Change in maximum standardized uptake value on repeat positron emission tomography after chemoradiotherapy in patients with esophageal cancer identifies complete responders

Robert J. Cerfolio, MD, FACS, FCCP,^a Ayesha S. Bryant, MSPH, MD,^a Amar A. Talati, BS,^b Robert M. Cerfolio,^b and Thomas S. Winokur, MD^b

Objective: The objective was to identify whether repeat positron emission tomography scan after neoadjuvant chemoradiotherapy in patients with esophageal cancer predicted a complete response.

Methods: A retrospective study using a prospective database was performed. Patients had esophageal cancer and underwent neoadjuvant chemoradiotherapy, an initial and repeat positron emission tomography, endoscopic ultrasound with fine-needle aspiration (at the same institution), and Ivor Lewis esophagogastrectomy with lymph node resection.

Results: There were 221 patients who underwent Ivor Lewis, 86 of whom had their initial and repeat positron emission tomography scans performed at the same center. Of these, 37 patients (43%) were complete responders. The median maximum standardized uptake value of esophageal cancer decreased by 72% in the 37 patients who were complete responders, by 58% in the 31 patients who were partial responders, and by 37% in the 18 patients who had a minimal pathologic response. When the maximum standardized uptake value decreased by more than 64%, the patient was likely to be a complete responder ($P = .003$, area under the curve = 0.75).

Conclusion: When initial and repeat positron emission tomography scans are performed at the same center at least 30 days after the completion of preoperative chemoradiotherapy, the percent change in the maximum standardized uptake value is a predictor of the response to chemoradiotherapy by a patient with esophageal cancer. When the maximum standardized uptake value decreases by 64% or more, it is likely that the patient is a complete responder. These data may help guide neoadjuvant therapy and identify patients for a future randomized study that compares observation with surgical resection in patients with esophageal cancer who appear to be complete responders.

In 2007, an estimated 15,560 patients were diagnosed with esophageal cancer and 13,940 deaths occurred from this insidious disease.¹ The 5-year survival is 50% to 80% for stage I esophageal carcinoma, 30% to 40% for stage II esophageal carcinoma, 10% to 30% for stage III esophageal carcinoma, and 0% to 15% for stage IV esophageal carcinoma.²⁻⁴ Patients are often offered preoperative chemoradiotherapy before resection in an attempt to increase the 5-year survivals. The treatment of esophageal cancer, as for most solid-organ tumors, is dictated by the stage. However, the clinical stage often does not accurately reflect the true pathologic stage. The best survivals after resection occur in patients who are "complete responders" and then undergo

esophageal resection. Neoadjuvant therapy may eradicate micrometastatic disease and thus prevents future metastatic recurrence. Some argue that these patients are best served by surgery, and others argue that because these patients' tumors are "all dead," they can avoid the morbidity and mortality of esophagogastrectomy. Although there are no data to support this position, some physicians and patients choose it. The idea of a randomized study of patients who are believed to be complete responders to receive either surgery or observation alone has been discussed. However, this discussion is moot, because the only current reliable way to determine who truly is a complete responder is to operate and resect the esophagus and perform pathologic confirmation. The objective of this study was to evaluate the efficacy and accuracy of repeat positron emission tomography (PET) scans in predicting the pathologic response in both the primary tumor and lymph nodes, and to determine who is a complete responder before surgery.

MATERIAL AND METHODS

Patients

This is a retrospective cohort study of a prospective database from 1 general thoracic surgeon in a university setting. The entry criteria for this study mandated that patients have biopsy-proven esophageal cancer, an integrated PET with computed tomography using fluorodeoxyglucose (integrated PET/CT), and an endoscopic ultrasound with fine-needle aspiration

From the Department of Surgery, Division of Cardiothoracic Surgery,^a Department of Anatomic Pathology,^b University of Alabama at Birmingham, Birmingham, Alabama. This is a nonfunded study.

