Review Article

State-of-the-art molecular imaging in esophageal cancer management: implications for diagnosis, prognosis, and treatment

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Abstract: Molecular imaging techniques are increasingly being used in addition to standard imaging methods such as endoscopic ultrasound (EUS) and computed tomography (CT) for many cancers including those of the esophagus. In this review, we will discuss the utility of the most widely used molecular imaging technique, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET). ^{18}F-FDG PET has a variety of potential applications ranging from improving staging accuracy at the time of initial diagnosis to assisting in radiation target volume delineation. Furthermore, ^{18}F-FDG PET can be used to evaluate treatment response after completion of neoadjuvant therapy or potentially during neoadjuvant therapy. Finally, we will also discuss other novel molecular imaging techniques that have potential to further improve cancer care.

Keywords: Positron emission tomography (PET); esophageal cancer; molecular imaging; neoadjuvant therapy

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Introduction

An estimated 18,170 new cases of esophageal cancer will be diagnosed in 2014 and approximately 15,450 of these patients will die from the disease (1). Although outcomes are improved with the addition of neoadjuvant chemotherapy or neoadjuvant chemoradiation (CRT) to surgery alone, outcomes for locally advanced esophageal cancer remain poor (2). Local failure rates even with the addition of CRT exceed 50% (3,4) in locally advanced patients.

The era of personalized medicine has brought increasing awareness that variations in tumor biology drive tumor genesis, response to treatment, and long-term prognosis. The advent of molecular imaging techniques has resulted in improvements in esophageal cancer staging and treatment. Although ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is the most commonly studied and clinically used approach, early results using other molecular imaging techniques suggest that further improvements in esophageal cancer care are possible.

Molecular imaging agents

^{18}F-FDG is the most commonly used agent for PET imaging. However, its sensitivity for very small tumors is low, and uptake is dependent on oxygen supply and glycolysis (5). Choline-derivatives, such as ^{11}C-choline, ^{18}F-fluoroethylcholine, and ^{18}F-fluorocholine have been investigated because of their more selective uptake in the mediastinum (6,7). Choline is a precursor in the biosynthesis of phosphatidylcholine, which is a major phospholipid constituent of the cell membrane; consequently, choline uptake is proportional to the rate of cell division. One advantage is that normal tissues, such as brain, lung, heart, bone, and skeletal muscle, have very low uptake of positron-labeled cholines. The more pronounced uptake in malignant mediastinal adenopathy is more striking when compared against low uptake in the lung, heart, and mediastinum. Another benefit of choline-derivatives is the rapid clearance of radiolabeled-choline from the blood after intravenous administration, allowing

for quick initiation of PET imaging, as soon as 2-3 min after radiotracer injection (6). Tian *et al.* compared ^{11}C-choline PET with ^{18}F-FDG PET in 38 patients with various tumors and found a high correlation in differentiation between malignant and benign lesion uptake (8). These researchers also observed differences in imaging acquisition timing, with PET performed 5 min after injection of ^{11}C-choline and 40 min after injection of ^{18}F-FDG. One important logistic limitation of ^{11}C-choline is a short half-life (20 min), which limits its use to facilities with an onsite cyclotron (8). ^{18}F-fluorocholine has a longer lived isotope, with a half-life of 110 min and has shown encouraging results with high tumor-to-background contrast within minutes of injection (9). The relatively low uptake of choline in normal brain tissue allows for good delineation of disease in the brain, and patients can be scanned within 20 min after intravenous injection. However, normal uptake of choline in the liver may potentially obscure identification of metastatic disease below the diaphragm (9).

L-[3-^{18}F]-α-methyltyrosine (^{18}F-FAMT) is an amino acid tracer developed for PET imaging. ^{18}F-FAMT is accumulated in tumor cells via an amino acid transport system, LAT-1, which plays an important role in cellular proliferation and is widely expressed in cancers, particularly in squamous cell carcinoma (SCC) (10). In oral SCC, uptake of ^{18}F-FAMT has been significantly correlated with LAT-1 expression, cell proliferation, maximal tumor size, and disease stage and is more specific for malignancy than ^{18}F-FDG (10). In a study of 21 patients with esophageal SCC, ^{18}F-FAMT demonstrated lower sensitivity for lymph node staging than ^{18}F-FDG (40% and 47%, respectively) but significantly higher specificity (100% and 50%, respectively) (11). ^{18}F-FAMT may also allow for better delineation of malignancy near the heart, because it does not show the intense cardiac physiologic uptake of ^{18}F-FDG. Use of ^{18}F-FAMT in conjunction with ^{18}F-FDG in PET may help reduce false positives resulting from inflammation. Further studies are needed to establish the relationship between intensity of uptake and patient prognosis with ^{18}F-FAMT.

