

Predictive Value of Initial PET-SUV_{max} in Patients with Locally Advanced Esophageal and Gastroesophageal Junction Adenocarcinoma

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Introduction: We have previously shown that in early clinical stage esophageal adenocarcinoma, a positron emission tomography standardized uptake values (PET SUV_{max}) of <4.5 is associated with earlier pathologic stage and predicts better survival. In this study, we analyze the impact of the pretreatment PET SUV_{max} in patients with locally advanced esophageal adenocarcinoma who undergo preoperative chemoradiotherapy.

Methods: We performed a retrospective analysis, selecting patients with adenocarcinoma of the esophagus who had a pretreatment PET scan and who received chemoradiotherapy before esophagectomy. Data recorded included demographics, PET SUV_{max}, treatment details, pathologic details, and survival data. Comparison of categorical variables was done by χ^2 analysis, continuous variables by *t* test, survival analysis by the Kaplan-Meier method, and comparisons of survival using the log-rank test.

Results: Between January 1996 and September 2007, 189 patients were appropriate for this analysis. The initial PET SUV_{max} was <4.5 in 28 patients and ≥ 4.5 in 161 patients. The two groups were similar with regards to demographics and treatment details. Patients in the low SUV group were less likely to show evidence of treatment response after chemoradiotherapy, including a higher likelihood of residual nodal disease and a lower likelihood of a pathologic complete response and estimated treatment response. However, both groups had similar survival.

Conclusions: Although the initial PET SUV_{max} does not predict survival in patients with locally advanced esophageal adenocarcinoma who receive preoperative chemoradiotherapy, patients with a high initial SUV_{max} respond better to preoperative therapy. These results can be used to better select esophageal cancer patients for combined modality treatment.

Key Words: Esophagus adenocarcinoma, PET scan, Preoperative chemoradiotherapy.

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Positron emission tomography (PET) using [¹⁸F]-fluorodeoxyglucose is commonly used in the workup of patients with esophageal cancer. The most established indication for its use is to determine the presence of otherwise undetected metastatic disease.¹ Other indications include monitoring response to induction chemotherapy,^{2,3} postneoadjuvant chemoradiotherapy prognostication, and staging.^{4–6} We recently published our results on an additional use of PET scan in surgically treated patients with esophageal cancer, namely to identify early clinical stage patients who might be at a higher risk for a poor prognosis.⁷ In that study, we showed that using a maximal standardized uptake values (SUV) of 4.5 (the median SUV_{max} of the study group) in patients with adenocarcinoma of the distal esophagus and gastroesophageal (GE) junction segregated patients into high-risk and low-risk groups, independent of clinical and pathologic stage.⁷ In this current study, we investigated whether a SUV_{max} greater or less than 4.5 could also stratify prognostically patients with locally advanced adenocarcinoma and GE junction adenocarcinoma who receive preoperative chemoradiotherapy.

METHODS

We reviewed the medical records of all patients identified in a database maintained by the Thoracic Surgery Service who underwent an esophagogastrectomy for adenocarcinoma of the distal esophagus or gastroesophageal junction (Siewert types 1 and 2) between January 1996 and September 2007. January 1996 was the date when an institutional electronic medical record system was initiated and therefore represents the date at which highly reliable information became available. Patients were eligible for inclusion in the study if they had histologically proven adenocarcinoma of the distal esophagus and gastroesophageal junction, and if they underwent planned preoperative treatment with chemoradiotherapy. The indication to receive preoperative therapy was clinical evidence of locally advanced disease (American Joint Committee on Cancer stage II–IVa), confirmed by computed tomography (CT), PET scan, or an endoscopic ultrasound (EUS) T₃ or N₁ lesion. When gross full thickness involvement of the esophageal wall was evident by CT, patients

