Predictive Value of 18-Fluoro-Deoxy-Glucose-Positron Emission Tomography (^{18}F-FDG-PET) in the Identification of Responders to Chemoradiation Therapy for the Treatment of Locally Advanced Esophageal Cancer

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Objective: To evaluate the utility of ^{18}F-FDG-PET in predicting response to concomitant chemoradiation in locally-advanced esophageal cancer.

Summary Background Data: Approximately 25% of esophageal cancer patients experience a pathologic complete response (pCR) to preoperative chemoradiation therapy. Computed tomography, endoscopy, and endoscopic ultrasound are unable to identify patients experiencing a pCR. Growing evidence supports the use of ^{18}F-FDG-PET in the staging of esophageal cancer in its ability to detect occult metastatic and lymph nodal disease. The identification of patients with a pCR to chemoradiation could potentially spare those patients the morbidity associated with a resection.

Methods: Eligibility criteria included T3-T4N0M0 or T1-T4N1M0 esophageal cancer. Patients underwent an initial ^{18}F-FDG-PET before treatment and then repeated 4 to 6 weeks after chemoradiation, prior to the esophagectomy. Chemoradiation consisted of: cisplatinum, 5-fluorouracil, and radiation to a median dose of 50.4 Gy. Pathologic response was determined from a systematic review of the esophagectomy specimens.

Results: Sixty-four patients have completed therapy to date. Response was as follows: pCR 27%, pathologic residual microscopic (pCR$_{micro}$) 14.5%, partial response 19%, and stable or progressive disease 39.5%. A pretreatment standardized uptake value (SUV$_{max1 hour}$) ≥15 was associated with an observed 77.8% significant response (pCR + pCR$_{micro}$) compared with 24.2% for patients with a pretreatment SUV$_{max1 hour}$ <15 ($P = 0.005$). Significant response was observed in 71.4% of patients with a decrease in SUV$_{max1 hour}$ ≥10 compared with 33.3% when the SUV$_{max1 hour}$ decreased <10 ($P = 0.004$).

Conclusions: Pretreatment and posttreatment ^{18}F-FDG-PET can be useful for predicting significant response to chemoradiation in esophageal cancer. These data should be considered in evaluation of patients for esophagectomy after chemoradiation.

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Over the last 2 decades, concomitant chemoradiation followed by esophagectomy for locally advanced esophageal cancer has become a standard treatment option despite conflicting results from randomized trials.[1–7] The prognosis of esophageal cancer following combined modality therapy remains poor, with long-term control rates of 25% to 35%.[8] In modern studies, chemoradiation results in complete eradication of tumor in histologic specimens in 11.4% to 51% of patients with only microscopic residual in as many as 54%.[5–7,9–12] When stratified by response to chemoradiation, investigators have identified a subgroup of patients with excellent long-term local control rates and improved long-term survival.[1,5,10,13] For this reason, identifying responders to chemoradiation has prognostic value that may change clinical management.

Recently, ^{18}F-FDG-PET was shown to improve sensitivity, specificity, and accuracy over computerized tomography (CT) and endoscopic ultrasound (EUS) in the initial staging of esophageal cancer patients.[14–17] This improvement has led to the avoidance of unnecessary resections in patients with occult metastatic disease missed by CT or EUS. Similarly, CT and EUS have been shown to be poor predictors of response to chemoradiation with low accuracy in the post-chemoradiation setting.[18] In head-to-head comparison, ^{18}F-FDG-PET was shown to be superior to CT and EUS in determining post-chemoradiation stage.[19] Several preliminary studies using ^{18}F-FDG-PET in the post-chemoradiation setting are now available demonstrating strong associations of a ^{18}F-FDG-PET-based response to histologic response and improved overall survival.[20–25] To further delineate the util-

ity of ^{18}F-FDG-PET in detecting response to chemoradiation in esophageal cancer, we conducted a prospective trial to correlate pre-chemoradiation ^{18}F-FDG-PET, with post-chemoradiation ^{18}F-FDG-PET, and pathologic tumor response assessed in esophagectomy specimens. In addition, we evaluated the test characteristics of ^{18}F-FDG-PET in determining post-chemoradiation restaging.