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Address for reprints: Robert J. Cerfolio, MD, FACS, FCCP, Department of Surgery, Chief of Thoracic Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, 703 19th St S, ZRB 739, Birmingham, AL 35294 (E-mail: robert.cerfolio@ccc.uab.edu).

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Abbreviations and Acronyms

CI	= confidence interval
EUS-FNA	= endoscopic ultrasound with fine needle aspiration
FDG-PET	= 18F-fluorodeoxyglucose positron emission tomography
maxSUV	= maximum standardized uptake value
NSCLC	= non-small cell lung cancer

(EUS-FNA) performed both initially and again after the completion of neoadjuvant chemoradiotherapy at the same center. Patients underwent radiation, most commonly using 50.4 Gy and concomitant chemotherapy (most commonly using 5-fluorouracil and cisplatinum), and then were restaged. Restaging took place no sooner than 30 days after the completion of the radiotherapy.⁵ If patients had a repeat integrated PET/CT at a different PET center or their maximum standardized uptake value (maxSUV) was not reported, they were excluded from this study. Surgical resection had to occur no later than 40 days from the completion of the repeat PET scan. Other exclusion criteria included age less than 19 years, the performance of any type of esophagogastrectomy other than an Ivor Lewis esophagogastrectomy (thus mandated that all lymph nodes were removed to fully assess the pathologic response), and incomplete course of neoadjuvant therapy. The University of Alabama at Birmingham's Institutional Review Board approved this review of our prospective database. Patient consent was obtained for the entry of their data in our prospective database but was waived for this particular study.

Imaging

The PET scans performed at the University of Alabama at Birmingham were conducted on an integrated PET-CT scanner (GE Discovery LS PET-CT Scanner, Milwaukee, WI). Patients were asked to fast for 4 hours and then subsequently received 555 MBq (15 mCi) of 18F-fluorodeoxyglucose (FDG) intravenously followed by PET after 1 hour. The maxSUV was determined by drawing regions of interest on the attenuation-corrected FDG-PET images around the primary tumor. It was then calculated by the software contained within the PET-CT scanner by a standard formula.⁶

$$\text{MaxSUV} = \frac{C(\mu\text{Ci/ml})}{\frac{\text{ID}(\mu\text{Ci})}{w(\text{kg})}}$$

where C = activity at a pixel within the tissue defined by region of interest and ID = injected dose per kilogram of patient's body weight (w). The maximum SUV within the selected regions of interest was used (maxSUV). The percent change of the maxSUV was calculated by the following formula:

$$\frac{\text{maxSUV initial} - \text{maxSUV final}}{\text{maxSUV initial}} \times 100.$$

Patients who had PET scans performed at outside hospitals were included in this trial if the scan was performed on a dedicated PET camera with bismuth germanate crystals. All patients were carefully staged, and biopsy of all regional lymph nodes was performed via EUS-FNA as previously described.⁷ However, if nodes were peritumoral, they were labeled malignant or benign on the basis of their echogenicity criteria as assessed by EUS. Only lymph nodes that were initially biopsied and proven to be malignant were considered in the analysis of the change in the maxSUV of malignant lymph nodes. Peritumoral nodes that were only judged as malignant or benign on the basis of their echogenicity were not included in this analysis. Biopsies were performed on all suspicious M1 metastatic lesions unless

cancer was suspected in the bone or brain, where magnetic resonance imaging was considered to be the gold standard.

Surgical Technique

All patients underwent Ivor Lewis esophagogastrectomy as previously described, which includes the removal of lymph nodes from the celiac axis and a thoracic lymphadenectomy.^{7,8} In brief, patients had a double-lumen endotracheal tube and an epidural placed (arterial lines and central lines were rarely used). A midline laparotomy incision was performed; after exploration, to rule out metastatic disease, the stomach was mobilized via the right gastroepiploic artery. The preferred treatment of the pylorus was injection of botulinum toxin, which was used exclusively instead of other emptying procedures for the latter part of this study.⁹ A feeding jejunostomy was placed. Patients then underwent a right thoracotomy using a muscle-sparing, rib-sparing, nerve-sparing technique,¹⁰⁻¹² and the esophagus was mobilized off the aorta and all regional lymph nodes were removed. A hand-sewn anastomosis was performed 2 to 4 cm above the divided azygous vein.

