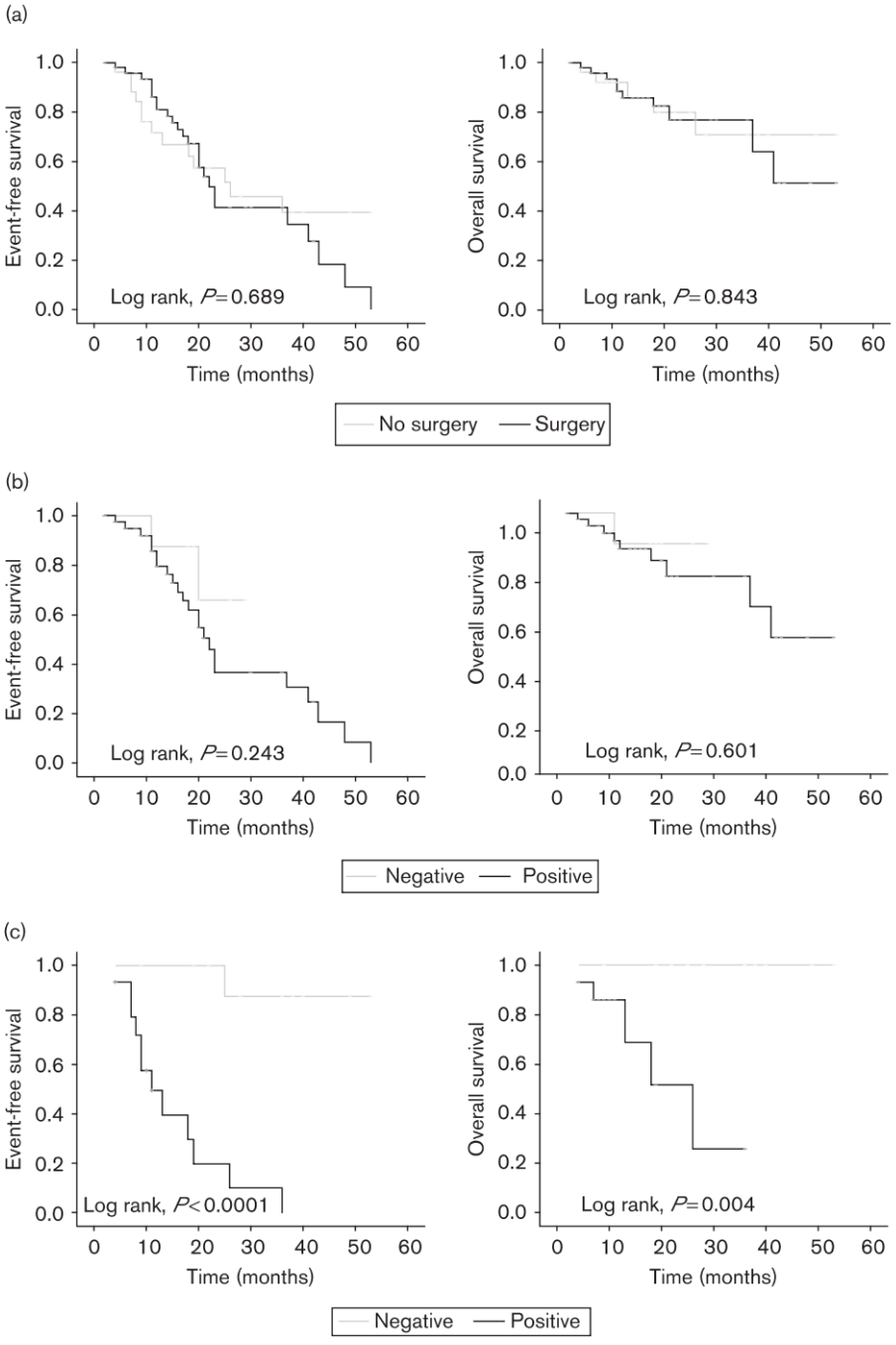
Fig. 1



Event-free and overall survival curves according to (a) PET/CT, (b) CT, and (c) pathological findings. CT, computed tomography.

Therefore, could metabolic imaging help the specialists in the choice between surgery and close follow-up? On the basis of our results we could assume yes, making some considerations. The current gold standard for surgically resectable patients is administration of neoadjuvant chemoradiation therapy followed by surgery [28]. Lordick *et al.* [29] declared that post-therapeutic ^{18}F-FDG uptake value has a prognostic impact and correlates with response, but the limited positive predictive value for complete histopathologic response does not guide decision making against surgical resection at this stage. Obviously, the metabolic evaluation of NAT cannot replace the gold standard test, namely, histology of the surgical specimen, but in the present study PET/CT was able to make a reliable prediction about prognosis. As stated by Swisher *et al.* [22], on multivariate analysis including three therapeutic modalities and histology, only postchemoradiation therapy ^{18}F-FDG PET and CT thickness were seen to be independent predictors of long-term survival.