did not always undergo a confirmatory EUS. All patients had a PET scan performed with an SUV_{max} reported before the initiation of chemoradiotherapy. Using our previously published cutoff, patients with an $SUV_{max} < 4.5$ were termed “low SUV,” and patients with an $SUV_{max} \geq 4.5$ were termed “high SUV.” All patients must have survived their perioperative course and received adequate follow-up for survival analysis. The data collected included patient demographics, PET scan data (including the primary tumor SUV as well as evidence of Fluorodeoxyglucose [FDG] avid lymph nodes), CT scan evidence of adenopathy, EUS assessment of primary tumor T and N stages (morphologic assessment by endoscopist), and preoperative treatment details (chemotherapy type, radiation dose, time from completion of radiation to surgery). Additional data collected included pathologic findings, nodal status, estimated percent treatment response, pathologic complete response (pCR, defined as no residual local or nodal disease), and survival. All pathologic data were reviewed by a single pathologist (LT). This review was performed after approval had been obtained from the Memorial Sloan-Kettering Cancer Center Institutional Review Board and in accordance with an assurance filed with and approved by the Department of Health and Human Services.

Technique of ^{18}F FDG Whole-Body PET

Over 80% of the PET scans were done at two facilities and were documented as performed on a dedicated conventional full ring high resolution dedicated position emission tomographs, with either the GE Advance (GEMS Milwaukee, WI) or the CTI Biograph (CTI Knoxville, TN). Patients were injected with pyrogen free F-18 FDG 10–15 mCi having been previously instructed to fast for at least 6 hours before scanning. All images were reconstructed using postemission transmission attenuation corrected data sets. Region of interest analysis tools, shipped with the scanners were used to calculate the maximal FDG concentration within the primary tumor mass. Standardized uptake values (SUV_{max}) were obtained by correcting for the injected dose and the patient’s weight, again using the standard software tools provided with the scanners. For the purposes of this study, only ^{18}F FDG uptake in the primary site of disease was analyzed. The remaining PET scans were done at various other facilities, and the documented primary tumor SUV_{max} was recorded based on the outside report without the possibility of further documentation.

Estimation of Treatment Effect and Pathologic Complete Response

The gross appearance of treated tumors varied from a mucosal ulceration, to a fibrous scar, or a prominent mass lesion in the case of a less than profound tumor regression. Photographs of the gross specimen were taken on all cases. The ulcerated or the scarred gross lesion at the gastroesophageal junction was blocked, sequentially and entirely submitted for histopathological evaluation. When the tumor was large in size (>5.0 cm), only representative

sections of the tumor were examined microscopically. At the microscopic level, a positive treatment-related effect was observed as the malignant epithelium was destroyed and replaced by reactive fibrosis or fibro-inflammation within the mucosa or the gastroesophageal wall. Ultimately, the pathologic response to treatment was determined by the amount of residual viable carcinoma that remained in relation to areas of fibrosis or fibro-inflammation within the gross lesion. The inverse of this number was then expressed as a percentage (%). Thus, a 100% treatment response indicated fibrosis or fibro-inflammation within an entire gross lesion without microscopic evidence of carcinoma, and a 0% treatment response represented an entirely viable tumor in the absence of any fibrosis or fibro-inflammation, respectively. Acellular mucin was regarded as a form of positive treatment response, not as a residual/viable tumor. A pCR was assigned when there was a 100% local treatment response.

Overall Outcome

The outcome evaluated was overall survival which was calculated from the time of operation, and the date of death was confirmed from the Social Security Death Index. Follow-up was tracked through February 2008, constituting our censoring date for survival.

Statistical Analysis

Patient characteristics are described using tables for categorical data, and medians and range for continuous variables. Comparison of categorical variables was done by χ^2 analysis and continuous variables by *t* test. Survival analysis was done using the Kaplan-Meier method, with comparison of survival using the log-rank test.