MATERIALS AND METHODS

From January 4, 2000 to August 24, 2004, 64 consecutive patients, with potentially curable, locally advanced esophageal cancer were either enrolled into a prospective phase II trial or formally monitored off-study. Institutional review board approval was obtained for both treatment groups. All patients underwent physical examination, chest and abdominal CT, endoscopy, baseline blood testing, and at least one ^{18}F-FDG-PET scan. Bone scan was performed only if clinically indicated. The clinical tumor-node-metastasis system stage was defined according to the 2002 (version 6.0), American Joint Committee on Cancer staging system. EUS was performed in 52 (81.3%) patients and EGD in 12 (18.7%). A total of 57 patients were staged with ^{18}F-FDG-PET before chemoradiation and 50 patients were staged with ^{18}F-FDG-PET after chemoradiation. Pre- and post-chemoradiation ^{18}F-FDG-PET imaging was available for 46 patients.

Treatment

Radiation Therapy

All patients received preoperative chemoradiation to a median radiation dose of 50.4 Gy concurrent with chemotherapy. Radiation was delivered in 1 of 2 fashions. Standard radiation was performed in 42 patients (66%) with 1.8- to 2-Gy fractions to an initial dose of 39.6 Gy followed by an off-cord boost for a total dose of 45 to 54 Gy. A total of 22 patients (34%) were enrolled on an institutional phase II trial and were treated with a hyperfractionated radiation schedule using a concomitant boost technique. During week 1 of the chemotherapy, patients received 1.6 Gy each AM to a large AP:PA field followed by 1.6 Gy treatments each PM to an off-cord oblique boost volume. During weeks 2 to 4, patients received 1.8 Gy once-daily to a large AP:PA field and no chemotherapy. During week 5, patients received chemotherapy and 1.6 Gy delivered twice-daily to an off-cord oblique boost volume. The total radiation dose delivered over the 5 weeks was 59 Gy.

Chemotherapy

Patients enrolled in the phase II trial received cisplatinum and 5-fluorouracil (5-FU)-based chemotherapy. The chemotherapy dosage was as follows: cisplatinum: 100 mg/m^2 on day 1 of radiation therapy along with 5-FU given at 1000 mg/m^2 per day by continuous infusion for 96 hours. The 5-FU was started immediately after completion of the cisplatinum infusion on days 1 to 4 and a second course of 5-FU was given during week 5 (days 29–32) concurrent with the radiation therapy. For patients not formally enrolled into the phase II trial, the chemotherapy regimens were as follows: cisplatin and 5-FU in 38 patients, carboplatinum and 5-FU in 8

patients, paclitaxel and carboplatinum in 3 patients, 5-FU as a single agent in 2 patients, and mitomycin C with 5-FU in 2 additional patients. Detailed chemotherapy records were not available in 9 patients who received concurrent chemoradiation. Chemotherapy was declined by 2 patients.

Surgery

Exploratory laparotomy was performed 4 to 6 weeks after chemoradiation in patients eligible for esophagectomy. Esophagectomy was not performed in 16 patients for the following reasons: 1 patient had undergone previous partial esophagectomy 12 years prior, 1 patient died during chemoradiation, 3 patients were upstaged to M1 after chemoradiation, 2 refused esophagectomy, and 9 were not offered esophagectomy based on medical comorbidities. Forty-eight patients underwent exploratory laparotomy with completion esophagectomy in 44. One patient undergoing esophagectomy who declined chemoradiation was excluded from this analysis. Of the 43 patients undergoing chemoradiation followed by esophagectomy, R0 resections were achieved in 38 (86.4%), R1 resections were performed in 4 (10.6%) with positive radial margins, and 1 had unknown margins. Unresectable disease was found in 4 patients at exploratory laparotomy due to matted celiac nodes (1), liver metastases (2), or peritoneal carcinomatosis (1). Total gastrectomy was performed in 2 patients for disease that was widely resectable via laparotomy alone. Esophagectomy was performed by transhiatal technique (21) or transthoracic technique (21) at the discretion of the treating surgeon.

