Preoperative Chemo-Radiation-Induced Ulceration in Patients with Esophageal Cancer: A Confounding Factor in Tumor Response Assessment in Integrated Computed Tomographic-Positron Emission Tomographic Imaging

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Hypothesis: Positron emission tomography can be useful in predicting response of esophageal cancer after preoperative chemo-radiation therapy (CRT). We evaluated the use of integrated computed tomography (CT)-PET among patients with esophageal cancer being considered for resection after CRT.

Methods: Three reviewers blinded to clinical and pathologic staging retrospectively reviewed the CT-PET scans of patients with esophageal cancer after preoperative CRT who underwent esophagectomy. [^{18}F]-fluoro-2-deoxy-D-glucose uptake for residual malignancy was determined by visual analysis and semi-quantitatively when standardized uptake value (SUV) was ≥4.

Results: Forty-two patients underwent esophageal resection. Using visual analysis, CT-PET had a sensitivity of 47% and specificity of 58% in detecting residual malignancy. Using semi-quantitative analysis, 19 patients had a SUV ≥4 in the region of the primary esophageal tumor and were interpreted as having residual malignancy (sensitivity 43%, specificity 50%). Of these 19, six had complete pathologic response to CRT. These false-positive results, due to therapy-induced ulceration detected at endoscopy, limit the use of CT-PET alone in detecting residual malignancy. Similarly, sensitivity (25%) and specificity (73%) of endoscopy/biopsy in detecting residual malignancy were poor. However, the accuracy of CT-PET in detecting residual malignancy was improved when combined with endoscopic findings. In the absence of ulceration at endoscopy, 8 of 8 patients with SUV ≥4 after chemo-radiation had residual malignancy at surgery.

Conclusions: CRT-induced ulceration results in false-positive results on CT-PET and precludes accurate detection of residual esophageal tumor. However, CT-PET in combination with endoscopy is useful in identifying patients with a high risk of residual tumor post-CRT.

Key Words: Esophageal, Cancer, CT-PET, Chemotherapy, Radiation therapy.

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Esophageal cancer, an uncommon neoplasm with an estimated incidence of approximately 13,000 cases in the United States in 2002, has been increasing in incidence over the last few decades.[1] There is no universally accepted standard therapy; therefore, treatment is usually determined by patient performance status, clinical disease stage, and location of the primary cancer. Historically, treatment modalities have included surgery alone or chemotherapy with radiation.[2,3] More recently, multimodality therapy using preoperative chemotherapy and/or radiation followed by surgical resection for suitable candidates has been used in an attempt to improve survival.[4–10]

Computed tomography (CT) and endoscopy/endoscopic ultrasonography (EUS) are usually performed after preoperative therapy to assess the primary tumor, detect nodal and distant metastases, and determine tumor response. However, a major limitation of these modalities is that they are inaccurate in this determination.[11–16] The use of positron emission tomography (PET) with [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) in the evaluation of patients with esophageal cancer has been reported to be useful in predicting pathologic response and the disease-free interval and overall survival of patients after preoperative therapy.[5,14,17–23] However, the poor spatial resolution of PET compared with that of CT often precludes accurate assessment of the primary tumor and localization of nodal metastases, as well as detection of pulmonary metastases. The recent use of integrated CT-PET

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imaging with co-registration of anatomical and functional imaging data may improve the localization of regions of increased FDG-uptake and accuracy of staging among patients with esophageal cancer.[24,25] However, the role of FDG-PET and integrated CT-PET imaging in patients with esophageal cancer after preoperative therapy has not been fully elucidated. Therefore, in this article, we evaluate the role of CT-PET imaging in determining response to preoperative chemo-radiation therapy of the primary tumor and nodal metastases in patients with esophageal cancer being considered for resection.

PATIENTS AND METHODS

We retrospectively evaluated 56 consecutive patients with biopsy-proven primary esophageal cancer who were treated with chemo-radiation therapy followed by esophagectomy at our institution between February 2003 and July 2004. To assess a more homogenous study group, patients were excluded from the study group if CT-PET imaging was performed more than 4 months after completion of chemo-radiation therapy ($n = 7$), esophageal resection was performed more than 3 months after CT-PET imaging ($n = 1$), and detection of metastases by CT-PET imaging performed after preoperative chemo-radiation therapy ($n = 4$). Two patients were excluded from the study group because of detection of an unsuspected hepatic metastasis ($n = 1$) and non-resectable local disease because of invasion of the aorta by esophageal malignancy ($n = 1$) at the time of surgery performed for planned esophagectomy. The M. D. Anderson Cancer Center Institutional Review Board approved this study.

Preoperative Staging and Treatment

All 42 patients included in this study were required to have histologically diagnosed adenocarcinoma or squamous cell cancer of the esophagus before undergoing multimodality therapy. EUS, CT of the chest and abdomen, and PET imaging (CT-PET [$n = 29$], PET [$n = 11$]) were performed to determine pretreatment clinical stage. All patients were assigned a tumor, node, metastasis classification and categorized according to American Joint Commission on Cancer's 2002 guidelines for pathologic and clinical staging as determined by using endoscopy/EUS, CT, and PET imaging.[26] Patients whose tumors were considered to be resectable were eligible to receive preoperative chemo-radiation therapy (CRT). Criteria for preoperative CRT included: clinical stage II-IVA, age <80 years old, consent to treatment, and ability to tolerate esophagectomy as judged by multidisciplinary assessment performed by a thoracic surgeon, medical oncologist, radiation oncologist, and diagnostic radiologist.