Fig. 2



Event-free and overall survival curves based on the surgical approach. (a) All patient population, (b) surgery group and PET/CT results, and (c) no-surgery group and PET/CT results. CT, computed tomography.

When we compared the Kaplan–Meier curves with histopathologic results and metabolic evaluation, a similar trend could be seen and both were prognostically significant (Fig. 1). This finding implies that PET/CT could be used as a preoperative prognostic weighted index that is later corrected by the results of pathological response to treatment.

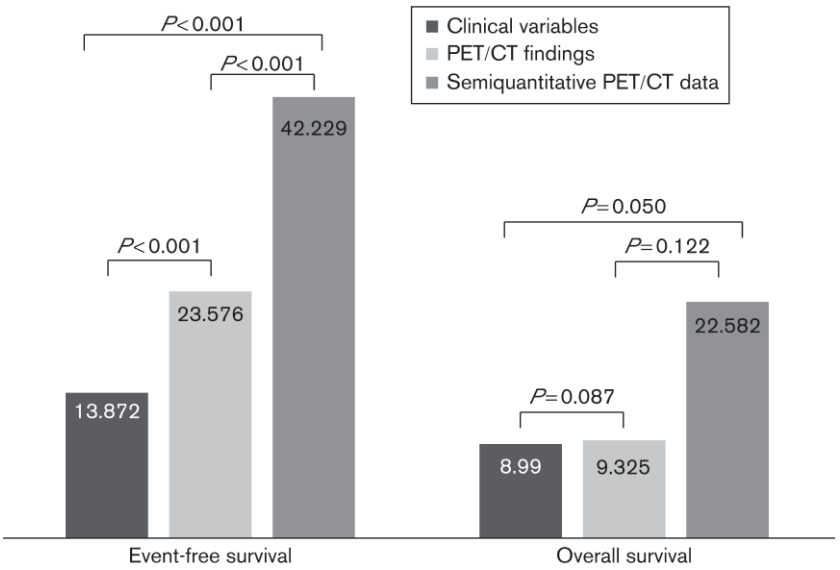
To date, the data reported from the literature have demonstrated a lack of linearity between response to treatment and prognosis; therefore, the correlation between prognosis and response to NAT in terms of the need for surgical intervention still remains crucial. For now, esophagectomy remains an essential part of EC treatment and can lead to improved OS if performed in

Table 3 Univariate and multivariate analysis

	Events						OS					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristics	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
SCC vs. AD	0.850	0.433–1.669	0.636				0.552	0.190–1.603	0.275			
Surgery vs. no surgery	0.872	0.444–1.715	0.692	–	–	–	0.897	0.3105–2.642	0.844	–	–	–
Complete response vs. no complete response	3.428	1.492–7.878	0.004	0.381	0.110–1.323	0.129	9.554	1.248–73.120	0.030	4.286	0.152–121.067	0.393
Positive PET vs. negative PET	0.136	0.042–0.445	0.001	0.279	0.015–5.055	0.387	0.128	0.017–0.980	0.048	1.533	0.010–230.005	0.867
Metabolic volume	0.999	0.994–1.004	0.700	–	–	–	0.999	0.990–1.008	0.746	–	–	–
X size	1.009	0.998–1.019	0.120	0.997	0.963–1.034	0.887	1.010	0.994–1.027	0.224	–	–	–
Y size	1.008	0.997–1.019	0.151	0.982	0.944–1.021	0.352	1.009	0.993–1.026	0.284	–	–	–
Z size	1.009	1.00–1.019	0.039	1.010	0.992–1.028	0.280	1.010	0.996–1.024	0.148	0.998	0.976–1.021	0.888
SUV_{max}	1.097	1.044–1.153	0.000	0.712	0.531–0.954	0.023	1.106	1.026–1.193	0.009	0.748	0.507–1.105	0.145
SUV_{min}	1.942	1.385–2.722	0.000	0.305	0.080–1.3164	0.082	1.762	1.059–2.933	0.029	0.359	0.063–2.047	0.249
SUV_{avg}	1.523	1.273–1.820	0.000	7.368	1.901–28.549	0.004	1.564	1.174–2.083	0.002	5.087	0.950–27.230	0.050
TLG	1.000	0.999–1.001	0.723	–	–	–	1.000	0.998–1.001	0.770	–	–	–

AD, adenocarcinoma; CI, confidence interval; HR, hazard ratio; OS, overall survival; SCC, squamous cell carcinoma; SUV, standardized uptake value; TLG, total lesion glycolysis.

