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Prognostic Significance of 2-Deoxy-2-[18F]-Fluoro-D-Glucose PET/CT in Patients With Locally Advanced Esophageal Cancer Undergoing Neoadjuvant Chemoradiotherapy Before Surgery

A Nonparametric Approach

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Abstract: To investigate the prognostic value of tumor metabolism measurements on serial 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography and computed tomography scans in patients with locally advanced esophageal cancer undergoing neoadjuvant chemoradiotherapy.

Forty-five patients (63 ± 7 years, 6 female) treated with concomitant chemoradiotherapy before surgery were followed up for 24 ± 18 months (range 4–71). Positron emission tomography and computed tomography scans were obtained within 1 week before the start (PET1) and 1 month after the completion of the treatment (PET2). Total body tumor metabolic activity was measured as the sum of the parameters: SUV-max, SUV corrected for lean body mass, and total lesion glycolysis ($TLG_{40/50/70\%}$). Then, delta values for the parameters between PET1 and PET2 were calculated and expressed as percentage of PET1 results.

At the time of the analysis, 27 patients were dead and 18 were alive. There was no difference between the 2 groups in terms of age, sex, site of the disease, histology, and the presence/absence of linfonodal metastases (P = NS). Survival random forest analysis (20,000 trees) resulted in an estimate of error rate of 36%. The nonparametric approach identified ΔTLG_{40} as the most predictive factor of survival (relative importance 100%). Moreover, T (17%), N (5%), and M (5%) stage of the disease, cancer histology (11%), TLG_{70} (5%) at the end of chemioradiotherapy, and ΔTLG_{50-70} (17%–5%) were positively associated with patient outcome.

The nonparametric analysis confirmed the prognostic importance of some clinical parameters, such as TNM stage and cancer histology. Moreover, ΔTLG resulted to be the most important factor in predicting outcome and should be considered in risk stratification of patients treated with neoadjuvant chemoradiotherapy.

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Abbreviations: 18F-FDG = 2-deoxy-2-[18F] fluoro-D-glucose, PET/CT = positron emission tomography and computed tomography, SUL = SUV values corrected for lean body mass, SUV = standardized uptake value, TLG = total lesion glycolysis, TNM = tumor-node-metastasis classification system, VOI = volume of interest.

INTRODUCTION

Esophageal cancer is a leading cause of cancer mortality worldwide. At diagnosis, the majority of patients is affected by a locally advanced disease, which, often, prevents a radical surgical resection.[1] In these patients, neoadjuvant chemoradiotherapy has become the standard choice for increasing the overall survival.[2–4] The noninvasive evaluation of response to medical therapy is critical for treatment personalization and the management of the patient. Molecular imaging with positron emission tomography (PET) and 2-deoxy-2-[18F] fluoro-D-glucose (18F-FDG) has shown to be promising in evaluating response to neoadjuvant therapeutic strategies.[5] A decrease in the tumor metabolic activity, measured as variations in standardized uptake value (SUV) from the pretherapy to the end of the treatment, resulted predictive of the outcome of the patient, despite a wide variability in the reported diagnostic accuracies.[5–6] More recently, the hybrid approach with PET and computed tomography (PET/CT) provided integrated morpho-metabolic information, such as total lesion glycolysis (TLG). TLG measures the volume of the metabolically viable tumor, and preliminary studies suggested that this could have an incremental value over SUV in assessing therapy response.[7–9] However, these studies differ in the methodological approach and in the reference gold standard. In particular, there is no consensus in the threshold to be used in calculating TLG. The aim of the present study was to investigate the predictive prognostic value of semiquantitative measurements obtained on serial 18F-FDG PET/CT scans in a general population of patients with locally advanced esophageal cancer undergoing neoadjuvant chemoradiotherapy before surgery.

METHODS

Patients

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and

its later amendments or comparable ethical standards. Procedures performed in the study were part of a diagnostic work-up, and no ethical approval was necessary. Informed consent was obtained from all individual participants included in the study.