Scoring of Response to Chemoradiation

All pathologic specimens were reviewed by a single pathologist who was blinded to the results of the ^{18}F-FDG-PET. Response was scored in 5 categories: pathologic complete response (pCR), pathologic microscopic residual disease (pCR$_{micro}$), pathologic partial response (pPR), pathologic stable disease (pSD), or pathologic progressive disease (pPD). pCR was defined as no tumor in the pathology specimen and pCR$_{micro}$ was defined as residual microscopic disease in the specimen with questionable viability. Partial response, stable disease, and progressive disease were defined as a post-chemoradiation T or N stage less than the pre-chemoradiation T and N stage, a post-chemoradiation T or N stage equal to the pre-chemoradiation T and N stage, or a post-chemoradiation T or N stage greater than the pre-chemoradiation stage, respectively. For comparisons, patients experiencing a pCR or pCR$_{micro}$ were termed significant responders and were compared with patients experiencing a PR, SD, or PD after chemoradiation. Patients with metastatic disease at any site were considered to have PD regardless of the response in the radiation field.

Positron Emission Tomography

Pretreatment and post-treatment ^{18}F-FDG-PET scans were performed. A GE Advance PET scanner was used in all patients with a standard resolution of 6 to 8 mm. Blood glucose was determined prior to injection of ^{18}F-FDG. Patients with blood glucose <150 mg/dL proceeded with radiopharmaceutical injection and imaging. Patients received 15 to

20 mCi ^{18}F-FDG after 4 hours of fasting. Emission images were obtained from the chin to the pelvis. Attenuation correction was performed using transmission scans. Imaging was performed 1 hour post-radiopharmaceutical injection. ^{18}F-FDG-PET images were interpreted by an experienced nuclear radiologist and correlated with CT. The qualitative criteria for malignancy included discrete areas of increased F-FDG activity greater than the blood pool activity. Quantitative and qualitative analysis of PET images was performed by one nuclear medicine physician. Regions of interest were placed over the qualitatively visualized area of maximum F-FDG activity within the tumor. Similar regions of interest were used on pre- and post-therapy scans. ^{18}F-FDG-PET studies that demonstrated a diffuse area of increased activity were scored as inflammation. Quantitative analysis was performed using standardized uptake values and calculated as the maximum value 1 hour post-radiopharmaceutical injection ($SUV_{max1 hour}$). The $SUV_{max1 hour}$ is the amount of radioactivity in the region corrected for decay, to the time of injection, normalized by the patient's lean body mass and the injected dose.

Of the 44 patients undergoing esophagectomy following chemoradiation, 31 patients had both a pre-chemoradiation and post-chemoradiation ^{18}F-FDG-PET imaging study, while 13 patients had a single ^{18}F-FDG-PET scan: 10 patients of which had a pre-chemoradiation study and 3 of which had post-chemoradiation imaging. Definitive pathologic specimens for correlation with ^{18}F-FDG-PET were available in 41 patients with pre-chemoradiation ^{18}F-FDG-PET staging and 34 patients with post-chemoradiation ^{18}F-FDG-PET staging. Based on the interpretation by the nuclear radiologist as either positive for cancer or negative for cancer, the test characteristics of the post-chemoradiation ^{18}F-FDG-PET scan were calculated.

After treatment, all patients were evaluated with history, physical examination, chest and abdominal CT scans every 3 months for the first 2 years, then every 6 months for the next 3 years, and then at the discretion of the treating physician.

Stastitical Anlysis

Treatment factors that were analyzed included pCR and pCR_{micro} after chemoradiation versus macroscopic residual disease after chemoradiation. ^{18}F-FDG-PET parameters that were analyzed included pretreatment $SUV_{max1 hour} \geq 15$ versus ≤ 15, magnitude decrease in $SUV_{max1 hour}$ following preoperative chemoradiation and percent decrease in $SUV_{max1 hour}$ following chemoradiation. Differences in pre- and post-chemoradiation $SUV_{max1 hour}$ were analyzed using a Student t test. χ^2 and Fisher exact test were performed using Graphpad Prism version 4.00 for Windows, Graphpad software (San Diego, CA; www.graphpad.com).