^{18}F-fluorothymidine (^{18}F-FLT) is a pyrimidine analog that is phosphorylated by thymidine kinase 1, an enzyme within the salvage DNA synthesis pathway. The activity of thymidine kinase 1 and therefore uptake of ^{18}F-FLT reflects cellular proliferation and is more specific than ^{18}F-FDG for differentiating neoplasms from inflammation (12). In a study of 22 patients, both uptake and sensitivity for detection of lymph node metastatic disease were lower with ^{18}F-FLT than ^{18}F-FDG (75% and 83%, respectively), but specificity was higher (99% and 96%, respectively) (13). ^{18}F-FLT has also shown promise in monitoring disease response to treatment (12). The major disadvantage of ^{18}F-FLT is increased risk of false negative results when used alone. ^{18}F-FDG remains the most widely used radiolabeled agent for staging and evaluating treatment response, but other molecular agents continue to be developed and assessed in clinical trials.

Diagnosis of premalignant esophageal lesions

The rate of esophageal cancer diagnosis, particularly in the lower esophagus and gastroesophageal junction (GEJ), has increased dramatically in recent years. One driver of this increase is the rising incidence of chronic gastroesophageal reflux disease (GERD), which leads to Barrett esophagus (BE). In BE, the normal stratified squamous epithelium of the esophagus is replaced by simple columnar epithelium with goblet cells. BE is associated with an increased risk of esophageal adenocarcinoma and is therefore considered a premalignant disease. Endoscopic surveillance is recommended for patients with BE in order to detect neoplastic changes at an early stage. Early detection of progression to malignancy can allow for more limited treatment and result in improved long-term outcomes.

Endoscopy alone for BE surveillance is not ideal because it cannot reliably detect regions of dysplasia. The flat appearance of dysplasia makes it difficult to visualize, despite the advantages accrued with narrow-band imaging, high-yield white-light endoscopy, and chromoendoscopy (14). Only a limited amount of tissue is evaluated with standard random biopsies in BE, allowing areas of dysplasia or invasive carcinoma to remain undetected (15).

Several molecular imaging techniques have been developed in an attempt to increase detection of subtle dysplastic changes within BE. Sturm *et al.* developed a peptide that binds to regions of esophageal high-grade dysplasia as well as adenocarcinoma (16). First-in-human results demonstrated that the peptide was not only safe but also appeared to effectively enhance identification of esophageal neoplasia. Confocal endomicroscopy in 25 patients was performed after topical administration of the peptide, resulting in a 3.8-fold higher fluorescence intensity in regions of high grade dysplasia and esophageal adenocarcinoma than in BE and normal squamous epithelium. This peptide may therefore allow for more directed and higher yield biopsies. Another technique,

probe-based confocal microscopy, uses biophotonics to visualize cellular details during endoscopy (17). Its capabilities for real-time assessment could save significant time and cost associated with biopsy analysis. Other promising molecular imaging strategies include gene expression analysis of stem cell clones from BE biopsy specimens (18,19), targeted proteomics (20-22), and mass spectrometry (23,24).

Esophageal cancer staging

Before routine clinical use of ^{18}F-FDG PET, computed tomography (CT) and endoscopic ultrasound (EUS) were the primary imaging modalities for esophageal cancer staging. These techniques have proven to be complementary; in many patients, CT is better able to determine tumor length and exclude invasion of adjacent structures whereas EUS can better determine the depth of invasion of the primary tumor and identify locoregional lymph node metastasis (25,26). A meta-analysis by Rösch *et al.* reported that the accuracy of EUS for staging the extent of primary tumor involvement was 89% (27).

In contrast to EUS, ^{18}F-FDG PET is less successful in accurately determining the depth of invasion of the primary lesion (26). ^{18}F-FDG PET does not clearly offer a significant benefit in nodal staging over EUS and CT (28). Significant ^{18}F-FDG uptake in the primary lesion may obscure increased uptake in locoregional nodes (29). However, ^{18}F-FDG PET is particularly useful as a complementary imaging tool for detecting distant metastases, which are quite common in patients with esophageal cancer (25,30-32). A study by Lowe *et al.* in 75 newly diagnosed esophageal cancer patients reported the respective sensitivity and specificity for distant metastases to be 81% and 91% for PET, 81% and 82% for CT, and 73% and 86% for EUS (26). A meta-analysis showed that the sensitivity and specificity for detecting distant metastases were 71% and 93%, respectively, for ^{18}F-FDG PET and 52% and 91%, respectively, for CT (25). The superior ability of ^{18}F-FDG PET in detection of occult distant metastasis during the initial staging process may provide sufficient evidence to avoid unnecessary surgery in up to 20% of patients (32,33). A multicenter prospective cohort study of 491 patients showed that PET/CT led to clinically significant changes in stage for 24% of patients (34). The American College of Surgeons Oncology Group Z0060 trial prospectively evaluated the utility of ^{18}F-FDG PET after standard staging workup by randomizing 262 potentially resectable esophageal cancer patients after CT to either ^{18}F-FDG PET or no PET imaging (35). ^{18}F-FDG PET identified biopsy-proven distant metastasis not detected by CT in 4.8% of patients who proceeded to surgery. An additional 9.5% of patients had PET-detected metastases that were not biopsy-proven. Of note, PET/CT coregistration was not performed in this trial.