Fig. 3



Incremental prognostic values for event-free survival and overall survival. CT, computed tomography.

a high-volume institution, although our results demonstrated no differences between the surgical and nonsurgical group (Fig. 2a).

Supporting the visual analysis with the semiquantitative evaluation of pathological findings, our data demonstrated on univariate and multivariate analysis that SUV_{max} and SUV_{avg} were independent prognostic factors of EFS, whereas only SUV_{avg} was an independent predictor of OS. Moreover, we showed that visual and semiquantitative PET/CT assessment added information for prediction of adverse events and OS over that provided by clinical and therapeutic data. We considered SUVs as a continuous variable and not as dichotomized when compared with the study by Swisher *et al.* [22]. The authors published results on 103 patients with histologically diagnosed adenocarcinoma ($n = 90$) and SCC ($n = 13$) and assessed the prognostic relevance of ^{18}F-FDG uptake after completion of NAT. An SUV of 4 or more was the best predictor of long-term survival ($P = 0.04$; HR: 3.5). The 18-month survival of patients with a postchemoradiation therapy SUV of 4 or more was 34%, compared with 77% for patients with an SUV less than 4 ($P = 0.01$). In contrast, several studies have evaluated the prognostic meaning of a decrease in ^{18}F-FDG uptake before and after NAT. In particular, Brucher *et al.* [18] found that

patients with an SUV_{avg} decrease of less than 52% had a significantly shorter median survival compared with patients with an SUV_{avg} decrease of more than 52% (8.8 vs. 22.5 months; $P < 0.001$). Similar to these latter results, Port *et al.* [16] reported that patients with a 50% or greater reduction in SUV_{max} of their primary tumor had a significantly better disease-free survival compared with patients with a less than 50% reduction in SUV_{max} (median disease-free survival, 35.5 vs. 17.9 months, respectively; $P = 0.03$).

Downey *et al.* [19] demonstrated that an SUV_{max} reduction of more than 60% was correlated with better 2-year disease-free survival (67 vs. 38%; $P = 0.055$). Finally, Kim *et al.* [20] revealed that complete metabolic response (reduction of $SUV_{max} > 80\%$) after completion of NAT predicted long-term outcome.

The limitations of the present study are (a) different histological subtypes of tumors and (b) lack of basal metabolic evaluation, losing the possibility of distinguishing between residual cancer and persistence of tumor with low glucidic metabolism. It has been suggested that adenocarcinoma and SCC probably have different carcinogenesis pathways that may influence the treatment response [30]. A recent meta-analysis found a significant survival benefit of NAT only in patients with adenocarcinoma, but not SCC [31]. Moreover, some authors recently suggested that histology could play a key role in treatment response and in long-term prognosis in patients treated with preoperative chemoradiation therapy; their findings nonetheless remain contradictory [32–35]. In our study no differences in EFS and OS were found between SCC and adenocarcinoma patients (47.5 vs. 51.5%; $P = 0.733$, and 15 vs. 24%; $P = 0.318$, respectively). Moreover, one of the limitations of ^{18}F-FDG PET is low spatial resolution, which significantly affects its accuracy in the presence of small residual disease; in addition it is sometimes difficult to distinguish fibrous residual tissue from residual disease in the presence of inflammatory reaction, particularly after radiation therapy. Both of these limitations could have affected the accuracy of ^{18}F-FDG PET/CT imaging in our case population. Finally, being a surgical procedure performed in 8/20 patients with negative and 44/59 patients with positive PET/CT findings, the comparison between responders and nonresponders could negatively affect the statistical analysis.

On the basis of the conclusions of Ott *et al.* [36] – that response and survival of nonavid patients were not significantly better than those of NMRs – we dichotomized our patient population into two groups, MRs and NMRs, without considering a threshold for metabolic response.

Conclusion

PET/CT could stratify the recurrence risk of EC patients based on treatment efficacy; in particular, a positive PET/CT after NAT should be followed by surgery for improving EFS. Moreover, a careful visual analysis of PET/CT after NAT can give important clinical and prognostic information, whereas the semiquantitative parameters are confirmed to be a support tool for nuclear medicine specialists to increase the meaning of pathological findings and stratify long-term survival.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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