RESULTS

Treatment Response

Patient characteristics are shown in Table 1. Of the 48 patients who underwent pathologic staging after chemoradiation, a pCR was found in13 patients (27.1%), a pCR_{micro} in was found in 7 patients (14.5%), a partial response was

TABLE 1. Patient Characteristics: All Patients (n = 64)

Characteristic	Value
Age (yr)	
Mean	60.6
Range	41.8–83.7
Male/Female (%)	82.8/17.2
Black/White/Hispanic or Asian (%)	12.5/85.9/1.6
Median ECOG	1
Range	0–2
Weight loss >10% body weight (%)	42.2
Histology (%)	
Adenocarcinoma	81.3
Squamous	14.1
Undifferentiated	4.7
Location (%)	
Cervical	6.3
Middle	10.9
Lower	37.5
Gastroesophageal junction	45.3
Surgery (%)	
Transhiatal esophagectomy	32.8
Ivor-Lewis esophagectomy	32.8
Exploratory laparotomy	6.3
None	28.1
Pretreatment 2002 AJCC staging (%)	
Stage I	3.1
Stage IIA	23.4
Stage IIB	15.6
Stage III	39.1
Stage IVa	12.5
Stage IVb	6.3
^{18}F-FDG PET (%)	
Pre-chemoradiation	21.9
Pre- and post-chemoradiation	71.9
Post-chemoradiation	6.3

ECOG indicates Eastern Oncology Cooperative Group performance status.

observed in 9 patients (18.75%), and either stable or progressive disease was found in 19 (39.5%) patients. Of the 29 patients (61.4%) experiencing significant clinical downstaging after chemoradiation, 20 were associated with having either no or microscopic residual disease (pCR or pCR_{micro}) in the esophagectomy specimen.

Predictive Value of Pre-chemoradiation ^{18}F-FDG-PET

Of the 57 patients with pre-chemoradiation ^{18}F-FDG-PET imaging, the mean $SUV_{max1 hour}$ was 9.9 (0–36.6) ± 1.0. Of the 49 patients with post-chemoradiation ^{18}F-FDG-PET imaging, the mean $SUV_{max1 hour}$ was 4.4 (0–9.7) ± 0.4. There was a significant decrease between mean $SUV_{max1 hour}$ before and after chemoradiation ($P = <0.001$). The mean $SUV_{max1 hour}$ was higher in patients experiencing a pCR or pCR_{micro} when compared with patients with macroscopic disease after chemoradiation (13.4 ± 2.5 versus 7.1 ± 2.5, $P = 0.02$). A pre-chemoradiation ^{18}F-FDG-PET $SUV_{max1 hour} \geq 15$ was associated with significant response to therapy with 7 of 9 patients

TABLE 2. Response to Chemoradiation by Pretreatment ^{18}F-FDG PET $SUV_{max1\ h}$

Pre-chemoradiation $SUV_{max1\ h}$	pCR or pCR_{micro}	Macroscopic Residual
>25	2	1
>20	2	0
>15	3	1
>10	1	3
>7.5	2	6
>5	3	5
>2.5	1	9
0–2.5	2	2

$SUV_{max1\ h}$ indicates maximum standardized uptake value at 1 hour post-radio-pharmaceutical injection; pCR, pathologic complete response; pCR_{micro}, <10% residual microscopic disease.

TABLE 4. Response to Chemoradiation by % ^{18}F-FDG PET $SUV_{max1\ h}$ Change

% Reduction in $SUV_{max1\ h}$ After Chemoradiation	Microscopic Disease Only	Macroscopic Disease
80–100	1	2
60–80	5	7
40–60	5	3
20–40	0	1
0–20	0	1
SUV increase	1	5

$SUV_{max1\ h}$ indicates maximum standardized uptake value at 1 hour post-radio-pharmaceutical injection.