RESULTS

Clinical Data

During the study period, 995 esophagectomies for cancer were performed, and 189 patients were appropriate for this analysis. Five hundred and twenty-eight patients were excluded because they did not receive chemoradiation. Of the remaining 467 patients, patients were excluded for the following reasons: 105 patients had squamous cell carcinoma, 83 patients did not have a PET scan, 46 patients had a PET scan but no SUV_{max} recorded, 42 patients had a Siewert 3 tumor, and 2 patients did not have survival data available. Of the 189 patients available for analysis, 28 patients (14.8%) were in the low SUV group, and 161 patients (85.2%) were in the high SUV group (Figure 1). As shown in Table 1, there were no significant differences in patient characteristics such as age and sex. Although there was a trend toward a more advanced clinical stage in the high SUV_{max} group, especially with regards to EUS N1 disease ($p = 0.14$) and PET adenopathy ($p = 0.12$), these differences were not statistically significant. The type of preoperative chemotherapy administered, the dose of radiation, and the time from radiation completion to surgery was the same in both groups.

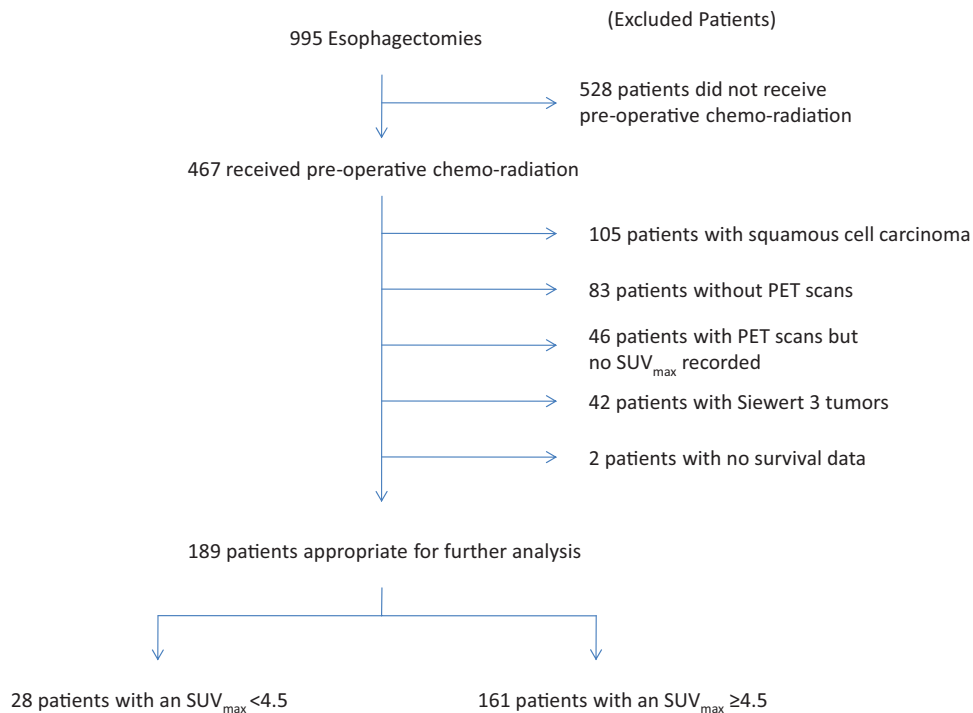


FIGURE 1. Reasons for the exclusions of patients from the analysis.

TABLE 1. Patient Characteristics

Characteristic	Low SUV Group (28)	High SUV Group (161)	<i>p</i>
Demographics			
No. of patients	28	161	
Age (mean)	62.7	61.4	0.50
Sex (female)	2 (7.1%)	23 (14.3%)	0.27
Clinical staging			
CAT nodal disease	6 (21.4%)	41 (26.1%)	0.36
EUS T3	24/26 (92.3%)	107/120 (92.2%)	0.62
EUS N1	17/27 (63.0%)	89/121 (73.6%)	0.14
PET nodal disease	4 (14.3%)	44 (27.3%)	0.12
Preop treatment			
Cisplatin based chemotherapy	24 (85.7%)	142 (88.2%)	0.72
XRT dose (mean)	5040 cGy	5045 cGy	0.88
XRT completion to surgery (mean)	59.3 d	60.8 d	0.89

Patient characteristics separated by SUV max group.
 CAT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography; XRT, radiotherapy; SUV PET, standardized uptake value.