Pathologic Analysis

The entire gastroesophageal junction was submitted at approximately 4-mm intervals. For the study, a single pathologist (T.S.W.) reevaluated the sections to arrive at a percentage of nonviable tumor. The number of sections considered to contain tumor included all sections with tumor, ulcer, scar and necrosis. The percent of nonviable tumor was defined as the combined percentage of scar and necrosis. The percent of tumor was derived from estimates of the amount of tumor in each section divided by the amount of scar and necrosis in that section. If only 1 of a few sections of ulcer or scar contained tumor, these were added to the total of scar and necrosis. For example, 2 of 6 sections contain approximately 25% tumor. The derived percent tumor would be $0.25 \times 2/6 \sim 10\%$ residual tumor. No attempt was made to estimate closer than $\pm 5\%$, except for those with minimal residual disease. Patients with mixed tumors were labeled with squamous cell or adenocarcinoma according to the predominant cellular type seen. Complete pathologic response was defined as 1% or less of viable tumor cells detected on pathologic review of the entire resected specimens. Partial response was defined as 20% to 98% cellular death of cancer, and minimal response was defined as less than 20% cellular death of cancer in the resected specimen.

In addition, the response of metastatic, regional esophageal lymph nodes that were initially biopsied and proven to be cancer was also assessed for pathologic response. Each lymph node measuring less than 1 cm was evaluated as a single cross-section. For larger lymph nodes, additional cross-sections were evaluated, approximately 1/5 mm. Lymph nodes were labeled as having recalcitrant disease, which was defined as having persistent cancer cell despite the neoadjuvant therapy given, or they were defined as benign or downstaged. This latter term was defined as no evidence of any malignant cells in the once malignant lymph node. The pathologists were blinded to all clinical, radiologic, and surgical findings.

Statistical Analysis

Analysis was conducted using SAS software 9.0 (SAS Corp, Cary, NC). Continuous data are presented as medians, and categorical data are presented as percentages. Fisher's exact test or Pearson's chi-square test was used to assess categorical data, and the Wilcoxon test was used to evaluate continuous variables. After ensuring data were normally distributed and homoscedastic, analysis of covariance was used to assess the relationship between the percent change in maxSUV and pathologic response. Multiple linear regression stepwise analysis was used to adjust for risk factors and to identify any variables that were independently associated with a complete response (age, gender, final pathologic stage, dose of radiation, cell type, and type of neoadjuvant therapy). The highest combined sensitivity and specificity values generated from the receiver operating characteristic curve that predicted complete pathologic responders were identified.¹³

TABLE 1. Patient characteristics (N = 86)

Median age (range) y	60 (36–78)
Gender, male	64
Initial stage	
Stage IIA (T2-3N0M0)	67
Stage IIB (T1-2N1M0)	13
Stage III (T3N1 or T4Nx)	6
Radiotherapy (median dose)	50.4 Gy
Median duration between last neoadjuvant treatment and surgery (range)	39 d (34–56 d)
Tumor histology	
Adenocarcinoma	53 (62%)
Squamous cell carcinoma	24 (28%)
Not otherwise specified/other	9 (10%)
Final pathology	
pCR (T0N0M0)	37
Stage I (T1N0M0)	22
Stage IIA (T2-3N0M0)	11
Stage IIB (T1-2N1M0)	9
Stage III-IV (T3N1 or T4Nx), M1	7

pCR, Complete pathologic response.