Integrated PET/CT has higher sensitivity and specificity for tumor staging than ^{18}F-FDG PET alone (36). In fused scans, the CT has two main purposes. The first is to serve as an attenuation map to correct for the fact that photons originating from deeper structures are more highly attenuated that those originating closer to the skin surface. This correction is essential not only to improve image quality but to allow for accurate quantitative measurements of metabolic activity performed using the standardized uptake value (SUV). The SUV is the ratio of metabolic activity (Bq/mL) in the region of interest to the decay-corrected activity of injected ^{18}F-FDG (Bq/g). The second purpose is to provide anatomic and structural reference data that complements the metabolic findings on PET imaging, fusing form (anatomic) and function (metabolic) information.

^{18}F-FLT may offer significant imaging advantages over ^{18}F-FDG for esophageal cancer staging with PET. One of the primary disadvantages of ^{18}F-FDG is its nonspecific uptake within benign lesions, which may result in inappropriate upstaging of patients (37). ^{18}F-FLT has higher uptake in proliferating tumors and better discrimination between malignant and benign lesions, as shown in both in vitro and in vivo studies (38). Han *et al.* compared the abilities of ^{18}F-FLT and ^{18}F-FDG PET in detection of regional lymph node metastasis in 22 patients with SCC of the esophagus using pathologic findings (13). Only three false-positive nodes were found using ^{18}F-FLT, whereas ^{18}F-FDG PET identified 14. The sensitivity and specificity of ^{18}F-FLT PET were 74% and 99%, respectively, and of ^{18}F-FDG PET were 83% and 96%, respectively. However, ^{18}F-FLT may result in a higher rate of false-negative results, as suggested by van Westreenen *et al.* (39). Additional work is needed to evaluate the benefits of ^{18}F-FLT in esophageal cancer staging, and ^{18}F-FDG remains the current agent of choice.

Pretreatment ^{18}F-FDG PET and prognosis

^{18}F-FDG PET is not only useful for staging but may be effective in determining prognosis prior to treatment. The

first report of ^{18}F-FDG PET in prognosis for esophageal cancer was in 1998, when Fukunaga *et al.* reported that patients with tumor SUV >7 had poorer outcomes (40). This correlation between higher maximum SUV (SUV_{max}) and worse overall and disease-free survival (OS and DFS, respectively) has since been supported by numerous studies (41-46). A literature review by Omloo *et al.* reported that 12 of 15 studies included in their analysis showed that pretreatment SUV is a predictor for survival in univariate analysis (46). However, only 2 studies showed that this significance persisted in multivariate analysis. Furthermore, it is unclear whether SUV_{max} is an independent prognostic factor when compared with tumor stage (46,47). Although pretreatment SUV may be prognostic, a wide range of SUV_{max} thresholds have been reported as being significant. For example, significant survival differences were shown by Rizk *et al.* (41), who used a SUV_{max} threshold of 4.5, whereas Cerfolio and Bryant suggested 6.6 as an ideal threshold (42). Better characterization of SUV_{max} thresholds in this disease setting is needed to better evaluate and apply the prognostic utility of this PET parameter.

The majority of ^{18}F-FDG PET studies define therapeutic response by quantifying the SUV_{max} of the tumor (*Table 1*). However, this metric does not account for the significant heterogeneity of ^{18}F-FDG tumor uptake or account for the fact that many tumors have both malignant and nonmalignant components. Spatial ^{18}F-FDG PET features such as tumor volume (57), tumor shape (58), and texture features (59) have been suggested to be more informative than SUV_{max}. Investigators also have evaluated metabolic tumor volume (MTV), or the volume of tumor with increased glycolytic activity above a specified SUV threshold, because it includes both anatomic tumor burden and metabolic information. Just as no standardized thresholds are agreed upon for SUV_{max}, various MTV definitions have been used; thus, it is difficult to compare studies and evaluate the usefulness of MTV. Emerging data suggest that MTV may be a significant predictor for survival, and perhaps may be more powerful than SUV_{max}. In 2010, Hyun *et al.* were the first to report the use of MTV in 151 esophageal cancer patients, most with SCC (60). Although SUV_{max} and MTV were each significant predictors of survival in univariate analysis, only MTV was significant in multivariate analysis, along with T and M stage. Chen *et al.* recently studied 90 patients with locally advanced SCC of the esophagus who received definitive CRT and underwent a pretreatment ^{18}F-FDG PET scan (61). These researchers reported that MTV 20% (tumor volume with at least 20% of SUV_{max}) >40 mL was the only significant predictor of survival in multivariate analysis. They also evaluated MTV2.5 (tumor volume with SUV_{max} ≥2.5), which was not significant. Another ^{18}F-FDG PET parameter is total lesion glycolysis (TLG), defined as the MTV multiplied by the mean SUV (SUVmean). Larger TLG values are believed to reflect increased amounts of hypoxia resulting from larger amounts of tumor being in glycolysis. Although data are limited with respect to TLG and esophageal cancer, a recent report by Li *et al.* suggests that TLG may be a useful prognostic factor (62).