From 2008 to 2013, 156 patients with esophageal cancer were referred to our PET/CT laboratory. All patients were preoperatively evaluated with a scheduled diagnostic work-up: upper endoscopy with biopsy; endo-ultrasonography; CT scan of the neck, thorax, and abdomen; and 18F-FDG PET/CT-scan. Staging of the disease was carried out according to the tumor-node-metastasis (TNM) classification system (7th edition, 2010) of the American Joint Committee on Cancer.[10]

Of the studied patients, 45 (29%) consecutive newly diagnosed locally advanced esophageal adenocarcinoma and squamous cell carcinoma patients were treated with concomitant chemoradiotherapy before surgery, and follow-up was available. The first 18F-FDG PET/CT scan was performed within 1 week before the treatment (PET1). The neoadiuvant standard therapy included 2 courses of cisplatinum in combination with 5-fluorouracil, and a median radiation dose of 45 to 50.4 Gy given in 180-cGy fraction per 5 days a week for 5/6 weeks. All patients were treated with a step-and-shoot Intensity-Modulated Radiation Therapy or rapid arc technique. Patients were restaged with an 18F-FDG PET/CT scan 1 month after the completion of the treatment plan (PET2). Within 2 weeks from the PET/CT scan, all patients underwent an Ivor Lewis or McKeown esophagectomy, based on tumor location. After surgery, patients were followed up for 24 ± 18 months (range 4–71).

18F-FDG PET/CT Protocol

Patients were studied under fasting conditions (at least 6 hours). After the positioning of a venous access, the glycemic status was evaluated; values <120 mg/dL were considered suitable for performing the PET study. Then, the radiotracer (18F-FDG) was injected (5.18 MBq/kg; 0.14 mCi/kg) and the patient was invited to have an adequate hydration drinking water. PET/CT imaging was obtained 60 minutes after the radiotracer administration using a Discovery RX VCT 64-slice tomograph (GE Healthcare, Milwaukee, WI), with a CT temporal resolution of 0.25 seconds and a PET spatial resolution of 5.8 mm full width at half maximum (FWHM). A low-dose scout acquisition, in free breath, was performed (10 mAs/120 KeV), followed by an attenuation CT scan (volumetric algorithm, average values: 80 mAs/120 KeV). Finally, the 3-dimensional (3D) PET acquisition was obtained with 6 to 9 positions from the base of the skull to the mid-thighs, 2 minute/position, for a total duration of the examination <20 minutes.

The acquired CT images were reconstructed for the calculation of the attenuation factors and for the anatomical identification of the hypermetabolic areas. PET images were reconstructed using an Ordered Subset Expectation Maximization iterative algorithm that provided an image resolution of 0.9 cm FWHM.

After reconstruction on coronal, sagittal, and transverse planes, PET images were interpreted qualitatively and semiquantitatively. The PET/CT study was repeated after the completion of the neoadjuvant treatment using the same dose, acquisition protocol, and interval time between the radiotracer injection and the acquisition time (tolerance ± 5 minutes).

PET/CT Imaging Analysis

The PET images were processed using an Advantage Workstation (GE Healthcare, Milwaukee, WI). Briefly, on the transaxial images, where the neoplastic mass was best represented, a spherical volume of interest (VOI) was drawn around the highest uptake, and manually adjusted (mean diameter 1.2 cm). SUVmax and SUV values corrected for lean body mass (SUL) were automatically calculated. Subsequently, isoactivity contours were automatically drawn at 40%–50%–70% thresholds of SUVmax in the VOI. For each threshold, the metabolic total volume (cm^3), mean SUV, and TLG were calculated. In the presence of metastatic lesions, semiquantitative parameters were calculated as described. Then, values in primary and secondary masses were summed to obtain total body quantification of metabolic activity. Response to therapy was calculated as delta values of the PET semiquantitative parameters between PET1 and PET2, expressed as percentage of PET1 measures.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation. Analysis was performed using MedCalc software (version 12.4; Mariakerke, Belgium). Statistical significance for all analyses was assessed at a P value <0.05. When indicated, differences were assessed by Student t test for paired or unpaired data. Binary logistic regression analysis with a stepwise approach determined which of the PET semiquantitative parameters was the strongest of all when associated with patient outcome.