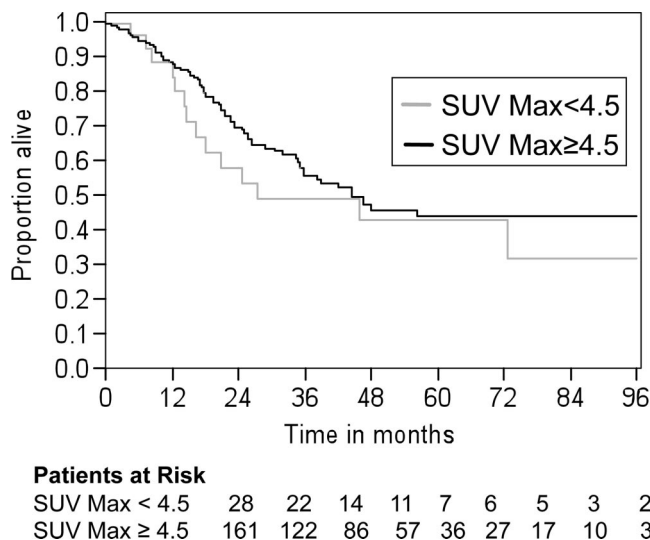


FIGURE 2. Overall survival based on SUV_{max} group.

Survival of Low SUV and High SUV_{max} Groups

As seen in Figure 2, the overall survival of the 2 patient groups was not significantly different (*p* = 0.40). At 3 years, 49.0% of the low SUV group was alive, and 57.9% of the high SUV group was alive.

Pathologic Findings of Low SUV and High SUV_{max} Groups

There was a significant difference in the findings on final pathologic examination between the two groups of patients. As shown in Table 2, the low SUV group was less likely to experience a pCR (*p* = 0.02), had less evidence of a treatment response (*p* = 0.02), and was more likely to have persistent node positive disease (*p* = 0.03).

TABLE 2. Pathologic Results

Characteristic	Low SUV Group (28)	High SUV Group (161)	<i>p</i>
Path CR	2 (7.1%)	41 (25.5%)	0.02
Depth of invasion (T)			
T0	2 (7.1%)	41 (25.5%)	0.09
T1	4 (14.3%)	26 (16.2%)	
T2	8 (28.6%)	42 (26.1%)	
T3	14 (50%)	49 (30.4%)	
T4	0	3 (1.9%)	
Treatment effect (mean %)	62%	77%	0.02
Node positive	13 (46.4%)	41 (25.5%)	0.03

Correlation of pathologic characteristics with SUV max group.
 CAT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography; XRT, radiotherapy; SUV: PET, standardized uptake value.