Current literature suggests that these pretreatment ^{18}F-FDG PET parameters are promising prognostic factors, but further validation is warranted. If these parameters are to become widely used in the clinic, standardization is critical (63).

^{18}F-FDG PET for radiation treatment planning

Gross disease must be accurately delineated in esophageal cancer patients who receive radiation therapy. This is particularly important when highly conformal radiation delivery techniques, such as intensity-modulated radiation therapy (IMRT), are used. Clearly distinguishing primary tumor from normal esophagus is challenging with CT alone. Using the assumption that the primary esophageal tumor volume identified by EUS was accurate, CT was found to routinely underestimate or overestimate the proximal and/or distal extent of the tumor by several centimeters (64). Thus, investigators have looked to ^{18}F-FDG PET to aid in more accurately defining the gross tumor volume (GTV) for esophageal cancer patients. Incorporation of ^{18}F-FDG PET has proven useful in radiation planning for other disease sites, such as lung (65,66), lymphoma (67), and head and neck (68).

The impact of ^{18}F-FDG PET on radiation treatment planning for esophageal cancer has been evaluated retrospectively and prospectively (69-71). Leong *et al.* studied 21 esophageal cancer patients scheduled to receive definitive CRT (69). Two GTVs were contoured, one using CT alone (GTV-CT) and another using both PET and CT. When the contours were compared, a portion of PET-avid disease was excluded in 69% of the GTV-CTs, which would have led to a "geographic miss" in 31% of patients. As expected, the proximal and distal extents differed in the majority of patients. However, the radiographic tumor extent was not confirmed pathologically. Moureau-Zabotto *et al.* also prospectively evaluated the use of ^{18}F-FDG PET

Table 1 Prospective studies evaluating metabolic response during or after neoadjuvant treatment in esophageal cancer patients

Study	No.	Tumor histology	Timing of 2nd PET	Chemotherapy	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response *vs.* nonresponders	P value	Survival of metabolic responders *vs.* nonresponders	P value
Wieder *et al.*, 2004 (48)	38	SCC	14 d	5FU	40 Gy	Decrease in SUV uptake ≥30% *vs.* <30%	SUV dec >30%: 100% R0 resection *vs.* 63% in SUV dec <30%	0.03	Median survival: 38 *vs.* 18 mo; 2-y OS: 79% *vs.* 38%	0.011
Song *et al.*, 2005 (49)	32	SCC	Week 8 (3-4 wk post CRT)	cis/5FU until 2002, then switched to 5FU and capecitabine induction + cis/capecitabine with RT	45.6 Gy in 1.2 Gy bid (n=7), later modified to 46 Gy in 2 Gy daily (n=25)	Initial SUV >4.0	pCR in 66% total group mCR: 71% *vs.* 25% in metabolic partial response	NR	NR	NR
Ott *et al.*, 2006 (43)	65	AC	14 d	cis/5FU ×2 cycles, AEG I tumors received paclitaxel	None	Decrease in SUV uptake ≥35%	44% *vs.* 5%	0.001	3-y survival: 70% *vs.* 35%. Median OS: not reached *vs.* 18 mo. Patients with mCR: >50 *vs.* 24 mo in metabolic nonresponders	0.01
Lordick *et al.*/ MUNICON, 2007 (50)	110	AC	14 d	Induction platinum + 5FU chemo	None	Decrease in SUV uptake ≥35%	49% *vs.* 0%	0.015	Median OS: not reached *vs.* 25.8 mo	0.015
Higuchi *et al.*, 2008 (51)	50	SCC	2-4 wk post chemo or CRT	Chemo (cis + doxorubicin + 5FU) or CRT (cis + 5FU)	40 Gy	SUV_{max} <2.5	87.5% of SUV_{max} <2.5 achieved good response *vs.* 6.9% of SUV_{max} ≥2.5 achieved good response	<0.0001	Median CSS in PET-neg group: 84.2 *vs.* 18.2 mo in PET + group. 5-y CSS 67.7% *vs.* 36.5%	0.0042; HR post tx SUV ≥2.5, 3.628, 0.0071
Javeri *et al.*, 2009 (52)	151	AC	5-6.5 wk post CRT	5FU with RT + either platinum or taxane, some received all 3	Either 45 or 50.4 Gy	>52% SUV_{max} decrease *vs.* ≤52% SUV_{max} decrease	21% with pCR, 63% had some degree of response to CRT (1% to ≤50% residual carcinoma in resected specimen)	NR	3-y OS: 72% *vs.* 43% in ≤52%. Median survival: not reached for responders *vs.* 2.49 y	0.02

Table 1 (*continued*)