Given the small sample size and the potentially complex relations that tie the clinical outcome to the considered predictors, a multivariate analysis was performed with random survival forest.[11] Survival random forest is a nonparametric approach to survival analysis. An ensemble of survival trees is grown on the data; each tree is learned on a different training set, randomly aggregating about two-third of the original number of patients, and successfully tested on the remaining group (''out-of-bag'' observations). Because the out-of-bag observations are not used in the fitting of trees, the out-of-bag estimates are essentially cross-validated accuracy estimates. Moreover, at each node of each tree, a subset of predictors is randomly selected for the splitting procedure, making the forest robust about predictor correlations. Although being a machine learning tool, principally aimed at optimal predictive performance, random survival forest furnishes a ranking of predictor importance in determining the accuracy of prediction. Random survival forest was implemented using the R package ''randomForestSRC'' (http://www.R-project.org/). In our analysis, a survival forest of 20,000 trees was created, using the log-rank splitting rule with 3 predictors randomly selected at each split.

RESULTS

At the time of the analysis, 27 patients were dead (group 1) and 18 were alive (group 2). There was no difference between the 2 groups in terms of age, sex, site of the disease (esophagus/cardias), histology (squamous cell carcinoma/adenocarcinoma), the presence/absence of linfonodal metastases, and TNM status (P = NS). Final pathology revealed positive resection margins in 4/45 (8.8%) of the surgical specimens: 2 in group 1 and 2 in group 2 (P = NS). The clinical results are summarized in Table 1. PET/CT data in group 1 and group 2 patients are showed in Table 2. Patients with adenocarcinoma histology showed a more frequent metastatic disease to lymph node (N0/N1/N2/N3: 5/11/5/10 vs 6/7/0/1; $P = 0.045$). Patients with squamous cell carcinoma had higher SUV (13.6 ± 2.4 vs 9.5 ± 0.9; $P = 0.05$) and SUL (10.3 ± 1.6 vs 6.7 ± 0.5;

TABLE 1. Clinical Findings

	Group 1	Group 2	*P*
Age	62.3 ± 8.1	62.6 ± 7.7	0.89
Sex (M/F)	23/4	16/2	0.72
Cancer location (esophagus/cardias)	21/6	16/2	0.33
Histology (SCC/adenocarcinoma)	9/18	5/13	0.69
Pathologic LFN (yes/no)	13/14	8/10	0.71
pT (T1/T2/T3/T4)	4/7/15/1	2/2/14/0	0.42
pN (N0/N1/N2/N3)	6/10/4/7	5/8/1/4	0.75
pM (M0/M1)	23/4	15/3	0.86
Resection margins (R0/R1)	25/2	16/2	0.91

F = female, LFN = lymphnode, M = male, SCC = squamous cell carcinoma.

$P = 0.01$) values at PET1, whereas there was no statistical difference between the 2 groups in terms of other PET/CT results. At logistic univariate analysis, among clinical and tomographic data, only PET/CT parameters $TLG_{40-50-70}$ at the end of the treatment, ΔSUVmax, ΔSUL, and $\Delta TLG_{40-50-70}$ resulted predictive of patient survival ($P < 0.05$). Logistic multivariate analysis failed to identify an independent predictor of patient outcome. Random forest out-of-bag global survival curve is showed in Figure 1. Survival random forest analysis resulted in an estimate of error rate of 36% (Figure 2). The relative importance of each analyzed clinical and PET/CT variables in predicting patient outcome has been reported in Figure 3. ΔTLG_{40} showed the higher prognostic power (relative importance 100%). Among the other studied variables, TNM stage of the disease (T 17.6%; N 5.8%; M 5.8%), adenocarcinoma histology (11.7%), TLG_{70} at the end of chemioradioterapy (5.8%), and ΔTLG_{50-70} (17.6% and 5.8%, respectively) were positively associated with patient outcome. Two examples of patients of group 1 and group 2 are showed in Figures 4 and 5, respectively.