DISCUSSION

The results from this study show that differences in the pretreatment PET SUV_{max} do not predict overall survival in patients receiving combined modality therapy. However, a high SUV_{max} is associated with a significantly better response to induction therapy at the time of resection, as evidenced by a higher pCR rate, a greater estimated treatment response, and a lower incidence of nodal disease. Our hypothesis before initiating this study was that patients in the low SUV_{max} group would have a better survival than patients in the high SUV_{max} group. Supporting this expectation were several studies, including findings in lung cancer⁸⁻¹⁰ and esophageal cancer,^{7,11} which have shown that a high SUV_{max} in patients undergoing surgery is a predictor of a more advanced clinical and pathologic stage and thereby a worse outcome. For instance, our previous study on patients with esophageal cancer who underwent surgery without preoperative chemotherapy or chemo-radiotherapy showed that a low PET SUV_{max} predicted a lower pathologic and clinical stage and was associated with a better overall survival compared with a high PET SUV_{max}.⁷ An additional expectation regarding postchemoradiotherapy outcomes is that survival is primarily associated with posttreatment nodal status and secondarily with the pathologic treatment response.¹² In our study, however, the high SUV_{max} group had more favorable postchemoradiotherapy pathologic characteristics, yet survival was no different than in the low SUV_{max} group. To reconcile these discrepant findings, a reasonable interpretation of the results is that high SUV_{max} tumors have an inherently worse outcome but are also more responsive to chemoradiation, on balance resulting in a similar survival between the two groups. Thus, while PET SUV_{max} ultimately does not predict overall prognosis, it identifies which patients are most likely to benefit from therapy.

PET scan is increasingly being used in patients undergoing neoadjuvant therapy for esophageal cancer to monitor their response to therapy.^{2,3} In general, the findings from these studies have shown that patients who have a larger change in SUV_{max} during treatment also show evidence of a better treatment response and improved

survival.^{2,3} For example, In the MUNICON trial, Lordick et al.² showed that a 35% or more decrease in SUV_{max} after 2 weeks of chemotherapy was associated with a greater histologic response as well as improved survival in patients with esophageal adenocarcinoma. Similar findings have also been reported in other tumor types, including lung cancer.^{13,14} Interestingly, in the MUNICON trial,² an additional noteworthy finding was that the median initial SUV_{max} of the nonresponders was lower than in the responders (6.8 versus 8.3, respectively). This finding was noted even though the trial excluded patients with a very low initial SUV_{max} (cutoff not provided). Similar findings that a high initial SUV was associated with a better treatment response have also been reported by Wieder et al.³ in esophageal squamous cell cancer. In this study, the patients who were found to have a major histopathologic response after chemoradiotherapy had a mean initial SUV_{max} of 9.6, whereas those without a major response had an initial SUV_{max} of 3.5. Similar findings have been noted by Dimtrakopoulou Strauss et al.¹⁵ in colorectal cancer, Cremerius et al.¹⁶ in lymphoma, and by Lee et al.¹⁷ in lung cancer.

Underlying mechanisms, which might not only explain why high SUV tumors would have a worse initial prognosis but also respond better to preoperative therapy, are not well defined. Among proposed reasons is that a low SUV might be associated with hypoxic tumors, that when left untreated may be less aggressive, but paradoxically may make the tumor more resistant to chemoradiotherapy.¹⁸ Other possible mechanisms include higher tumor proliferation indices in high SUV tumors¹⁹ which in turn makes them more sensitive to preoperative therapy,¹⁷ in vitro evidence of chemo resistance is associated with high rates of membrane glucose transport,²⁰ and disruption of the membrane glucose transporter which is associated with decreased FDG uptake and multiresistant cell lines.²¹

The major limitation of this analysis is that it is retrospective and as such the PET SUV results are subject to both methodological and analytical variability. In addition, given the strong association between high SUV_{max} and advanced clinical stage and the fact that our institution treats patients with locally advanced disease with preoperative chemoradiotherapy, the number of patients in the low SUV group was small. However, the strengths of this study include the large number of patients studied over a short time period, uniformity of induction therapy, and the homogeneity of the patient population with respect to the tumor type and location. In addition, a meticulous pathologic assessment of the resected tumor was possible in every patient.

In conclusion, this study shows that in patients with adenocarcinoma of the distal esophagus and GE junction who undergo chemoradiotherapy before surgery, while a low pretreatment SUV likely provides an inherent survival advantage over a high SUV, this advantage is negated because of the more dramatic response of high SUV tumors to the preoperative chemoradiotherapy. This find-

ing has implications for the design of future clinical trials, and significant implications for a more appropriate selection of patients for preoperative chemoradiotherapy.

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