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Study	No.	Tumor histology	Timing of 2nd PET	Chemotherapy	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response *vs.* nonresponders	P value	Survival of metabolic responders *vs.* nonresponders	P value
Roedl *et al.*, 2009 (53)	49	SCC	Avg 13.1 d post CRT (SD =6.5 d)	Cis +5 FU	50.4 Gy	Diameter-SUV index >55%	Diameter-SUV index >55% associated with 91% sensitivity and 93% specificity in predicting histopathologic response	AUC =0.931 optimal cutoff value of 55%	Mean DFS 32 *vs.* 16 mo	<0.001
Vallböhmer *et al.*, 2009 (54)	119	53 AC, 66 SCC	2-3 wk post CRT	Neoadj CRT with cis and 5FU	36 Gy	No specific cutoff values	Major histopathologic response seen in 39.5% in entire group	NR	5-y survival for major pathologic responders: 34% *vs.* 14% for minor responders, HR 2.2	0.005
zum Büschenfelde, *et al.*/ MUNICON II, 2011 (55)	56	AC	14 d	Induction platinum + 5FU chemo. If responder: continue 2 cycles of neoadj chemo. If nonresponder: 2 cycles cis or 5FU + RT	32 in 1.6 Gy bid only in metabolic non-responders. No RT for metabolic responders	Decrease in SUV uptake ≥35%	36% *vs.* 26%	0.561, NS	Median survival: not reached *vs.* 18.3 mo; 2-y OS estimate 71%±8%, 42%±11%	NR; NS
van Heijl *et al.*, 2011 (56)	100	82 AC, 18 SCC	14 d	Paclitaxel + carboplatin	41.4 Gy	Any SUV decrease (0% cutoff value)	90.6% pathCR *vs.* 9.4%	NR	NR	NR

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil; cis, cisplatin; RT, radiation therapy; CRT, chemoradiation therapy; SD, standard deviation; SUV, standard uptake value; OS, overall survival; NR, not reported; CSS, cancer-specific survival; pCR, pathologic complete response; DFS, disease-free survival; NS, not significant; mCR, metabolic complete response; HR, hazard ratio; AEG, adenocarcinoma of esophagogastric junction.

in radiation treatment planning in 34 esophageal cancer patients (70). Compared to CT alone, the addition of PET resulted in a GTV decrease in 35% of patients and a GTV increase in 21%. Changes to GTV also influenced dose-volume histograms of neighboring organs. The total lung volume receiving at least 20 Gy changed in nearly 75% of patients, including 12 with dose reductions and 13 with dose increases. The total volume of heart receiving at least 36 Gy increased in 11 patients and decreased in 12 patients. This trial did not correlate pathologic tumor extent with radiographic tumor extent.

Although limited information is available about the use of ^{18}F-FLT PET for esophageal radiation planning, a study by Han *et al.* suggests that ^{18}F-FLT PET can be used to accurately define the GTV and may allow for decreased dose to normal organs (13). A particular strength of this study is that GTV delineation using ^{18}F-FLT and ^{18}F-FDG PET was validated against pathologic findings. Various normal tissue parameters, such as mean lung dose and mean heart dose, were improved using ^{18}F-FLT PET. The authors noted that ^{18}F-FLT PET should be used cautiously for esophageal radiation planning until these findings have been validated.

^{18}F-FDG PET for treatment response assessment

Treatment for esophageal cancer, similar to that for other solid malignancies of the thorax, depends on the stage of the malignancy at the time of diagnosis. Although patients with stage IV disease do not benefit from surgical resection, studies have shown that most patients with stages 0-III esophageal cancer will benefit from surgical intervention. The timing of surgical intervention and schedule of associated chemotherapy and radiation will vary depending on the stage of disease. For example, those with stage 0 esophageal cancer or stage I esophageal cancer with a T1 lesion (no invasion of muscularis propia) often undergo surgery as a first-line treatment. However, a survival benefit and lower recurrence rates have been shown in those with more locally advanced disease who respond to concurrent chemotherapy and radiation therapy prior to surgical resection (72-75). Local failure rates after CRT can exceed 50% (3,4). Nonresponders are exposed to the toxic side effects of CRT therapy while appropriate surgical therapy is delayed (76-78). Therefore, it is important to be able to differentiate responders from nonresponders early during treatment so that future management can be optimal for each patient.

Invasive, minimally invasive, and noninvasive methods are available to assess treatment response. Endoscopic biopsy is limited in this effort, because it samples only the most superficial layers of mucosa; thus, biopsy may miss superficial in situ tumor as a result of sampling error, and cannot accurately determine the presence of residual nodal disease. In one large study of 118 patients with negative endoscopic biopsy after neoadjuvant therapy, only 37 patients (31.4%) demonstrated a complete pathologic response after esophagectomy (79). Similar findings were seen in a smaller study with 52 patients with negative endoscopic biopsies, 40 of whom (77%) had residual disease at resection (80). Given these limitations of biopsy, noninvasive methods have been used to help assess for residual disease after neoadjuvant therapy.