TABLE 2. PET/CT Image-derived Results

	Group 1	Group 2	*P*
SUVmax PET1	10.0 ± 7.8	12.0 ± 7.7	0.32
SUVmax PET2	6.4 ± 5.8	3.8 ± 2.9	0.08
SUL PET1	6.9 ± 5.0	9.1 ± 3.6	0.12
SUL PET2	5.0 ± 4.6	2.7 ± 2.2	0.05
TLG_{40} PET1	163505 ± 135887	268485 ± 203379	0.04
TLG_{40} PET2	266229 ± 190336	25012 ± 23166	<0.001
TLG_{50} PET1	113173 ± 112357	169306 ± 160765	0.17
TLG_{50} PET2	170621 ± 160739	16409 ± 15290	<0.001
TLG_{70} PET1	49613 ± 66158	102261 ± 123439	0.07
TLG_{70} PET2	70923 ± 88854	6246 ± 6823	<0.004
ΔSUVmax (%)	−22.6 ± 53.7	−67.6 ± 15.9	<0.001
ΔSUL (%)	−20.9 ± 56.1	−69.5 ± 16.4	<0.001
ΔTLG_{40} (%)	240.2 ± 656.6	−89.5 ± 5.9	<0.04
ΔTLG_{50} (%)	281.9 ± 964.0	−79.2 ± 41.3	0.09
ΔTLG_{70} (%)	293.2 ± 1146.0.6	−88.9 ± 11.0	0.16

PET1 = positron emission tomography performed within 1 week before the treatment, PET2 = positron emission tomography obtained 1 month after the completion of the treatment plan, SUL = SUV values corrected for lean body mass, SUV = standardized uptake value, $TLG_{40/50/70}$ = total lesion glycolysis calculated using 40%-50%-70% thresholds of SUVmax in the VOI.

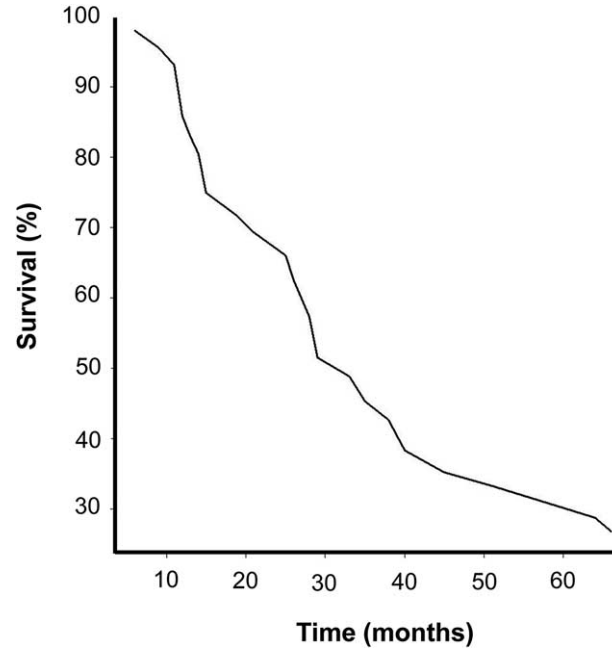


FIGURE 1. Random forest out-of-bag global survival curve.

DISCUSSION

To our knowledge, this is the first study using a statistical nonparametric analysis to evaluate the prognostic power of

