Impact of pretreatment PET on disease control and treatment decisions in locoregionally advanced esophageal cancer patients treated with chemoradiotherapy

Patricia L. Watkins, MS,[1] John M. Watkins, MD,[1] A. Jason Zauls, MD,[2] Daniel T. Lackland, DrPH,[3] M. Boyd Gillespie, MD,[4] Thomas C. Hulsey, ScD,[5] and Joseph M. Jenrette III, MD[6]

[1]Bismarck Cancer Center, North Dakota; [2]Good Samaritan Medical Center, Brockton, Massachusetts; Departments of [3]Neuroscience, [4]Otorhinolaryngology-Head and Neck Surgery, [5]Pediatrics, and [6]Radiation Oncology, Medical University of South Carolina, Charleston

Most patients with esophageal cancer are diagnosed with locoregionally advanced disease at presentation, with an overall 5-year survival rate of 19%.[1] Clinical trials have failed to specify the optimal treatment regimen; however, a multimodal approach to therapy is considered the standard of care for patients with locoregionally advanced disease.[2] Most often, patients are treated with chemoradiotherapy with or without subsequent esophagectomy. Curative-intent interventions for advanced esophageal cancer are necessarily aggressive and may be associated with significant morbidity and even treatment-related mortality. Appropriate selection of patients for intervention is necessary so that those who are most likely to benefit can initiate curative-intent therapy, whereas those who are unlikely to benefit from intervention may be appropriately initiated on less toxic palliative-intent treatment. The use of positron emission tomography (PET) in esophageal cancer staging has improved the ability to detect distant disease at diagnosis,[3-7] an important factor in determining the appropriate treatment regimen and prognosis. Recently, a retrospective study of patients with nonmetastatic esophageal cancer who were treated with concurrent cisplatin, irinotecan, and chemoradiotherapy showed an association between pretreatment PET and disease control end points (including locoregional control).[8] This secondary analysis finding implies that PET may help to appropriately shape treatment decisions not only in its superior ability to detect metastatic disease at diagnosis, but also in the setting of nonmetastatic disease. The current study endeavors to further explore this finding in a larger, heterogeneously treated population, with subanalyses focusing on the impact of PET on treatment decisions in patients with locoregionally advanced esophageal cancers treated with chemoradiotherapy, with or without subsequent esophagectomy.

Methods

We created a research database with study-specific patient, tumor, treatment, and outcome data fields from 2 participating institutions (Medical University of South Carolina in Charleston, SC, and Bismarck Cancer Center in Bismarck, ND). Specifically, tumor location was stratified into "proximal" and "distal" based on whether the tumor was above or below the midthoracic esophagus; tumors that spanned

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Correspondence John M. Watkins, MD, Bismarck Cancer Center, 500 N 8th St, Bismarck, ND 58501 (john.m.watkins.md@hotmail.com).

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both regions were not included in the subset analysis. Eligible cases were identified through review of departmental quality assurance database and office management software. Patients with complete medical records were included in the study if the following criteria were met: resectable or unresectable squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction (pathology-proven); initiation of curative-intent concurrent chemotherapy and radiotherapy; and absence of distant metastatic disease at diagnosis.

Treatment selection

Individual treatment regimens were determined by the multidisciplinary team of oncologists who coordinated each patient's care. Pretreatment (or "staging") evaluations were included at minimum endoscopy and chest computed tomography (CT). Additional evaluations, including endoscopic ultrasonography (EUS) and PET or PET−CT imaging, were performed at the discretion of the treating physician, most often based on availability of the technology at the treating facility. In all cases, patients were prescribed radiotherapy to 45-60 Gy, at the discretion of the radiation oncologist, with a median dose of 50.4 Gy prescribed at each participating institution. Chemotherapy regimen was similarly decided on by the medical oncologist; however, almost all patients received platinum-based doublet therapy, administered every 3-4 weeks for a total of 4 cycles. For patients treated with cisplatin plus 5-fluorouracil or carboplatin plus paclitaxel, radiotherapy was initiated with cycle 1 of chemotherapy. For patients treated with cisplatin plus irinotecan, radiotherapy was initiated with cycle 3. These regimens account for 83% of the chemotherapy regimens used within the present study population. Finally, resectability and clinical operability were determined by the surgical oncologist. In general, tumors were considered resectable if there was no invasion of adjacent structures or involvement of an extended length of esophagus. Clinical operability was determined individually, based on patient age, performance status, and severity of comorbid conditions.