Treatment Plan

All patients who were candidates for preoperative CRT were treated with chemotherapy followed by concurrent CRT ($n = 21$) or with concurrent CRT alone ($n = 21$). Three agents (fluorouracil, cisplatin, or a taxane) were used for preoperative chemotherapy. For radiation therapy planning, clinical target volume was defined as the gross tumor volume plus a 5-cm margin superior to the highest extension and inferior to the lowest extension of the cancer with a 2-cm radial margin. The total dose of radiation therapy was 45 Gy in 25 fractions or 50.4 Gy in 28 fractions prescribed to cover at least 95% of the planning target volume.

After CRT, patients were clinically reassessed by endoscopy with or without EUS and whole-body integrated CT-PET imaging. Esophagectomy was performed if a patient could physiologically tolerate surgical resection and was assessed as having stable disease or complete or partial response of the primary tumor or nodal metastases to therapy without interval development of systemic metastases. The type of esophagectomy performed depended on the tumor's location and individual surgeon's preference. Either a transthoracic approach (Ivor-Lewis [two-field] or total [three-field]) or a transhiatal approach to resection was used. Mediastinal and celiac lymph nodes were resected in all patients who underwent surgery.

CT-PET Imaging Parameters

An integrated CT-PET scanner (Discovery ST-8; General Electric Medical Systems, Milwaukee, MN) was used. PET images were acquired during shallow breathing in the two-dimensional mode for 3 minutes per bed position 60 to 90 minutes after the intravenous administration of 555 to 740 MBq of FDG. PET images were reconstructed using standard vendor-provided reconstruction algorithms with ordered subset expectation maximization. Emission data were corrected for scatter, random events, and dead-time losses with the manufacturer's software program, and images were reconstructed both with and without attenuation correction. Non–contrast-enhanced CT images were acquired in helical mode (speed, 13.5 mm/rotation) from the base of the skull to the mid thighs during suspended mid-expiration at 3.75-mm slice thickness, 140 kVp, and 120 mA.

CT-PET Imaging Interpretation

Clinical staging of disease after CRT was performed with CT-PET to assess for the presence of residual primary esophageal cancer and or nodal metastases. Residual esophageal malignancy was considered present if FDG-uptake in the region of the primary cancer was increased compared with the adjacent esophagus; lymph nodes, regardless of size, were interpreted as positive for metastasis if their FDG-uptake was increased. To determine the sensitivity, specificity, and accuracy of CT-PET in identifying residual esophageal cancer and nodal metastasis after preoperative CRT and before esophagectomy, three reviewers (two thoracic radiologists [J.J.E., R.F.M.] and one nuclear medicine physician [H.A.M.]) blinded to the results of post-CRT endoscopy and surgical pathology retrospectively interpreted the CT and PET scans, and findings were recorded by consensus. Clinical history, endoscopic reports, and all imaging studies performed at the time of the initial diagnosis were available to the readers.

The CT and PET images were reviewed on a Xeleris workstation (General Electric Medical Systems). CT, PET, and co-registered CT-PET images were available for review in all standard planes along with maximal intensity whole-body coronal projection images. PET scans were analyzed

visually and semi-quantitatively. FDG uptake was considered to be abnormal on visual analysis when uptake in the region of the primary tumor was substantially greater than the background activity of the adjacent esophagus on the attenuation-corrected images. Increased FDG-uptake in the primary tumor, loco-regional nodes, and distant metastatic disease was recorded. Additionally increased FDG-uptake in the region of the primary tumor was graded as diffuse (craniocaudal extent >3 cm) or focal (craniocaudal extent ≤3 cm). Diffuse and focal increased FDG-uptake was also visually assessed as central, eccentric mural, or symmetric circumferential. A pixel region of interest was outlined within regions of increased FDG-uptake and measured on each slice. Images were not corrected for lean body mass, and maximal pixel values were used. The highest recorded FDG-uptake was semi-quantitatively analyzed, after correction for radioactive decay, according to the following formula: maximal standardized uptake value (SUV) = mean region of interest activity (mCi/mL)/injected dose (mCi)/body weight (g). To reduce errors in the SUV measurements, standard calibrations as recommended by the vendor were performed using 68-Ge phantom cylinders, two- and three-dimensional normalization, single attenuation daily uniformity/reference scans, and monthly detector scans.

The CT scans were assessed for anatomic abnormality of the esophagus, presence and location of enlarged thoracic and abdominal lymph nodes and distant metastases. The esophagus was evaluated for residual mass and wall thickening (radius ≥0.75 cm). Wall thickening was measured and graded as symmetric or asymmetric and diffuse (craniocaudal extent >3 cm) or focal (craniocaudal extent ≤3 cm).