(77.8%) experiencing a pCR or pCR_{micro} at the time of surgery. Patients with a pre-chemoradiation $SUV_{max1\ hour}$ <15 however, were less likely to experience a significant response; only 9 of 34 patients or 26.4% were found to have a pCR or pCR_{micro} at the time of pathologic review ($P = 0.005$). A pre-chemoradiation $SUV_{max1\ hour} \geq 10$ was associated with, but less likely to predict for, a significant response to treatment; only 10 of 15 patients (67%) demonstrated a significant response to treatment compared with 8 of 30 (26.7%) having a significant response with a pre-chemoradiation $SUV_{max1\ hour}$ <10 ($P = 0.043$). Table 2 provides a complete report of the correlations between response to therapy and pre-chemoradiation $SUV_{max1\ hour}$.

In the 31 evaluable patients with pre- and post-chemoradiation ^{18}F-FDG-PET imaging and definitive pathology, the mean decrease in $SUV_{max1\ hour}$ for patients with significant response (pCR or pCR_{micro}) to chemoradiation was 10.9 ± 2.9 whereas the mean difference in $SUV_{max1\ hour}$ for the patients with macroscopic disease after chemoradiation was 4.8 ± 1.5 ($P = 0.05$). Pathologic response based upon magnitude of $SUV_{max1\ hour}$ changes are shown in Table 3. In patients with a magnitude $SUV_{max1\ hour}$ decrease of >5 units, 9 of 17 patients (52.9%) had a significant response to chemoradiation versus 3 of 14 patients (21.4%) with a $SUV_{max1\ hour}$ decrease <5 ($P = 0.155$). For patients experiencing an $SUV_{max1\ hour}$ decrease >10, which was limited to only 7 patients, 5 of those 7 patients (71.4%) experienced a

TABLE 3. Response to Chemoradiation Grouped by Decrease in ^{18}F-FDG PET $SUV_{max1\ h}$

Decrease in $SUV_{max1\ h}$ After Chemoradiation	Microscopic Disease Only	Macroscopic Disease
>15	4	1
>10	1	1
7.5–10	0	3
5–7.5	4	3
2.5–5	1	4
0–2.5	1	2
SUV increase	1	5

$SUV_{max1\ h}$ indicates maximum standardized uptake value at 1 hour post-radio-pharmaceutical injection.

significant response to chemoradiation versus only 7 of 21 patients (33.3%) with an $SUV_{max1\ hour}$ decrease ≤ 10 ($P = 0.004$).

The median percent decrease in $SUV_{max1\ hour}$ after chemoradiation was 52.8% (100% decrease to 84% increase). There was no difference in percent $SUV_{max1\ hour}$ reduction between patients experiencing a significant response (pCR or pCR_{micro}) to therapy versus those patients having less of a response (PR, SD, or PD) after chemoradiation ($P = 0.871$). Pathologic response based on percent $SUV_{max1\ hour}$ change is shown in Table 4. With a decrease in $SUV_{max1\ hour}$ >40%, 11 of 23 (47.8%) experienced a significant response to compared with only 1 of 8 patients (12.5%) with a $SUV_{max1\ hour}$ decrease $\leq 40\%$ ($P = 0.108$).