Postchemoradiotherapy interventions and surveillance

Restaging evaluations were performed for clinically operable patients with resectable disease, and included endoscopy (with or without ultrasonography) with CT and/or PET. Restaging endoscopy was performed within 1-2 weeks, and clinical responses by endoscopy were recorded as "no evidence of disease" or "suspicious for residual disease" (with positive or negative biopsy, or without biopsy). CT and/or PET were performed within 4 weeks of chemoradiotherapy completion. For resectable tumors in clinically operable patients without metastatic disease, esophagectomy was recommended at the discretion of the cardiothoracic surgeon. Pathologic response rates were recorded in accordance with the *American Joint Committee on Cancer Staging Manual*[9] and described as "downstaged," "unchanged," or "upstaged," relative to the pretreatment clinical stage. After patients had completed their treatment, they were followed at a minimum of every 3 months for 2 years, then every 6 months for 3 years, and annually thereafter. Subsequent surveillance studies included chest CT and/or PET at 4-6 months, and then on clinical suspicion for recurrence thereafter. Endoscopy was also performed on clinical suspicion for recurrence.

Outcome measures

The principal outcome measure of the current study was local recurrence-free survival, measured from the date of treatment initiation to the date of local failure or last follow-up. Secondary outcome measures included overall survival, disease-free survival, radiation treatment field change due to PET, and rate of esophagectomy.

Disease control and survival endpoint definitions

We recorded each patient's status at the date of last follow-up as "alive, no evidence of disease," "alive with disease," "died of treatment toxicity," "died of/with disease," "died of other cause," or "died of unknown cause," so that we would be able to assess disease control and survival end points. Patients were considered to have died of other cause if there was no evidence of recurrence within 3 months of death, in which case both disease control and survival endpoints were calculated through the date of death. Patients were considered to have died of unknown cause if there was no evidence of recurrence, and death occurred more than 3 months beyond the last clinical encounter (with disease-free survival recorded through last clinical encounter, and survival calculated through date of death).

Initial site of disease failure was recorded as "no failure," "locoregional failure only," "distant failure only," or "locoregional plus distant failure." For the present study, only the initial site(s) of disease were recorded. Any residual or recurrent disease at the primary site (whether in-field or at margin) or within regional lymphatics was considered an event for the local disease control endpoint. Specifically, residual disease identified at esophagectomy was also recorded as a local failure of definitive chemoradiotherapy (calculated at the date of esophagectomy). A patient was considered to have died of treatment-associated toxicity if there was clear association between toxicity and death or if the patient died during or within 30 days of hospitalization attributable to treatment toxicity (without other evident cause). Treatment-associated mortality was considered an event for disease control endpoints. If a patient died of unclear cause, but was known to have had active recurrent

disease prior to death, the patient was considered to have died of/with disease.

Overall survival was measured from the date of treatment initiation to the date of death or last follow-up; disease-free survival was measured from the date of treatment initiation to the date of first evidence (clinical, radiographic, or pathologic) of disease recurrence. Biopsy confirmation was pursued at the discretion of the managing physician or physicians, and was not required for definition of failure for this investigation. Generally, biopsy was performed only in situations in which there was a questionable finding or possible alternative pathologic process (eg, pulmonary nodule), but otherwise not performed when the clinical presentation was suggestive of disease recurrence and/or progression.