Treatment Response Criteria

Resected specimens underwent routine histopathologic examination and were also reviewed for tumor viability to determine pathologic response. Residual esophageal cancer was assessed semi-quantitatively based on the estimated percentage of viable cancer in relation to total cancer area, including the amount of radiation-induced tissue injury in mural histologic sections.[27] The extent of viable cancer in the esophagectomy specimen was assigned to one of three categories: no viable cancer (complete response), 1% to 50% viable cancer (partial response), and >50% viable cancer (no response) as modified from selected published grading systems for esophageal and gastric cancers.[27–29]

STATISTICAL ANALYSIS

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT-PET imaging in assessing pathologic response in the primary tumor were determined. The SUV of the esophagus after treatment was compared with pathologic assessment of tumor response using the one-way analysis of variance. Univariate analyses were performed by χ^2 analysis. A two-tailed P value of ≤ 0.05 was considered significant. Data analysis was performed by our departmental biostatistician (A.M.C.) using SPSS software (SPSS, Chicago, IL).

RESULTS

The final study group for assessment of the primary tumor and nodal disease consisted of 42 patients (37 men, 5 women; mean age, 60 years [range, 23–75 years]). These patients all underwent integrated CT-PET imaging within 3 months after chemo-radiation therapy (mean 33 days; range, 23-85 days) and esophageal resection within 3 months of CT-PET imaging (mean 19 days; range, 3-86 days). Thirty-five patients had adenocarcinoma, and six patients had squamous cell cancer. In one patient, tumor morphology was mixed. The primary tumor was located in the mid-esophagus in three patients (7%) and in the lower esophagus or gastroesophageal junction in 39 patients (93%). Pretreatment clinical stage was IIA/B (n = 14), III (n = 24), and IVA (n = 4). After chemo-radiation and esophageal resection, 11 patients (26%) had pathologic stage 0 disease, five (12%) had stage I, 16 (38%) had stage IIA/B, nine (21%) had stage III, and one (2%) had IVA disease. Pathologic response of the primary esophageal tumor was complete (no viable cancer) in 12 patients (29%) and partial (1–50% viable cancer) in 25 patients (60%). Five patients (12%) had no response (>50% viable cancer) of the primary esophageal malignancy to therapy.

CT-PET Response Evaluation

Visual Analysis

Nineteen patients had increased FDG-uptake in the region of the known primary tumor greater than the FDG activity in the adjacent irradiated esophagus by visual analysis and were interpreted as having residual malignancy. FDG-uptake in the esophagus in the 19 patients in the region of the primary esophageal malignancy was central (n = 12) and eccentric mural (n = 7). Esophageal wall thickening in the region of the primary malignancy (mean radius, 1.7 cm; range, 0.9–2.8 cm) was symmetric and diffuse (mean craniocaudal extent 8.0 cm; range, 4–14 cm) in 15 patients and symmetric and focal (mean craniocaudal extent 3 cm) in four patients. Although these patients were interpreted as having residual malignancy on CT-PET imaging, residual malignancy was present in 14 patients at surgical resection (partial response, n = 9; no response, n = 4). Six of 19 patients (32%) had a complete pathologic response to therapy despite an abnormal CT-PET interpretation.

Twenty-three patients had FDG-uptake in the region of the known primary esophageal tumor the same or less than FDG activity in the adjacent normal irradiated esophagus by visual analysis and were interpreted to have no residual malignancy. FDG-uptake in the region of the primary esophageal malignancy was central (n = 8), eccentric mural (n = 7), and symmetric circumferential (n = 8). Esophageal wall thickening in the region of the primary malignancy (mean radius, 1.4 cm; range, 0.8–2.1 cm) was symmetric and diffuse (mean craniocaudal extent 7.6 cm; range, 4–16 cm) in 22 patients and symmetric and focal (craniocaudal extent 2 cm) in one patient. Although these patients were interpreted as having no residual malignancy on CT-PET imaging, complete pathologic response to therapy was present in only seven of 23 patients, primarily because CT-PET was unable

to detect residual malignancy in partial pathologic responders. Histopathologic examination of resected specimens revealed residual malignancy in 16 patients (partial response, $n = 15$; no response to therapy, $n = 1$).

In the assessment of the primary esophageal tumor after therapy, visual analysis of CT-PET had a sensitivity and specificity of 47% and 58%, respectively, in evaluating for residual esophageal tumor (PPV 74%, NPV 30%, accuracy 50%). Multiple assessments were also performed on the post-CRT CT-PET scans, including esophageal wall thickness and length of involvement on CT and SUV of primary malignancy and distribution of FDG-uptake on PET. Univariate logistic regression analysis of multiple imaging findings demonstrated that there were no factors that predicted residual tumor (Table 1).

Semi-Quantitative Analysis

In the semi-quantitative assessment of the primary esophageal tumor using a SUV of ≥4 as residual esophageal tumor, CT-PET had a sensitivity and specificity of 43% and 50%, respectively (PPV 68%, NPV 26%, accuracy 45%), for detecting residual malignancy. As SUV increased the sensitivity of CT-PET decreased and the specificity increased (Table 2). At a SUV designation of ≥7, the specificity increased to 100%, but three of the 28 false-negative patients had viable cancer >50%.