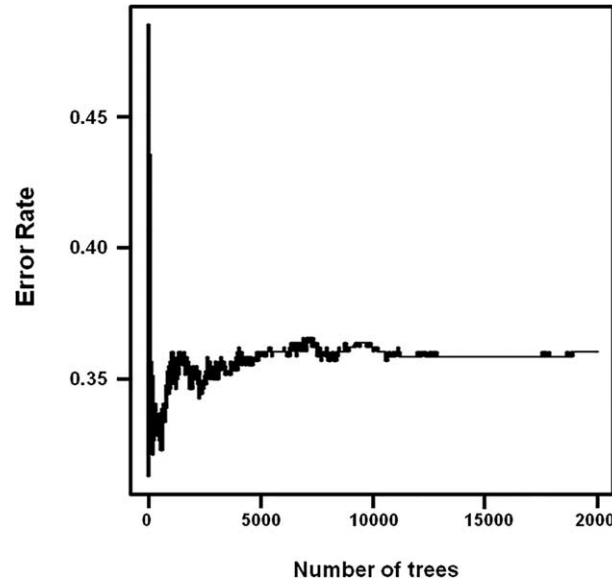
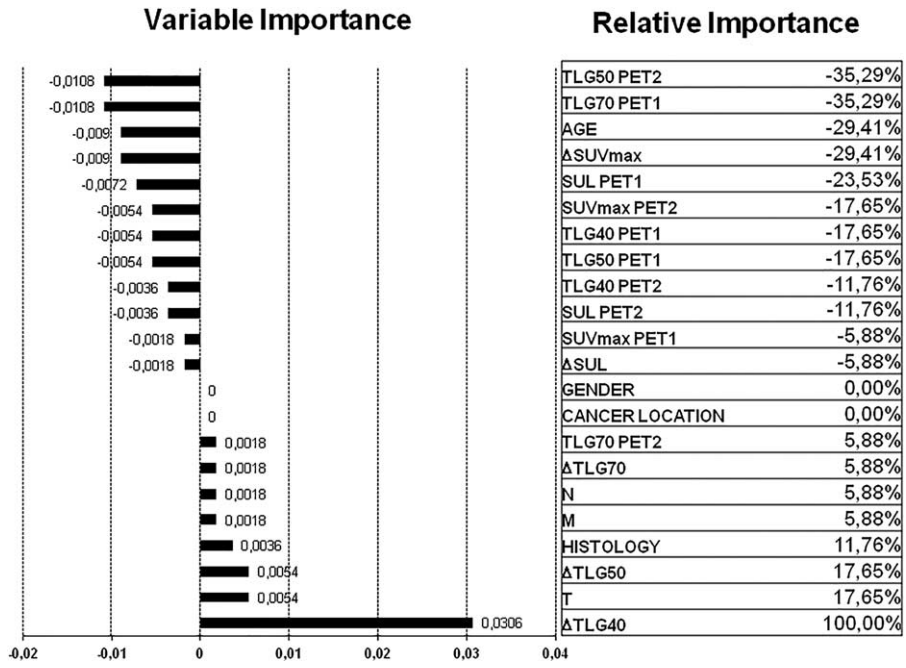


FIGURE 2. Survival forest of 20,000 trees was created, using the log-rank splitting rule with 3 predictors randomly selected at each split. Survival random forest analysis resulted in an estimate of error rate of 36%.



Relative Importance	
TLG50 PET2	-35,29%
TLG70 PET1	-35,29%
AGE	-29,41%
ΔSUVmax	-29,41%
SUL PET1	-23,53%
SUVmax PET2	-17,65%
TLG40 PET1	-17,65%
TLG50 PET1	-17,65%
TLG40 PET2	-11,76%
SUL PET2	-11,76%
SUVmax PET1	-5,88%
ΔSUL	-5,88%
GENDER	0,00%
CANCER LOCATION	0,00%
TLG70 PET2	5,88%
ΔTLG70	5,88%
N	5,88%
M	5,88%
HISTOLOGY	11,76%
ΔTLG50	17,65%
T	17,65%
ΔTLG40	100,00%

FIGURE 3. Importance of each analyzed clinical and PET/CT variables in predicting patients' outcome. Survival random forest analysis furnishes a ranking of predictors' importance in determining the accuracy of prediction. ΔTLG_{40} showed the higher prognostic power (relative importance 100%). PET/CT = positron emission tomography and computed tomography, TLG = total lesion glycolysis.

clinical and PET/CT-derived measures in patients with advanced esophageal cancer. Our results confirmed the prognostic importance of some clinical parameters, such as TNM stage and cancer histology. Moreover, among the analyzed variables, PET/CT ΔTLG resulted to be the most important in predicting patient outcome after neoadjuvant chemoradiotherapy before surgery.