Treatment decision endpoints

We examined 2 subsets of the study population to assess the impact of pretreatment PET on radiotherapeutic and surgical clinical decision making. The first subset included patients with pretreatment endoscopy, CT, and PET who were available for report and image review in the electronic medical record system. For each patient who fit these criteria, an experienced radiation oncologist was asked to design a treatment field based solely on endoscopic and CT data. Subsequently, the physician reviewed the patient's PET scan images and recorded whether or not information provided by the PET scan resulted in an alteration in the treatment field design. The rate of field modification within this subset population was recorded. The second subset included clinically operable patients with resectable tumors from the original study population. Statistical analyses were performed to assess whether pretreatment PET was associated with significantly different attempted rates of esophagectomy in this resection-eligible subpopulation.

Statistical analyses

Disease control and survival were assessed through application of the Cox proportional hazards model using SPSS version 10. Tumor response was determined by logistic regression modeling of postchemoradiotherapy (post-CRT) endoscopic findings. The difference in rates of esophagectomy between groups was determined by Fisher's exact test. Patient demographic information for the study population was compared between those who received pretreatment PET and those who did not, using chi-square tests without correction for multiple comparisons. Demographic information for the subset of clinically operable patients was compared between those who received pretreatment PET and those who did not, using Fisher's exact test. All statistical analyses were performed using SAS version 9.1, except where noted.

TABLE 1 Patient, tumor, and staging characteristics

Characteristic	n (%)
Age, median (range), y	63 (44–60)
Sex	
Men	93 (81)
Women	22 (19)
Race	
White	82 (71)
Black, Hispanic, Asian	33 (29)
Prior cancer	
Yes	16 (14)
No	99 (86)
Weight loss, >10% body weight	
Yes	47 (41)
No	68 (59)
Tobacco use during/after CRT	
Yes	30 (26)
No	85 (74)
Histology	
AC	67 (58)
SCC	48 (42)
Location[a]	
Proximal	48 (45)
Distal	59 (55)
Staging	
EUS[a]	87 (82)
PET	75 (65)
Completed therapies	
Intended course of RT	106 (92)
≥ 3 cycles platinum chemotherapy	78 (95)
Hospitalization during CRT	50 (43)
Post-CRT procedures	
Endoscopy	80 (71)
Esophagectomy	49 (43)
cT stage[b]	
1	6 (5)
2	15 (14)
3	69 (63)
4	20 (18)

Abbreviations: AC, adenocarcinoma; CRT, chemoradiation therapy; cT, computer tomography; RT, radiotherapy; SCC, squamous-cell carcinoma.
[a] 107 patients; [b] 110 patients.

Results

Patient, tumor, and staging characteristics

Between 2000 and 2010, 115 patients were identified for inclusion in the present study. The median age of the

TABLE 2 Comparison of demographic data for no-PET and PET patients

Characteristic	No-PET 40 patients n (%)	PET 75 patients n (%)	*P*[a]
Age, median (range), y	64 (44-90)	62.5 (44-82)	.3496
Sex			.5023
Men	31 (78)	62 (83)	
Women	9 (23)	13 (17)	
Race			.8213
White	28 (70)	54 (72)	
Black, Hispanic, Asian	12 (30)	21 (28)	
Prior cancer			.7492
Yes	5 (13)	11 (15)	
No	35 (87)	64 (85)	
Weight loss, >10% body weight			.7118
Yes	17 (43)	30 (40)	
No	23 (58)	45 (60)	
Tobacco use during/after CRT			.801
Yes	11 (28)	19 (25)	
No			
Histology			.1172
AC	19 (48.5)	47 (63)	
SCC	21 (53.5)	28 (37)	
Location[b]			.0193
Proximal	16 (44)	16 (23)	
Distal	20 (56)	55 (77)	
Staging, EUS	30 (75)	57 (76)	.9053
Therapies completed			
Intended course of RT	36 (90)	70 (93)	.5001
≥ 3 cycles platinum chemotherapy[c]	23 (96)	55 (95)	> .999[d]
Hospitalization during CRT	17 (43)	33 (44)	.8772
Post-CRT procedures			
Endoscopy	28 (70)	52 (69)	.941
Esophagectomy	11 (28)	26 (35)	.4333
cT stage[e]			.1248[d]
1	1 (3)	5 (7)	
2	5 (14)	10 (14)	
3	19 (53)	50 (68)	
4	11 (31)	9 (12)	