The poor sensitivity of CT-PET in differentiating those patients who had residual cancer from those with a complete response to therapy is, in large part, the result of the small volume of disease below the detectability of FDG-PET imaging and the presence of therapy-induced FDG-avid esophagitis and or ulceration. In this regard, 29 of the 42 patients (69%) had esophagitis, and 25 (56%) had esophageal ulceration detected at endoscopy/EUS. FDG-uptake in the region of the primary malignancy in the 25 patients with ulceration ranged from 1.0 to 6.5 (mean, 3.7). The CT-PET appearance, i.e., diffuse or focal wall thickening on CT and central, eccentric mural, or symmetric circumferential FDG-uptake, was not useful in differentiating those patients with residual tumor from those with complete response and ulceration. Of the 25 patients with therapy-induced ulceration, 11 had a complete response to therapy. FDG-uptake in the region of the primary malignancy in these 11 patients ranged from 1.0 to 6.5 (mean, 4.1); using SUV ≥4 as residual tumor, six patients had a false-positive CT-PET. Among the 17 patients with no ulceration at endoscopy, 13 had esophagitis. Eight of the 17 patients without ulceration had increased uptake of FDG at the tumor site with a SUV ≥4 (mean SUV, 8.4; range, 4.0–30.0) and were considered to have residual tumor. Three of these patients with >50% viable cancer and five with 1% to 50% viable cancer (5–10% viable cancer in four patients and 15% in one patient) were correctly identified. Nine patients had a SUV <4 (mean SUV, 2.3; range, 1–3.9). One patient had a complete response to therapy, seven had a partial response, and one patient failed to respond to therapy.

TABLE 1. Univariate logistic regression analysis of imaging findings for residual disease*

				95% CI	
	Patients	*P* value	OR	Lower	Upper
Wall radius (cm)		0.932	0.938	0.218	4.039
SI length (cm)		0.956	0.995	0.823	1.203
SUV at tumor site		0.825	1.019	0.859	1.210
SUV post >5					
No (Reference)	30		1.000		
Yes	12	0.241	0.426	0.102	1.773
SUV post >4					
No (Reference)	23		1.000		
Yes	19	0.695	0.765	0.200	2.927
PET focal uptake					
Single (Reference)	33		1.000		
Multiple	9	0.722	0.750	0.154	3.654
Central, eccentric, symmetric		0.771			
Central (Reference)	20		1.000		
Eccentric	14	0.502	0.600	0.135	2.662
Symmetric	8	1.000	1.000	0.151	6.643
Endoscopy ulceration					
No (Reference)	17		1.000		
Yes	25	0.022	12.571	1.437	110.009

OR, odds ratio; CI, confidence interval; SUV, standardized uptake value; PET, positron emission tomography; SI, superior-inferior.

TABLE 2. Accuracy of Post-CRT PET in Detecting Residual Disease[1]

PET Criteria	Sensitivity[a]	Specificity[b]	Accuracy[c]
Abnormal primary tumor (%) (visual, no SUV criteria)	47	58	50
SUV criteria:			
>4	43	50	45
>5	23	58	33
>6	7	83	29
>7	7	100	33

SUV, standardized uptake value; PET, positron emission tomography.
[a] Sensitivity = TP / (TP + FN).
[b] Specificity = TN / (TN + FP).
[c] Accuracy = (TP + TN) / (TP + FP + TN + FN).

Endoscopy/EUS Response Evaluation

All patients underwent endoscopy. Twenty-six patients also had EUS, and biopsy was performed in 39. Compared with resected esophageal specimens, 18 patients with partial response (1–50% viable cancer) and three patients with no response to therapy (>50% viable cancer) had false-negative biopsies. There were three false-positive biopsies, most likely the result of progressive tumor death in the interval (mean, 23 days) between endoscopic biopsy and resection. Eight patients with complete response to therapy and seven patients with persistent disease were correctly identified. The sensitivity, specificity, PPV, NPV, and accuracy of endoscopic biopsy in detecting malignancy were 25%, 73%, 70%, 28%, and 38%, respectively.

The finding of no ulceration on endoscopy after preoperative chemo-radiation was associated with a lack of response to preoperative chemo-radiation and high chance of residual cancer (Table 1). This factor was more predictive than either the visual analysis or semi-quantitative SUV PET analysis. The combination of increased SUV ≥4 and no ulceration revealed a high-risk group of patient with malignancy in all patients ($n = 8$) (Table 3). Compared with SUV ≥4 and ulceration (5 of 11 patients with residual malignancy), the combination of SUV ≥4 and no ulceration (8 of 8 patients with residual malignancy) is better able to identify patients with a high probability of residual malignancy ($P = 0.018$).

TABLE 3. Accuracy of Post-CRT CT-PET and Endoscopy in Detecting Residual Disease Using a SUV Threshold of >4 and Endoscopic Ulceration