Multiple noninvasive or minimally invasive imaging procedures are used to evaluate treatment response after neoadjuvant therapy and include CT, EUS, and ^{18}F-FDG PET. Although CT is an important tool in evaluating treatment response in many thoracic malignancies, its sensitivity (33-55%) and specificity (50-71%) in esophageal cancer after treatment are relatively poor (81). This is likely the result of the infiltrative growth pattern of esophageal cancers, which makes accurate measurements difficult, especially when tumors are small or extend into the stomach. This can limit the ability to assess response using the Response Evaluation Criteria in Solid Tumors criteria (82). Assessing treatment response can become even more challenging in the setting of radiation therapy, where inflammation, edema, and scarring can be difficult to differentiate from residual esophageal disease (*Figure 1*) (83). In addition, because many newer cancer therapies are cytostatic instead of cytocidal, good tumor response may occur without a major reduction in tumor size (84).

By providing information on the metabolic activity of tumor cells, ^{18}F-FDG PET has become a powerful tool in assessment of treatment response in malignancies throughout the body. In one large meta-analysis assessing the performance of ^{18}F-FDG PET after CRT in patients with esophageal cancer, sensitivities and specificities of PET ranged from 71% to 100% and 55% to 100%, respectively (81).

Given that the metabolic change on PET imaging is an important indicator of tumor response, new criteria were created to refine and validate quantitative approaches to monitoring PET tumor response (84). PET Response Criteria in Solid Tumors (PERCIST) is used to evaluate tumor response through quantitative assessment of changes in metabolic activity. The primary measurement of

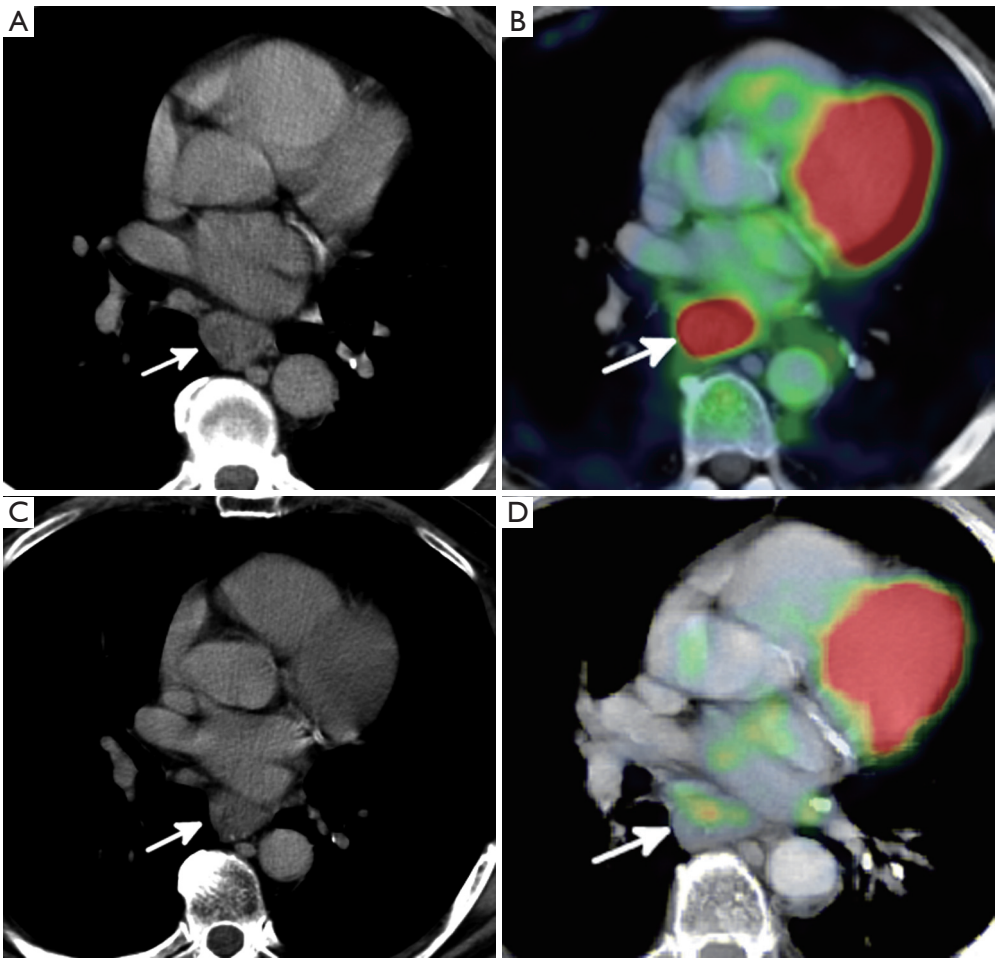

Figure 1 Pretreatment and posttreatment imaging in a 61-year-old man with stage II esophageal cancer. (A) Pretreatment CT showing focal circumferential thickening of the midesophagus (arrow); (B) PET/CT acquired on the same day showing intense uptake in the area of thickening (arrow) secondary to tumor; (C) posttreatment CT scan after concurrent chemotherapy and radiation therapy prior to esophagectomy showing persistent thickening of the midesophagus (arrow), nearly identical to the pretreatment scan; (D) PET/CT acquired on the same day showing near-complete absence of metabolic uptake in the area of residual thickening (arrow). Histopathologic analysis after esophagectomy found no viable tumor in the specimen (complete pathologic response), although areas of radiation-induced inflammation were noted, accounting for increased uptake on posttreatment PET/CT. PET, positron emission tomography; CT, computed tomography.