Abbreviations: AC, adenocarcinoma; EUS, endoscopic ultrasound; CRT, chemoradiation therapy; cT, computer tomography; PET, positron-emission therapy; RT, radiotherapy; SCC, squamous-cell carcinoma.
[a] *P* values of chi tests shown; [b] n = 36 for no-PET, 71 for PET; [c] n = 24 for no-PET, 58 for PET; [d] Fishers' exact test; [e] n = 36 for no-PET, 74 for PET.

patients was 63 years (range, 44-90 years), and 81% were men. Patient-, tumor-, and staging-specific data are shown in Table 1. Pretreatment PET was performed in 65% of patients; of the 75 patients included in the PET group, 35 were imaged by PET alone and 40 were imaged by PET and CT (PET-CT). Within the PET group, distal esophageal tumors comprised 73% of the population (55 distal tumors, 16 proximal tumors, 4 not classified). A comparison of patient-, tumor-, and treatment-related factors for patients who did and did not undergo

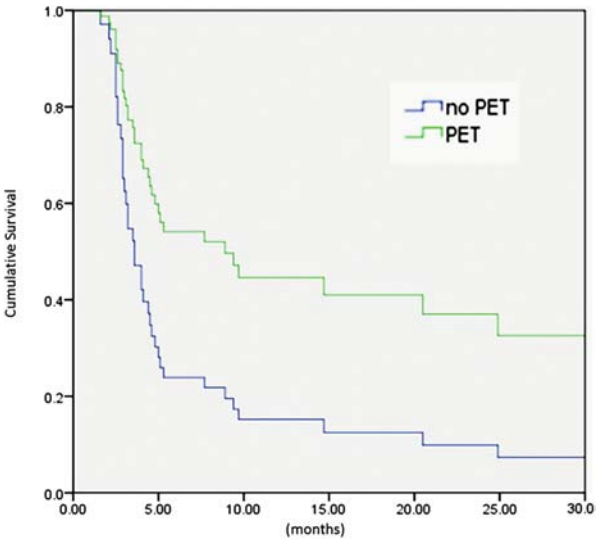

FIGURE 1 Local recurrence-free survival in distal esophageal tumors with or without pretreatment PET.

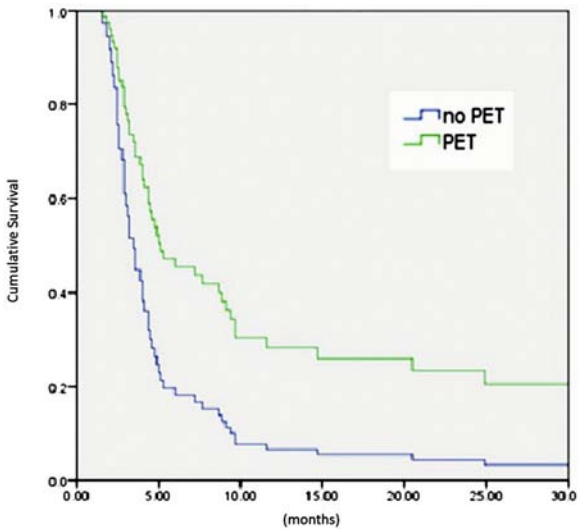

FIGURE 2 Freedom from failure in distal esophageal tumors with or without pretreatment PET.

PET is shown in Table 2; of note is that there were significantly more proximally located primary tumors in the group that did not undergo pretreatment PET (44% vs 23%, respectively; $P = .0193$).

Disease control and survival: pretreatment PET

At a median survivor follow-up of 30.2 months (range, 3.5-182), 38 patients were alive (32 without evidence of recurrence) and 77 patients had died (57 of or with disease). In 86 patients with disease recurrence, the initial sites of disease recurrence were locoregional in 59, distant in 19, and locoregional plus distant in 8 patients.