Patient	Days from treatment end to CT-PET	Days from CT-PET to surgery	SUVmax esophageal cancer	CT-PET interpretation of residual cancer by visual analysis	CT-PET interpretation of residual cancer by SUV> 4	Endoscopy ulceration	Endoscopy and CT-PET SUV >4 prediction of residual cancer	Response to therapy
1	>30	<30	30	Yes	Yes	No	Yes	No
2	>30	>30	8.7	Yes	Yes	No	Yes	No
3	>30	<30	6.5	Yes	Yes	Yes	No	Complete
4	>30	>30	6.2	Yes	Yes	Yes	No	Complete
5	>30	<30	5.5	Yes	Yes	Yes	No	Complete
6	>30	<30	5.4	Yes	Yes	Yes	No	Complete
7	<30	<30	5.2	Yes	Yes	No	Yes	Incomplete
8	<30	<30	5.2	No	Yes	Yes	No	Complete
9	>30	<30	5.2	Yes	Yes	No	Yes	Incomplete
10	>30	>30	5.1	Yes	Yes	No	Yes	Incomplete
11	>30	<30	5	Yes	Yes	No	Yes	No
12	<30	<30	5	No	Yes	Yes	No	No
13	>30	<30	4.7	Yes	Yes	Yes	No	Incomplete
14	>30	<30	4.7	Yes	Yes	Yes	No	Incomplete
15	>30	<30	4.7	No	Yes	Yes	No	Incomplete
16	>30	>30	4.6	Yes	Yes	Yes	No	Incomplete
17	>30	<30	4.6	No	Yes	Yes	No	Complete
18	<30	<30	4	No	Yes	No	Yes	Incomplete
19	<30	<30	4	No	Yes	No	Yes	Incomplete
20	>30	<30	3.9	No	No	No	No	Complete
21	<30	<30	3.5	Yes	No	No	No	No
22	>30	>30	3.4	Yes	No	Yes	No	Incomplete
23	<30	<30	3.4	Yes	No	Yes	No	Incomplete
24	<30	>30	3.4	Yes	No	Yes	No	Complete
25	>30	<30	3.3	No	No	No	No	Incomplete
26	<30	<30	3	No	No	Yes	No	Incomplete
27	<30	<30	3	No	No	Yes	No	Incomplete
28	>30	<30	2.8	Yes	No	No	No	Incomplete
29	<30	>30	2.7	No	No	Yes	No	Complete
30	<30	<30	2.4	No	No	Yes	No	Complete
31	<30	<30	2.4	No	No	Yes	No	Incomplete
32	>30	<30	2.4	No	No	Yes	No	Incomplete
33	>30	<30	2.4	Yes	No	Yes	No	Incomplete
34	>30	>30	2	No	No	Yes	No	Incomplete
35	<30	<30	1.8	No	No	No	No	Incomplete
36	>30	<30	1.8	No	No	Yes	No	Complete
37	<30	<30	1.7	No	No	No	No	Incomplete
38	>30	>30	1.5	No	No	No	No	Incomplete
39	>30	<30	1.5	No	No	Yes	No	Incomplete
40	>30	<30	1.4	No	No	No	No	Incomplete
41	<30	<30	1	No	No	No	No	Incomplete
42	<30	<30	1	No	No	Yes	No	Complete

SUV, standardized uptake value; PET, positron emission tomography; CT, computed tomography.

N Staging

There were no enlarged or FDG-avid nodes in the neck, thorax, and abdomen of 39 patients (93%), and CT-PET scans were interpreted as N0 (no regional metastases present). Twenty-eight patients (67%) had N0 status confirmed pathologically after surgical resection. Eleven patients had microscopic N1 disease in non-enlarged (<1 cm) nodes (nodal metastases in the regional lymph nodes) pathologically. Sensitivity and specificity for residual nodal disease were 0% and 100%, respectively.

DISCUSSION

Multimodality treatment with chemotherapy, radiation, and surgical resection is increasingly being used in patients with locally advanced esophageal cancer.[2,5,30] The appropriate selection of patients who undergo preoperative CRT followed by surgical resection is important, as this therapy is associated with significant morbidity. In this regard, a significant improvement in survival has been shown among patients who respond to preoperative CRT with a complete pathologic response.[4,6,8,10,30,31] Thus, the clinical importance of correctly differentiating these patients from those who fail to respond to therapy may be important. Unfortunately, assessment of TNM status by CT or endoscopy/endoscopic biopsy after CRT often does not correlate with pathologic response.[11–13,16] In our study, endoscopy had limited clinical utility in detecting esophageal malignancy after preoperative CRT (sensitivity 25%, specificity 73%, accuracy 38%). Interestingly, three of the five patients with no response to therapy (>50% viable cancer) had false-negative biopsies.

CT-PET has been shown to have an important role in the staging of esophageal cancer by identifying patients with unsuspected metastatic disease, thus precluding surgical resection or definitive chemo-radiation.[32,33] Recent studies have also suggested that FDG-PET imaging may be useful in assessing the response and prognosis of patients with esophageal cancer after induction therapy.[14,17–23,34] The results of these studies are varied: some authors report reliable assessment of response to therapy,[17–19,21,23] whereas others have found that there is no correlation between decrease in SUV and histopathology and that PET does not add to the evaluation of loco-regional resectability.[20,34] To determine whether patients who fail to respond to CRT can be differentiated from those with partial or complete response, we had previously evaluated the ability of FDG-PET imaging to predict pathologic response.[35,36] We reported that although PET is unable to distinguish small-volume residual disease from a complete pathologic response (0% viable cancer), PET is able to identify patients who fail to respond to preoperative CRT and have a poor long-term prognosis using a SUV threshold of ≥4.[35,36] However, the results of our current study show that when a SUV ≥4 is used to identify patients who have failed to respond (>50% viable cancer) to preoperative CRT, the accuracy of CT-PET is poor, with 15 of the 19 patients having a false-positive result. This high false-positive rate is most likely the result of the presence of metabolically active leukocytes and macrophages associated with the inflammatory esophagitis and ulceration that follow radiation therapy.[37] In our current study, 25 patients (60%) had esophageal ulceration detected at endoscopy; 11 of these patients had a SUV ≥4. If a threshold SUV ≥4 is used to determine therapeutic failure, 10 patients (91%) had a false-positive CT-PET (six with complete response and four with partial response [1–50% viable cancer]). In contrast, of the 17 patients without ulceration at endoscopy, eight had a SUV ≥4. Three of these patients were correctly identified as non-responders (>50% viable cancer) (Fig. 1). The five