Analysis of ^{18}F-FDG-PET Parameters and Response by Treatment Received

Forty-two patients received daily radiation to 45 to 54 Gy and 22 received accelerated hyperfractionated radiation with dose escalation to 59 Gy. The treatment duration was 5 weeks in both groups. There was a higher proportion of patients experiencing pCR or pCR_{micro} in the daily radiation treatment group versus the hyperfractionated group (55% versus 25%, $P = 0.045$). Overall, pretreatment and post-chemoradiation ^{18}F-FDG-PET mean $SUV_{max1\ hour}$ values, between treatment groups (daily versus twice daily radiation) were similar (11 versus 9.3, $P = 0.45$). Likewise, the magnitude change in the ^{18}F-FDG-PET mean $SUV_{max1\ hour}$ values between groups was similar (5.8 versus 8.1, $P = 0.39$). Also, the timing of ^{18}F-FDG-PET was similar where pre- and post-chemoradiation ^{18}F-FDG-PET were separated by a median of 2.5 months in both groups. In the hyperfractionated radiation group, patients experiencing a pCR or pCR_{micro} had a higher pretreatment $SUV_{max1\ hour}$ when compared with nonresponders (17.3 versus 8.2, $P = 0.022$). In the once daily radiation group, there was a trend toward higher mean $SUV_{max1\ hour}$ in patients experiencing pCR or pCR_{micro} (11.6 versus 6, $P = 0.11$).
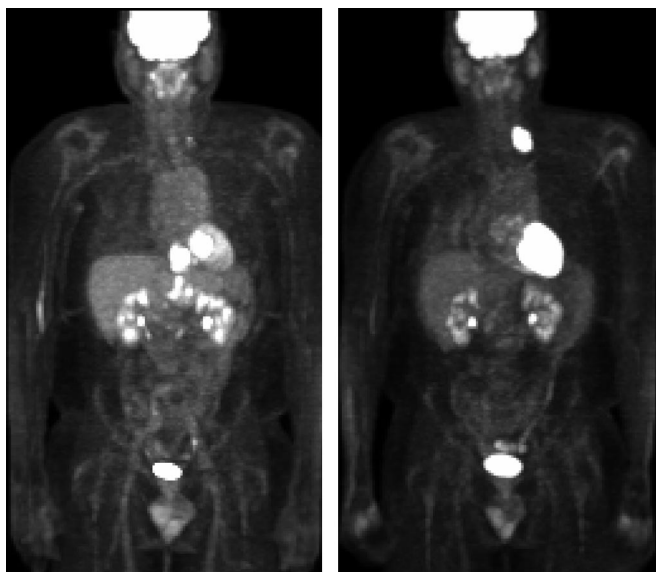
Patterns of Failure in Patients Experiencing pCR and pCR_{micro}

Of the 20 patients with significant response in this series (pCR and pCR_{micro}), 8 patients are alive without disease, 7 patients have died without disease, and only 5

patients experienced disease recurrence (2 local and distant failure, 2 with distant failure only, 1 with out-of-radiation portal nodal failure). After excluding patients who died within 90 days of surgery, the median overall survival for patients experiencing a pCR or a pCR_{micro} was 36 months compared with 24 months in poorly responding patients ($P = 0.4$).

Sensitivity and Specificity for Post-chemoradiation ^{18}F-FDG-PET

Definitive pathologic specimens were available in 41 patients with post-chemoradiation ^{18}F-FDG-PET imaging. Figure 1 provides examples of pre- and post-chemoradiation imaging with ^{18}F-FDG-PET. The best detection of primary disease was accomplished with an $SUV_{max1\ hour}$ cutpoint of 4 with sensitivity, specificity, and positive and negative predictive values of 61.3%, 60.0%, 82.6%, and 33.3%, respectively. See Table 5 for the complete characteristics of post-chemoradiation ^{18}F-FDG-PET. Table 6 demonstrates the test characteristics of ^{18}F-FDG-PET in the detection of disease outside the primary tumor. Scans were interpreted as either positive or negative for this calculation. Sensitivity and specificity for the detection of metastatic disease were 83.3% and 88.2% with a positive and negative predictive value of 55.6% and 96.7%, respectively. Test characteristics for detecting lymphadenopathy in the mediastinum, perigastric, and celiac areas were associated with high specificity and negative predictive value ranging from 85.7% to 100% and 82.4% to 92.3%, respectively. Also, post-chemoradiation ^{18}F-FDG-

TABLE 5. Test Characteristics of ^{18}F-FDG PET$_{max1\ h}$ for Esophageal Cancer

$SUV_{max1\ h}$ Cutpoint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0	96.7	9.1	75.0	50.0
2	88.9	16.7	70.6	40.0
4	61.3	60.0	82.6	33.3
5.5	35.7	70.0	76.9	28.0
6	28.5	80.0	80.0	28.6
8	11.1	90.9	75	29.4
10	0	90.9	0	29.7

$SUV_{max1\ h}$ indicates maximum standardized uptake value at 1 hour post-radiopharmaceutical injection; PPV, positive predictive value; NPV, negative predictive value.