Within the entire study population, there was suggestion of an association between absence of pretreatment PET and subsequent local tumor recurrence; however, this was not significant (hazard ratio, 1.442; $P = .144$). Subset analysis identified tumor location as a significant factor; for distal esophageal tumors, there was a significantly higher risk of local failure in patients who did not undergo PET (HR, 2.331; $P = .017$; see Figure 1). This association was not appreciated for proximal tumors (HR, 1.230; $P = .578$).

With regard to overall disease control, the association between nonuse of PET and disease-free survival was once again not significant (HR, 1.315; $P = .220$); however, on subset analysis there was a significant association noted for distal tumors (HR, 2.155; $P = .014$; Figure 2). Again, this association was not appreciated for proximal tumors (HR, 1.088; $P = .798$).

When evaluated for overall survival, no significant associations were found for performance of PET, either for the overall population or on subset analysis.

Treatment decisions

Radiation treatment fields. Within the overall study population, of 56 patients who underwent successful pretreatment endoscopy, CT, and PET, 52 patients had complete medical and radiographic records available for review. Examination of pretreatment PET scans after review of endoscopy and CT information resulted in a radiation treatment field change for 11 patients (21%).

Esophagectomy. A total of 60 patients in the present study were deemed clinically operable with resectable disease. Of those patients, 41 (68%) underwent pretreatment PET. A comparison of patient, tumor, and treatment characteristics was performed within this operable or resectable subpopulation. The 2 groups were well balanced without significant differences (Table 3). With respect to performance of esophagectomy, there was no significant difference between the no-PET and PET groups (58% vs 63%, respectively; $P = .7779$).

Discussion

The use of PET for the detection of metastatic esophageal cancer has been firmly established.[3-7] Indeed, upstaging by PET in a study resulted in a 2-year survival of 17%, compared with 64% survival in comparably treated patients without distant PET-positive disease.[6] The present study expands on our previously reported secondary analysis finding, which identified an association between pretreatment PET and disease control outcomes in a smaller, uniformly treated population of locoregionally advanced esophageal cancer patients.[8] It is not surprising that the significant improvement in local disease control holds in overall disease control, because the predominant pattern

TABLE 3 Comparison of demographic data in resectable, clinically operable subpopulation

Characteristic	No-PET 19 patients n (%)	PET 41 patients n (%)	*P*[a]
Age, median (range), y	59 (44-76)	63 (44-79)	.1639
Sex			.4927
Men	14 (74)	34 (83)	
Women	5 (26)	7 (17)	
Race			> .999
White	16 (84)	35 (85)	
Black, Hispanic, Asian	3 (16)	6 (15)	
Prior cancer			.6541
Yes	1 (5)	5 (12)	
No	18 (95)	36 (88)	
Weight loss, >10% body weight			> .999
Yes	6 (32)	14 (34)	
No	13 (68)	27 (66)	
Tobacco use during/after CRT			.801
Yes	4 (21)	9 (22)	
No	15 (79)	32 (78)	
Histology			.5247
AC	13 (68)	32 (78)	
SCC	6 (32)	9 (22)	
Location[b]			.7097
Proximal	3 (19)	6 (15)	
Distal	13 (81)	33 (85)	
Staging, EUS	12 (63)	34 (83)	.1108
Therapies completed			
Intended course of RT	17 (89)	40 (98)	.2181
≥ 3 cycles platinum chemotherapy[c]	9 (90)	29 (97)	.4423
Hospitalization during CRT	8 (42)	16 (39)	> .999
Post-CRT procedures			
Endoscopy	14 (74)	31 (76)	> .999
Esophagectomy	11 (58)	26 (63)	.7779
cT stage[d]			0.5513
1	1 (6)	4 (10)	
2	2 (12)	4 (10)	
3	13 (76)	33 (80)	
4	1 (6)	0 (0)	

Abbreviations: AC, adenocarcinoma; EUS, endoscopic ultrasound; CRT, chemoradiation therapy; cT, computer tomography; PET, positron-emission therapy; RT, radiotherapy; SCC, squamous-cell carcinoma.
[a] *P* values from Fisher's exact test shown; [b] n = 16 for no-PET, 49 for PET; [c] n = 10 for no-PET, 30 for PET; [d] n = 17 for no-PET, 41 for PET.

of failure in esophageal cancer continues to be locoregional (with or without concomitant distant disease).[8] Collectively, the evidence suggests that local and distant disease control in patients with distal esophageal tumors is optimized when staging PET is used.