Clinical Results

Many clinical factors have been previously considered as potential predictors of therapeutic response and patient outcome. In our study, TNM stage and cancer histology were positively associated with prognosis. TNM staging of the disease is known to be a prognosticator in esophageal cancer.[12] Besides stage, the most important differentiating factor in the

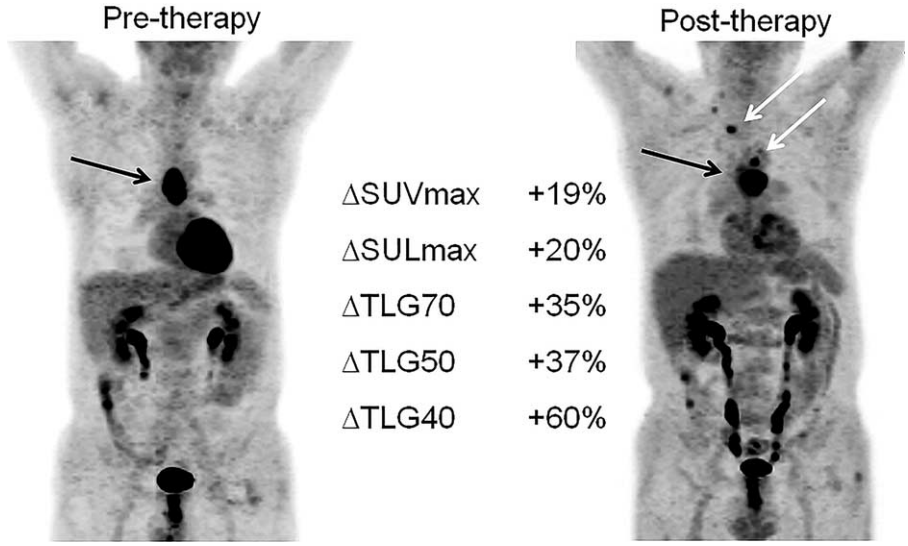


FIGURE 4. PET results in a patient of group 1 with a squamous cell carcinoma of the mid-esophagus. Pretherapy scan (right) showed an increased uptake of 18F-FDG into the esophageal lesion (black arrow). Posttreatment PET (left) revealed the persistence of hypermetabolic disease into the esophagus and the appearance of new areas of radiotracer uptake (white arrows). The best PET predictor of the outcome of the patient was ΔTLG40 value. 18F-FDG = 2-deoxy-2-[18F] fluoro-D-glucose, PET = positron emission tomography, TLG = total lesion glycolysis.