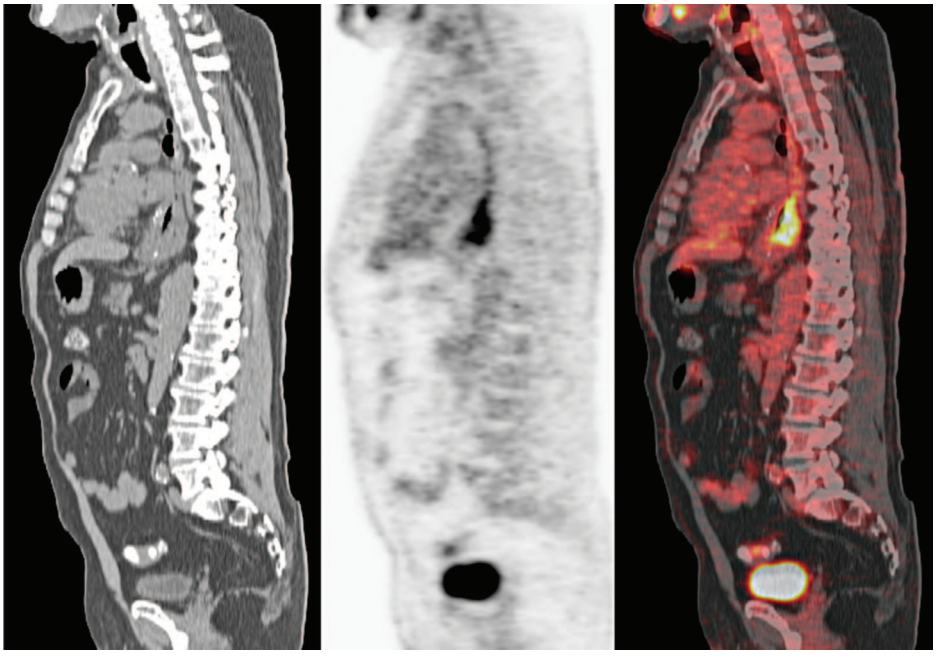

FIGURE 1. *A*, Sagittal CT. *B*, PET. *C*, Integrated CT-PET. Diffuse uptake of [18F]-fluoro-2-deoxy-D-glucose in the treated esophagus with SUV 8.7 in the region of the primary malignancy. Endoscopy/EUS showed absence of esophagitis and ulceration. CT-PET in combination with endoscopy/EUS was interpreted as therapeutic failure. At resection, histopathology confirmed >50% viable tumor.

patients interpreted as non-responders all had residual malignancy (range, 5-15%).

A limitation of our study is the retrospective nature and the variable periods of time between completion of chemo-radiation and CT-PET. We attempted to correct for this limitation by excluding patients who underwent surgery more than 3 months after completion of chemo-radiation and stratified for this limitation by grouping patients into those who received their CT-PET more or less than 30 days after completion of chemo-radiation. There was no clear correlation shown between the timing of the CT-PET and the ability to predict pathologic response, but these limitations highlight the importance of confirming our findings with a prospective, multi-institutional trial. Our study suggests that, used independently, CT-PET was limited by the number of false-positive results, and endoscopy/EUS and biopsy were limited by the number of false-negative results. However, the accuracy of CT-PET in determining therapeutic response can be improved when findings of ulceration on endoscopy/EUS are incorporated into CT-PET interpretation. In this regard, if patients with SUV $\geq$4 were found to have ulceration on endoscopy, CT-PET was interpreted as response to therapy (Table 3). In our study, 19 of the 42 patients (45%) had a SUV $\geq$4 and would have been interpreted as having residual tumor. Of these 19 patients, 11 had ulceration. Using ulceration at endoscopy as a discriminator, six of these patients with a complete response to therapy and five patients with a partial response would have been correctly identified. Three of the four patients with no response to therapy had no ulceration and would have been correctly identified. The fourth patient had a discrete 3-cm ulcerated mass with $>$50% viable tumor, which would have been interpreted as residual malignancy on endoscopy. However, when combining endoscopy and CT-PET, the presence of ulceration would have been a confounding factor leading to misinterpretation as therapeutic response.

In terms of CT-PET assessment of response of esophageal malignancy to preoperative CRT, esophagitis and ulceration are important confounding factors (Fig. 2). Although the form of preoperative therapy (radiation versus concurrent chemo-radiation versus preoperative chemotherapy before concurrent chemo-radiation) can affect ulceration rates, another factor to consider is the timing of the post-CRT CT-PET imaging. In our study, CT-PET was performed 4 to 6 weeks after CRT because of the need to perform a planned esophagectomy during the prescribed time period. Clinical studies have shown that the onset of inflammation/esophagitis occurs approximately 2 weeks after the start of radiation.[38] Weber and colleagues have reported low false-positive rates for FDG-PET imaging when performed 2 weeks after the initiation of preoperative chemotherapy for esophageal cancer (sensitivity 93%, specificity 95%).[21] Furthermore, in a study by Wieder et al., diffuse esophageal uptake of FDG suggesting esophagitis was only observed in 15% of patients (4 of 27 patients) when PET imaging was performed 14 days after chemo-radiation therapy.[15] Besides a lower incidence than that in our study, the diffuse SUV uptake in their study was low (mean SUV 2.6 $\pm$ 0.3) and was unlikely to have been interpreted as residual disease. Patients in the study by Weber et al. were treated with chemotherapy only, and it is uncertain whether the earlier imaging contributed to the lower false-positive rate or whether this was the result of differences in therapeutic management.