The impact of pretreatment PET on disease control may be linked to more informed clinical decision making. Previously published studies have demonstrated improved correlation of prognosis with PET-based staging compared with conventional staging with contrasted CT.[10]

PET-based staging may present the clinician with a more accurate appreciation of disease extent than does endoscopic or CT-based staging. This enhanced knowledge may allow for more appropriate selection of treatment and, more specifically, superior radiation treatment field design. The present study found that PET information prompted a change in proposed radiation treatment fields in 21% of patients. These results align with the findings of a smaller study with 16 patients in which the examination of PET information resulted in changes in the cranial and caudal extent of proposed radiation treatment fields in a proportion of patients.[11] The enhancement of treatment field design may explain the superior local control of distal disease seen in the present study.

PET is valuable not only for its ability to identify disease extent, but for its ability to yield semi-quantitative metabolic activity data in the form of standardized uptake values (SUVs). The use of SUV in prognosis and patient stratification in esophageal cancer has received a great deal of attention in the past decade. Several groups have shown that serial PET can yield information on response to chemotherapy.[12-14] Responders to therapy were shown to have larger magnitude changes in SUV between pre- and posttreatment PET scans,[12] as well as earlier assessments at just 2 weeks into therapy.[13,14] The association of large SUV changes with chemotherapy response may allow physicians to better select patients for changes in therapy, such as early modification of an ineffective chemotherapy regimen, or (more optimistically) identification of patients with favorable early response. In a study of patients undergoing post-CRT PET before esophagectomy, a single post-CRT SUV reading of more than 4 was correlated with decreased 2-year survival.[15] These findings were extended in a study of post-CRT PET in which a complete metabolic response to therapy (negative post-CRT PET) was significantly associated with favorable survival, regardless of whether the patient proceeded to esophagectomy.[16] Further examinations of the impact of SUV on prognosis have found that a high pretreatment SUV portends a poor prognosis in terms of recurrence-free survival[17] and overall survival.[18] Our findings of a trend toward decreased treatment response and resultant disease control in patients with elevated pretreatment SUV are consistent with these earlier works.

Although our findings were consistent with the trends seen in other treatments of PET in the context of esophageal cancer, the present study failed to demonstrate survival or disease-control differences associated with pretreatment PET in the overall population. The finding of significantly improved disease control in distally located tumors bears further consideration. First, the limited number of patients with proximal tumors may have resulted in insufficient power to detect a difference. Second, it is possible that there is a differential benefit of chemoradiotherapy for esophageal adenocarcinomas over squamous-cell carcinomas (which predominate proximally),[19] however, these data are based on outdated treatment techniques, and subsequent reports have not identified either histology or tumor location as significantly associated with tumor control.[20,21] A third possibility relates to the quality of PET imaging within the study period; more specifically, the use of PET alone or (more recently) combined PET−CT. Combined PET−CT allows for accurate localization of a metabolically active region with its anatomic correlate. The superior diagnostic accuracy of PET−CT over PET alone has been previously demonstrated in esophageal cancer.[22] However, further subset analysis of PET versus PET−CT within the present study subpopulation was limited because of the small sample size.

In conclusion, the present study demonstrates an association between pretreatment PET and disease control endpoints, including locoregional control, for distally located, locoregionally advanced esophageal tumors treated with chemoradiotherapy. These results support those of our previous secondary analysis, now in a larger, heterogeneously treated population that is more reflective of the spectrum of clinical practice. The underlying reason for this improvement remains to be determined; however, our findings align with the existing data regarding radiotherapy field modification attributable to PET. PET has proven superior in terms of accurate locoregional and distant tumor delineation at diagnosis, but further investigation is needed to determine whether additional PET parameters could assist in individualization of therapy, including early modification based on response.

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