PET detected gastric invasion with high specificity, sensitivity, and predictive values.

DISCUSSION

This prospective analysis reports the predictive power of pretreatment ^{18}F-FDG-PET imaging for identifying patients likely to experience a significant pathologic tumor response following a course of preoperative chemoradiation. To our review, only a limited number of prospective studies have been published addressing the value of ^{18}F-FDG-PET for determining response to chemoradiation in this clinical setting.[20–24,26] An early trial reported by Weber et al describes an analysis of 40 esophageal cancer patients undergoing ^{18}F-FDG-PET imaging prior to chemotherapy and then repeated 14 days after chemotherapy.[21] The authors observed a strong correlation between ^{18}F-FDG-PET tumor response and the clinical response to therapy: a 35% reduction in tumor SUV_{max} post-chemotherapy was associated with an improved response and survival. In a separate report by Flamen et al, 36 patients with carcinoma of the esophagus underwent ^{18}F-FDG-PET imaging prior to receiving neoadjuvant therapy and then repeated prior to surgery.[23] The investigators observed that an 80% or greater reduction in the tumor-to-liver uptake ratio between the 2 ^{18}F-FDG-PET studies was predictive for clinical response and improved survival. Downey et al, in a study of 39 patients with adenocarcinoma of the esophagus undergoing ^{18}F-FDG-PET before and after chemoradiation, were also able to demonstrate an association between a large decrease in the post-chemoradiation tumor SUV_{max} with a significant response to treatment and survival.[24] In a larger series from Swisher et al, a strong correlation was observed between patient survival and a post-chemoradiation ^{18}F-FDG-PET $SUV_{max1\ hour} < 4$.[22] Interestingly, PET was not found to discriminate between complete response and microscopic residual disease as observed in our report. Further, the predictive values were poor for identifying residual esophageal disease, with a false negative rate of 18% and a false positive rate of 71%.

In contrast to our study, an elevated pretreatment ^{18}F-FDG-PET $SUV_{max1\ hour}$ has not been associated with significant response in any previous report. The reasoning for this remains unknown, but clear differences in the timing of

FIGURE 1. Demonstration of response and restaging by ^{18}F-FDG-PET. Left, Pre-chemoradiation imaging is displayed, revealing an abnormality consistent with malignancy within the esophagus (SUV 24), retroperitoneum, and celiac nodal station. Right, Post-chemoradiation imaging is displayed revealing resolution of the abnormality within the esophagus, retroperitoneum, and celiac nodal station. Interval development of a left supraclavicular lymph node is noted.

TABLE 6. Detection of Lymphadenopathy, Gastric Involvement, or Distant Metastasis by Postchemoradiation ^{18}F-FDG PET

Site	Number Assessable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Mediastinal or periesophageal lymph nodes	32	50	85.7	33.3	92.3
Perigastric lymph nodes	31	25	100	NA	90
Gastric involvement	31	100	95.7	88.9	100
Celiac involvement	37	14.3	93.3	50.0	82.4
Metastatic disease	40	83.3	88.2	55.6	96.7

PPV indicates positive predictive value; NPV, negative predictive value; NA, not available due to small sample size.

^{18}F-FDG-PET, the length of treatment, and calculation of ^{18}F-FDG-PET uptake intensity exist between available studies. In the report from Swisher et al, all patients underwent induction chemotherapy followed by concurrent chemoradiation.[22] Thus, the interval between pretreatment ^{18}F-FDG-PET and the completion of chemoradiation was 2 months longer than in our trial. Also, the SUV calculation in the series by Swisher et al did not correct for lean body mass, which was corrected in the present study. In the trial by Downey et al, the timing of ^{18}F-FDG-PET was similar to ours and SUVs were calculated, but only 17 patients underwent esophagectomy and ^{18}F-FDG-PET prediction of response was only suggested in their discussion.[24] Finally, Flamen et al reported liver-to-tumor ratios and did not report SUVs.[23]