In addition to showing that CT-PET interpreted together with findings on endoscopy/endoscopic biopsy decreases the number of false-positive results and can identify patients who have residual disease after preoperative CRT, our study concurs with prior studies that show that a negative CT-PET is inaccurate in determining complete response to therapy, i.e., CT-PET is unable to distinguish microscopic residual disease from a complete pathologic response[22,34,39] (Fig. 3). In our study, 23 of the 42 patients (55%) had a SUV

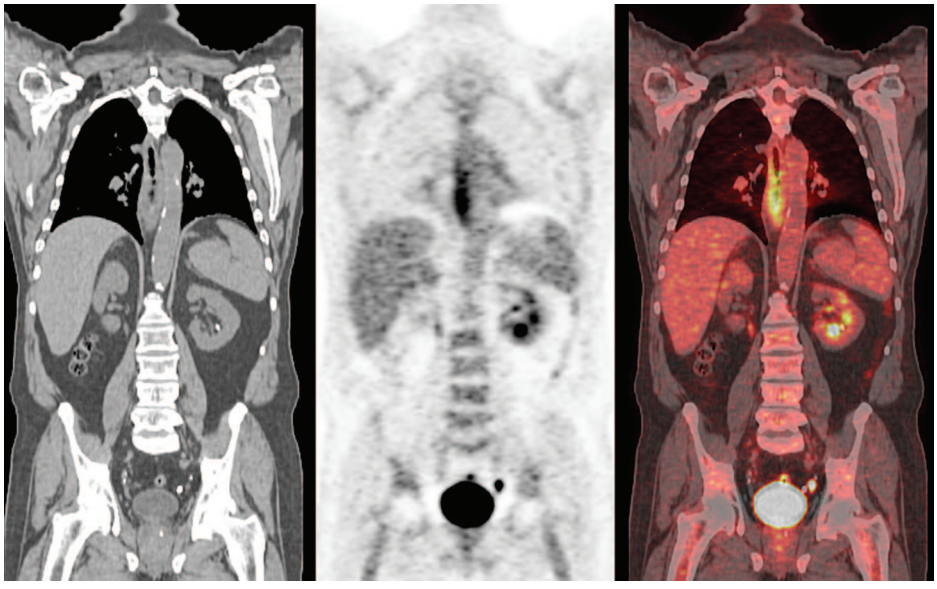

FIGURE 2. *A*, Coronal CT. *B*, PET. *C*, Integrated CT-PET. Focal increased [18F]-fluoro-2-deoxy-D-glucose uptake in the region of the esophageal malignancy SUV 6.5. Endoscopy/EUS showed esophagitis and ulceration. CT-PET in combination with endoscopy/EUS was interpreted as response to therapy. At resection, histopathology revealed complete response with 0% viable tumor.

FIGURE 3. *A,* Axial CT. *B,* PET. *C,* Integrated CT-PET. Absence of [18F]-fluoro-2-deoxy-D-glucose uptake in the treated esophagus. CT-PET was interpreted as response to therapy. At resection, histopathology revealed partial response with 20% viable tumor. CT-PET is unable to detect residual microscopic disease after CRT.

<4 (Table 3). These patients were interpreted as having no residual malignancy on CT-PET imaging. However, only six (26%) had a complete pathologic response. Although the specificity of FDG-PET imaging after preoperative CRT is poor, this can be improved by increasing the SUV cutoff, but sensitivity is adversely affected (Table 2).[36] The clinical implication of this observation is that patients with an apparently complete response after CRT can have residual disease and that CT-PET imaging should not be used as the sole criterion to determine whether patients should proceed to esophagectomy. This recommendation is supported by the study of Nakamura et al., who reported loco-regional recurrence in 42% of the patients who were treated with definitive chemo-radiation and had a complete response according to FDG-PET imaging.[40]

Another important observation of our study is that the use of integrated CT-PET imaging with co-registration of anatomical and functional imaging data was not accurate in assessing response to therapy among patients with esophageal cancer after CRT. In fact, multiple assessments performed on the post-CRT CT-PET demonstrated that there were no factors that predicted residual tumor or failure of response to therapy (Table 1). However, it is important to emphasize that the use of CT-PET and endoscopy together allowed the accurate identification of a subset of patients with residual malignancy. In our study, eight of eight patients with a SUV of ≥4 without ulceration as assessed by endoscopy had residual malignancy at surgical resection. Currently, a treatment option for patients with loco-regionally advanced esophageal cancer is definitive chemo-radiation, followed by observation and selective surgery for recurrent cancer. Our study suggests that the group of esophageal cancer patients with a SUV ≥4 and no ulceration on endoscopy after CRT has a high risk of residual malignancy and should not be observed. If these patients are physiologically fit and do not have distant metastases, they should be considered for esophagectomy. The retrospective nature of our study limits an overall recommendation for a treatment algorithm. However, clinicians who choose to treat their patients with definitive chemo-radiation rather than chemo-radiation and surgery may find these criteria useful in identifying a group of patients with a high likelihood of having residual cancer for whom continued observation alone may not be appropriate.