metabolic activity is the SUV, which is calculated by dividing metabolic activity by the injected dose and body weight. For PERCIST criteria, the SUV is corrected for lean body mass (SUL), because this metric is less susceptible to variations in the patient's body weight (85). Metabolic response using PERCIST criteria is determined by assessing changes in the peak SUL, measured by drawing a spherical region of interest 1.2 cm in diameter (which correlates to a voxel size of 1 cc) over the area of greatest uptake in the tumor. It is important to note that the peak SUL measurement on repeat imaging may be placed on a different area within a tumor or in a different lesion altogether when assessing tumor response (57).

Based on changes in peak SUL, PERCIST defines four categories of treatment response. In complete metabolic response, the metabolic uptake in all lesions is less than the average SUL of liver and equal to normal surrounding tissue SUL (*Figure 2*). Partial metabolic response is defined as a >30% decrease in peak SUL (*Figures 1* and *2*). Progressive metabolic disease is defined as is >30% increase in the peak SUL. Stable metabolic disease occurs when PET findings do not meet any of these criteria. Recent studies have

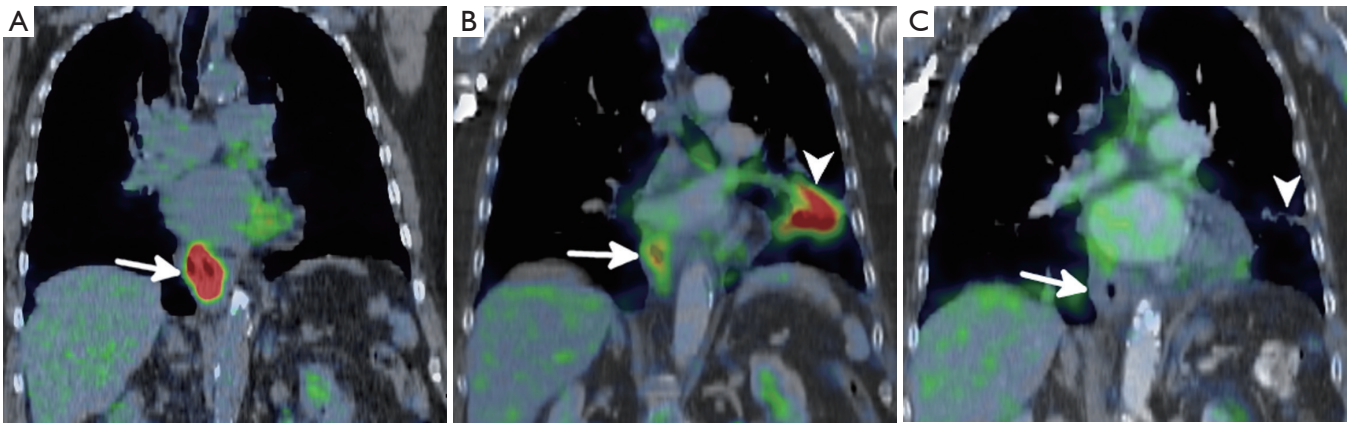

Figure 2 Progression of metabolic response on PET/CT during course of chemotherapy and radiation therapy in a 77-year-old man with a distal esophageal cancer. (A) Pretreatment PET/CT showing distal circumferential thickening of the esophagus with avid FDG uptake (arrow) and an SUV_{max}=14.8; (B) posttreatment PET/CT obtained 4 weeks after initiation of concurrent chemotherapy and radiation therapy (CRT) demonstrating a significant decrease in thickness of the distal esophagus as well as a marked reduction in FDG uptake (arrow), with an SUV_{max}=4.6, consistent with a partial metabolic response. The area of intense uptake in the left lower lobe (arrowhead) was secondary to a bacterial pneumonia; (C) posttreatment PET/CT scan acquired 12 weeks after initiation of CRT, demonstrating mild persistent thickening of the distal esophagus with complete absence of FDG uptake (arrow), consistent with a complete metabolic response. The left lower lobe pneumonia has also resolved, although a small amount of residual scarring (arrowhead) is visible. Histopathologic examination after esophagectomy showed no residual tumor. PET, positron emission tomography; CT, comupted tomography.

shown that PERCIST criteria are an independent predictor of survival in those with advanced esophageal cancer (82).

Although PET imaging is a strong noninvasive tool for assessment of treatment response in patients with esophageal cancer, it is by no means infallible. Increased ^{18}F-FDG uptake can be seen in any process that leads to an increased metabolic rate, such as infection or inflammation (*Figure 2*). Because radiation therapy leads to direct esophageal injury, subsequent inflammation and ulceration will often demonstrate increased uptake on PET imaging and can be mistaken for residual tumor (*Figure 1*) (86,87). Because radiation esophagitis usually begins 2 weeks after initiation of therapy and is more common with higher radiation doses, evaluating treatment response within the first 2 weeks of treatment, before esophagitis has had time to develop, may be more accurate and less prone to false-positive findings (88).