One limitation to the present study is the inclusion of 2 separate treatment cohorts (conventional versus hyperfractionated radiation therapy). One cohort received twice-daily hyperfractionated radiation therapy to 59 Gy concurrent with 5-FU and cisplatinum chemotherapy. The second cohort received conventional once-daily radiation to 45 to 54 Gy concurrent with chemotherapy at the discretion of the treating physician. There was no difference between timing of ^{18}F-FDG-PET or treatment duration between groups. Also, there was no difference between pretreatment and post-chemoradiation ^{18}F-FDG-PET mean $SUV_{max1\ hour}$ values between treatment groups. Likewise, there was no difference in the magnitude change in the ^{18}F-FDG-PET mean $SUV_{max1\ hour}$ values between treatment groups. Interestingly, there was a higher response rate in the daily (conventional) radiation treatment group versus the hyperfractionated group. When analyzed by treatment received, the association of high pretreatment $SUV_{max1\ hour}$ with a significant response remained statistically significant in the hyperfractionated radiation group and approached significance in the daily radiation group. Despite the higher likelihood of significant response in patients receiving once-daily radiation therapy, there were no ^{18}F-FDG-PET-related differences identified that would signify any correlation of $SUV_{max1\ hour}$ with treatment given.

In contrast to other series, we scored pathologic specimens with only microscopic residual cells to be significant responders. These patients were coupled with the completely responding patients to improve statistical power in this study. The survival advantage in those patients experiencing a complete response to preoperative therapy are well documented.[25,27,28] Also, recent evidence indicates that patients with only microscopic residual disease after chemoradiation (those with less than 10% viable cells) experience excellent long-term disease-free and overall survival when compared with historical controls.[25,27,28] In this series, microscopic disease only (pCR$_{micro}$) is equivalent to the term "less than 10% viable cells" used elsewhere.[25,27,28] In comparison, our data support those earlier works. Further, while not statistically significant, the median survival of significant responders was 1 year longer than nonresponders. Also, in significant responders, there were only 4 out of 20 patients dead of disease, with 1 patient salvaged after an out of radiation-field nodal failure at last follow-up. In summary, the group of significant responders identified by ^{18}F-FDG-PET in this series had excellent disease-free and overall survival.

In using ^{18}F-FDG-PET-directed patient selection in esophageal cancer, the timing of ^{18}F-FDG-PET is strongly debated. Some investigators have suggested that the survival advantage for chemoradiation responders is realized only in patients undergoing esophagectomy.[6,12,29,30] Clearly, there is a subgroup of patients who experience long-term control after chemoradiation without surgical resection.[31,32] A recent European trial of locally advanced squamous cell carcinoma of the esophagus has demonstrated no overall survival benefit to the addition of esophagectomy to chemoradiation therapy.[33] On subgroup analysis, there was a significant survival detriment in nonresponders to chemoradiation, and survival was found to be improved for nonresponders undergoing R0 esophagectomy. It is not clear to us if the above results can be extrapolated to patients with adenocarcinoma of the esophagus. Our strategy would be to incorporate ^{18}F-FDG-PET for identifying a patient subgroup with a high probability of response, based on a pretreatment ^{18}F-FDG-PET. Following the results of this trial, patients with a low $SUV_{max1\ hour}$ could be managed with surgery alone or chemoradiation followed by esophagectomy, where potential responders might be managed by chemoradiation alone. Only a prospective trial of ^{18}F-FDG-PET-directed treatment can confirm the utility of such an approach stratifying treatment with ^{18}F-FDG-PET.

This study provides support for the utility of ^{18}F-FDG-PET to identify responders to chemoradiation. To determine if ^{18}F-FDG-PET SUV and pCR/pCR$_{micro}$ response in our study predicts for an improved overall survival will require additional long-term follow-up. Based upon our preliminary data and those studies previously discussed, we conclude that ^{18}F-FDG-PET is a useful tool for identifying esophageal cancer patients likely to experience a significant response to preoperative chemoradiation. Clearly multi-institutional prospective stud-

ies are needed to determine the feasibility of ^{18}F-FDG-PET for directing therapy for patients with locally advanced esophageal cancer.

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