In summary, our study shows that post-CRT CT-PET imaging interpretation for patients with esophageal cancer is confounded by the presence of FDG-avid therapy-induced ulceration. The high number of false-positive results precludes the use of CT-PET to definitively identify patients with residual disease. However, the use of CT-PET in combination with endoscopy is useful in identifying a subset of patients with a high risk of residual malignancy.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2006;1:10–30.
2. Swisher SG, Hunt KK, Holmes EC, et al. Changes in the surgical management of esophageal cancer from 1970 to 1993. *Am J Surg* 1995;6:609–614.
3. Muller JM, Erasmi H, Stelzner M, et al. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990;8:845–857.
4. Roth JA, Pass HI, Flanagan MM, et al. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988;2:242–248.
5. Swisher SG, Ajani JA, Komaki R, et al. Long-term outcome of phase II trial evaluating chemotherapy, chemoradiotherapy, and surgery for locoregionally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 2003;1:120–127.
6. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;7:462–467.
7. Donington JS, Miller DL, Allen MS, et al. Tumor response to induction chemo-radiation: influence on survival after esophagectomy. *Eur J Cardiothorac Surg* 2003;4:631–636.
8. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemo-radiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;2:305–313.
9. Forastiere AA, Orringer MB, Perez-Tamayo C, et al. Preoperative chemo-radiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 1993;6:1118–1123.
10. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998;27:1979–1984.
11. Beseth BD, Bedford R, Isacoff WH, et al. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. *Am Surg* 2000;9:827–831.
12. Jones DR, Parker LA Detterbeck FC, et al. Inadequacy of computed tomography in assessing patients with esophageal carcinoma after induction chemoradiotherapy. *Cancer* 1999;5:1026–1032.
13. Cerfolio RJ, Bryant AS, Ohja B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2006;6:1232–1241.
14. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy–systematic review. *Radiology* 2006;3:841–851.
15. Wieder HA, Brucher BL, Zimmermann F, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol* 2004;5:900–908.

16. Yang Q, Cleary KR, Yao JC, et al. Significance of post-chemo-radiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. *Dis Esophagus* 2004;1:38–43.
17. Kroep JR, Van Groeningen CJ, Cuesta MA, et al. Positron emission tomography using 2-deoxy-2-[18F]-fluoro-D-glucose for response monitoring in locally advanced gastroesophageal cancer: a comparison of different analytical methods. *Mol Imaging Biol* 2003;5:337–346.
18. Flamen P, Van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002;3:361–368.
19. Kato H, Kuwano H, Nakajima M, et al. Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. *Am J Surg* 2002;3:279–283.
20. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. *J Clin Oncol* 2003;3:428–432.
21. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001;12:3058–3065.
22. Brucher BL, Weber W, Bauer M, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. *Ann Surg* 2001;3:300–309.
23. Song SY, Kim JH, Ryu JS, et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. *Int J Radiat Oncol Biol Phys* 2006;4:1053–1059.
24. Bar-Shalom R, Guralnik L, Tsalic M, et al. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2006;8:918–924.
25. Cerfolio RJ, Ojha B, Mukherjee S, et al. Positron emission tomography scanning with 2-fluoro-2-deoxy-d-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma. *J Thorac Cardiovasc Surg* 2003;4:938–944.
26. American Joint Commission on Cancer. Esophagus. In: Greene FL PD, Fleming ID, Fritz AG, et al, Eds. *American Joint Commission on Cancer Cancer Staging Manual.* 6th Ed. New York: Springer-Verlag, 2002;301–346.
27. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: clinicopathologic correlations. *Cancer* 1994;11:2680–2686.
28. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer* 2003;7:1521–1530.
29. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemo-radiation. *Cancer* 2006;7:1347–1355.
30. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2006;19:4330–4337.
31. Swisher SG, Hofstetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemo-radiation (CRT). *Ann Surg* 2006;5:810–817.
32. van Westreenen HL, Heeren PA, van Dullemen HM, et al. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. *J Gastrointest Surg* 2006;1:54–61.
33. Liberale G, Van Laethem JL, Gay F, et al. The role of PET scan in the preoperative management of oesophageal cancer. *Eur J Surg Oncol* 2004;9:942–947.
34. Brink I, Hentschel M, Bley TA, et al. Effects of neoadjuvant radiochemotherapy on 18F-FDG-PET in esophageal carcinoma. *Eur J Surg Oncol* 2004;5:544–550.
35. Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg* 2004;4:1152–1160.
36. Swisher SG, Erasmus J, Maish M, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemo-radiation in patients with esophageal carcinoma. *Cancer* 2004;8:1776–1785.
37. Bhargava P, Reich P, Alavi A, et al. Radiation-induced esophagitis on FDG PET imaging. *Clin Nucl Med* 2003;10:849–850.
38. Hautzel H, Muller-Gartner H. Early changes in fluorine-18-FDG uptake during radiotherapy. *J Nucl Med* 1997;1384–1386.
39. Arslan N, Miller TR, Dehdashti F, et al. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. *Mol Imaging Biol* 2002;4:301–310.
40. Nakamura R, Obara T, Katsuragawa S, et al. Failure in presumption of residual disease by quantification of FDG uptake in esophageal squamous cell carcinoma immediately after radiotherapy. *Radiat Med* 2002;4:181–186.