RESULTS

There were 253 patients who underwent esophagogastrectomy between January 1997 and June 2008 by 1 surgeon, and 221 patients underwent an Ivor Lewis approach. The remaining 32 patients underwent a transhiatal total esophagogastrectomy with a gastric to pharyngeal anastomosis, thoracoabdominal, or colonic interposition esophagogastrectomy and were not included in this study. Eighty-six of these patients who underwent Ivor Lewis esophagogastrectomy had an initial and repeat PET scan performed at the same center and formed the cohort of this study. The patient characteristics of these 86 patients are shown in Table 1. The median number of lymph nodes that were removed were 24 (range, 14–41). Of these 86 patients, 37 (43%) were complete responders and the median maxSUV of their esophageal cancer decreased by 72% (range 20%–100%, 95% confidence interval [CI] 68%–85%). The median maxSUV decreased by 58% in the 31 patients who were partial responders (range 0%–99%; 95% CI, 52%–65%). The median maxSUV of the primary tumor decreased only 37% in 18 patients with a minimal response (range –38%–93%; 95% CI, 29%–43%). These differences were statistically significant ($P < .001$).

There were 37 complete responders. Receiver operating characteristic analysis, as shown in Figure 1, indicates that when the maxSUV decreased by more than 64% (64% sensitivity, 81% specificity), the patient was likely to be a complete responder ($P = .003$, area under the curve 0.75). Six patients who had a decrease in their maxSUV of 64% or greater of the primary tumor were not complete responders, but tumors had more than 80% cellular death in all 6 patients, were pathologic node negative in all but 1 patient, and were T1 or T2N0M0 on final pathology in 4 of 6

FIGURE 1. Receiver operating characteristic curves of sensitivity (solid lines) plotted against 100 minus specificity for FDG-PET. When the maxSUV decreased by less than 64% (64% sensitivity, 81% specificity), the patient was likely to be a complete responder ($P = .003$, area under the curve = 0.75). Dashed line indicates 95% confidence interval.

patients. In addition to the percent change in the primary tumor's maxSUV, the percent change in the maxSUV of biopsy-proven metastatic regional lymph nodes was also assessed. Sixteen patients had 1 or more lymph nodes that had its maxSUV recorded during their initial PET scan and had biopsy-proven cancer. The median percent change in the maxSUV of these lymph nodes in patients whose nodes were initially malignant and then removed and were pathologically benign was 73% (11 patients). Five patients had recalcitrant disease in a removed lymph node, and the median percent change in that node was only 45% (Table 2). There was no statistically significant difference between these groups ($P = .325$).

DISCUSSION

The clinical importance of determining pathologic response is well documented for patients with both non-small cell lung cancer (NSCLC) and esophageal cancer. This information, if accurate, can be used to change chemotherapeutic regimens, add radiotherapy, and help decide who is best served by surgery. The concept of a prospective study that would randomize patients with esophageal cancer who appear to be complete responders to receive either surgery or observation has been discussed at several national and international meetings. However, the ability to accurately make this determination before surgical resection is elusive. Until now, surgical resection has been the only reliable manner to discern who is a pathologic complete responder. This

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TABLE 2. Change in the maximum standardized uptake value of biopsy-proven metastatic esophageal lymph nodes based on pathologic response

Type of pathologic response of lymph node	No. patients	% change in maxSUV, median (range)
Benign after neoadjuvant chemoradiotherapy	11	73% (–16% to –100%)
Recalcitrant nodal disease	5	45% (+24% to –100%)

maxSUV, maximum standardized uptake value.

article presents data showing that repeat PET (when both PET scans have been performed at the same centers no sooner than 30 days after the completion of the neoadjuvant chemoradiotherapy) may be a reliable tool to provide such information. In this retrospective study, we showed that the percent change in the maxSUV was a sensitive predictor of complete response. Moreover, the decrease in percent change was less as the response of the tumor to the therapy was less. Akhurst and colleagues in 2002¹⁴ reported a retrospective series on 56 patients and found that FDG-PET after induction therapy accurately detected residual viable primary tumor. Our 3 previous reports have demonstrated the change in maxSUV of patients with NSCLC. Repeat PET was shown to predict the response of mediastinal (N2) lymph nodes in NSCLC in 2003,¹⁵ and in 2004¹⁶ we showed a near linear relationship between the percent of necrotic lung cancer and the percent decrease in the maxSUV. However, Port and colleagues in 2004¹⁷ showed that the change in the maxSUV was not an accurate predictor of pathologic response in patients with NSCLC. In that study though, Port and colleagues did not specify that the repeat PET was performed at the same center as the initial PET. In 2005¹⁸ we showed the role that repeat PET and the change in maxSUV (as well as repeat EUS-FNA) play in the restaging of patients with esophageal cancer. Despite their early negative study results on repeat PET in patients with lung cancer, Port and colleagues¹⁹ in 2007 reported that a decrease in maxSUV by 50% or more after induction therapy was significantly associated with complete response or pathologic downstaging.