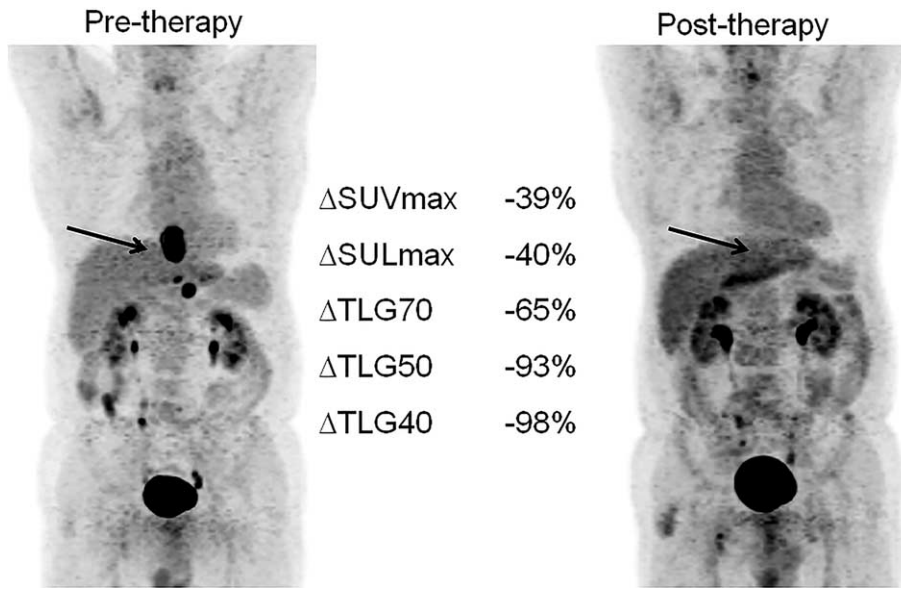


FIGURE 5. PET results in a patient of group 2 with a squamous cell carcinoma of the distal esophagus. Pretherapy scan (right) showed an increased uptake of 18F-FDG at the level of the esophageal lesion (black arrow). Posttreatment PET (left) revealed the disappearance of radiotracer uptake. Again, the best PET predictor of the response to therapy and patients' outcome was ΔTLG40 value. 18F-FDG = 2-deoxy-2-[18F] fluoro-D-glucose, PET = positron emission tomography, TLG = total lesion glycolysis.

treatment and prognostication of esophageal cancer is histology; in fact, patients with adenocarcinoma have a worse prognosis.[12–13] Our data confirm previous observation demonstrating that complex interplay of TNM classification, and also nonanatomic factors, including histopathologic cell type, influence the prognosis of patients with esophageal cancer.

PET/CT Results

As in other oncological diseases, the noninvasive evaluation of response to medical therapy is critical for treatment personalization and the management of the patient. Molecular imaging with PET and 18F-FDG has shown to be promising in evaluating response to neoadjuvant therapeutic strategies. A decrease of the tumor metabolic activity, measured as variations in SUV from the pretherapy to the end of the treatment, has been shown to be predictive of histopathologic response[5–6] and the outcome of the patient.[5] However, other studies failed to confirm the predictive value of SUV. Systematic meta-analysis showed a significant heterogeneity in diagnostic accuracies of the included studies, concluding that 18F-FDG PET should not be used in clinical routine to guide neoadjuvant therapy decisions.[6] Our data are partially in agreement, demonstrating that SUVmax and ΔSUVmax values were not associated with patient outcome. Similarly, normalization for the lean body mass (SUL) did not improve the prediction of patient survival. More recently, the hybrid approach with PET/CT provided integrated morpho-metabolic information, such as TLG. TLG measures the volume of the metabolically viable tumor and the degree of the abnormal glycolytic metabolism within it. Preliminary studies in patients with esophageal cancer suggested that TLG could have an incremental value over SUV in assessing therapy response.[5–7] However, these studies differed in the methodological approach and in the reference gold standard. In particular, most of the studies were based on small patient populations, and there was no consensus in the threshold to be used in calculating TLG. In our study, we compared the total body tumor metabolic activity calculated using different thresholds. Our analysis confirmed the incremental value of total lesion glycolysis over SUV in predicting treatment response and patient outcome. Noteworthy, the relative predictive prognostic importance was higher for a 40% VOI isocontour analysis. A possible explanation of this finding could be the wider the ROI used the better the measures of the metabolic tumor volume and its variation after chemoradiotherapy. This result was in agreement and confirmed previous observation obtained in different clinical populations.[7,9,14]

Finally, we used a nonparametric statistical approach that is relatively independent to the dimension of the studied patient population and permits to identify the relative importance of different parameters in predicting patients' outcome. Moreover, the clinical predictors can be conveniently associated with PET/CT results with an incremental prognostic value when the information was combined.

Our study has limitations. A potential cause of error in measurement was at the delineation of the margins of the primary tumor and metastatic disease. Inaccuracy in tumor mass delineation by the software meant the extent of disease could be under or overestimated. However, we used different thresholds in tumor delineation which resulted in similar clinical result. The measurements performed by the operator were in part subjective, and no assessment of inter or intraobserver variability has been included.

CONCLUSIONS

This is the first study evaluating the prognostic power of clinical parameters and PET/CT metabolic measures in patients with locally advanced esophageal cancer using a statistical nonparametric analysis. Our results confirm and expand previous observations demonstrating the incremental prognostic value obtained by the integration of clinical, histological, and

imaging data. Moreover, PET/CT measures, such as ΔTLG, were the most important in predicting patients' outcome after neoadjuvant chemoradiotherapy before surgery.

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