The maxSUV remains a controversial part of PET scan reporting. During the past several years, more nuclear radiologists are reporting this number because of the large number of studies that have shown its clinical importance.^{20,21} The differences in techniques used by various centers influence the SUV values. Our goal is for the maxSUV at one center to have the same “oncologic clinical meaning” as the maxSUV at another center and for the values to be universally translatable. However, this has not come to fruition. Because the formula has only 3 variables, one would think this goal should be easy to accomplish. The formula for the maxSUV has 3 variables. One variable is the activity at a pixel, which should be universally reproducible at all centers on the basis of the software used to calculate it. The second variable is the

patient’s weight, which also should be globally reproducible. The third variable is the injected dose of FDG. This variable may be the most difficult to standardize because the entire dose of FDG may not be given intravenously and the wells that calibrate the amount of FDG given may not be accurate. Finally, other variables make the maxSUV different at various centers, for example, the time between the completion of the injected FDG and the scanning, and the patient’s glucose level at the time of the scan. We believe these differences will be slowly resolved; however, for now the maxSUV from one center is too different from the maxSUV at another center. For these reasons, we mandated that the initial and repeat PET be performed at the same center.

Limitations and Strengths

Limitations of the study include the following: a) its retrospective nature; b) only 86 of the 221 Ivor Lewis esophagogastrectomies were included in the analysis because many patients did not receive neoadjuvant therapy, standardized uptake values were not reported, or patients did not have both the initial and the repeat PET scans at the same center; and c) an accuracy of only approximately 75%, as suggested by the area under the curve in Figure 1. Strengths of the study include the following: a) stringent entry criteria; b) the study was performed on a consecutive series of patients; c) patients underwent surgery within 40 days of the repeat PET scan; d) all patients had their initial and repeat PET scans performed at the same center; e) all patients had an Ivor Lewis esophagogastrectomy, and thus their lymph nodes were removed in addition to the esophagus (some patients have pTON1 disease); and f) the consistent timing between the last dose of the neoadjuvant chemoradiotherapy and the repeat PET scan. Our previous study for repeat imaging for NSCLC showed that PET was most efficacious when repeated at 4 weeks after the last dose of neoadjuvant therapy.⁵ Studies show that repeat PET at a shorter duration may result in a low negative predictive value. Mamede and colleagues²² performed PET scans at 22.3 ± 14.5 days from completion of treatment and observed a low negative predictive value because of inflammation (41%–83%). Swisher and colleagues²³ performed PET scans between 21 and 35 days from completion of treatment and again noted the difficulty in differentiating inflammation from residual tumor when PET was performed too soon after completion of radiation. In 2007, Kim and colleagues²⁴ performed PET scans between 14 and 21 days and reported many false-positive specimens.

CONCLUSIONS

This retrospective study showed that when initial and repeat PET scans are performed at the same center at least 30 days after the completion of preoperative chemoradiotherapy, the percent change in the maxSUV is a predictor of

the response to chemoradiotherapy by a patient with esophageal cancer. When the maxSUV decreases by 64% or more, it is likely that the patient is a complete responder. These data may help identify patients for a future randomized study that compares observation with surgical resection in patients with esophageal cancer who appear to be complete responders. However, until that study is completed, our preference remains surgical resection for the complete responder.

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