The accuracy of PET imaging can be limited by respiratory motion artifact, which is greatest at the level of the diaphragm (*Figure 3*), and has been reported to occur in up to 84% of patients undergoing PET/CT (89,90) This can lead to quantitative inaccuracies in the calculation of SUV_{max} by up to 50%, which can lead to misalignment of 2-4.5 cm between the CT and PET (91). These artifacts can be counterbalanced by incorporating respiratory-gated CT imaging or volume-average CT imaging (88,89,91,92).

PET is also limited because metabolic response is determined by assessing only a small focal area with the most intense tracer uptake. However, this fails to evaluate the entire tumor; recent studies have emerged suggesting that spatial PET/CT features, including tumor volume, tumor shape, total glycolytic volume, and spatial patterns, are more informative than the traditional response measure of SUV_{max} in various tumors (41,93).

^{18}F-FDG PET and response during treatment

Many patients with locally advanced esophageal cancer are referred to neoadjuvant therapy with either chemotherapy alone or CRT because of the potential OS benefit (2). However, it is well recognized that individual patient response to neoadjuvant therapy is variable, and it has been suggested that only 40-50% of patients will have a significant response to neoadjuvant therapy (94). Therefore, some patients may experience treatment-related toxicity without any significant benefit. Individualizing treatment to maximize treatment effect and minimize toxicity using noninvasive parameters would be ideal, and attempts have been made to correlate findings on ^{18}F-FDG PET with clinical and pathologic outcomes.

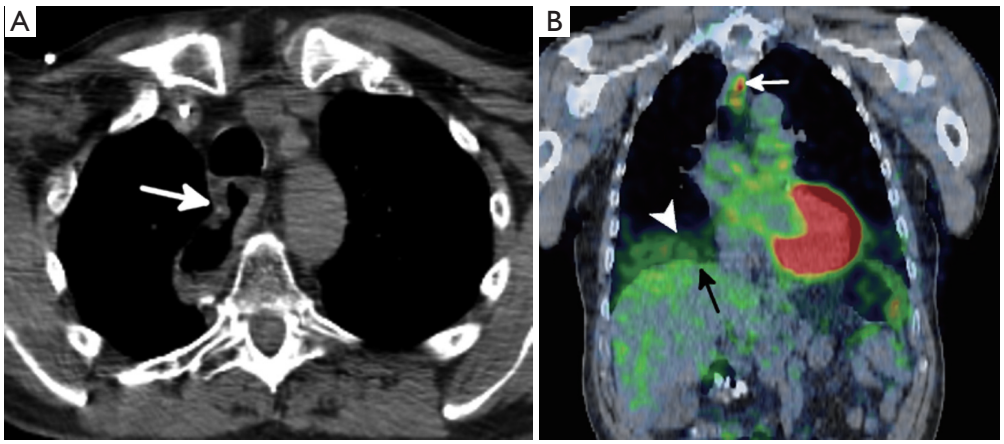

Figure 3 Local recurrence of esophageal cancer after esophagectomy. (A) Axial CT image from a PET/CT scan, showing minimal thickening of the esophagus at the anastomotic site (arrow) that was not prospectively detected; (B) fused coronal PET/CT showing uptake in the thickened portion of the esophagus at the anastomotic site (white arrow). Biopsy confirmed recurrent adenocarcinoma in this 55-year-old man. Misregistration is apparent between the physiologic liver uptake on the PET image (arrowhead) and the anatomic location of the liver (black arrow) on the study. PET, positron emission tomography; CT, computed tomography.

Weber *et al*. published data in 2001 suggesting that locally advanced esophageal cancer patients receiving neoadjuvant chemotherapy could be stratified into metabolic responders and nonresponders based on ^{18}F-FDG PET response and that this differentiation was directly correlated to disease control and survival (95). Patients underwent ^{18}F-FDG PET imaging prior to treatment and 14 days after starting cisplatin-based chemotherapy. A dramatic difference in tracer uptake was seen in responders (54%) and nonresponders (15%), and the authors proposed an optimal cutoff value to be 35% reduction in initial ^{18}F-FDG uptake. This cutoff was later prospectively validated by Ott *et al*. (43). Significantly more resected patients who were metabolic responders had either histopathologically complete or subtotal tumor regression than those who were not responders (53% and 5%, respectively). Metabolic response also predicted for longer time to disease progression (P=0.01) and longer overall survival (P=0.04).

Wieder *et al.* performed a similar assessment in 27 patients with esophageal SCC who underwent ^{18}F-FDG PET imaging at baseline and 14 days after initiation of neoadjuvant therapy (48). Unlike the study by Weber *et al.*, patients in this study received neoadjuvant radiation therapy in addition to chemotherapy, and the definition of metabolic response was slightly different (≥30% decrease in SUV uptake). Similar to the results of the study by Weber *et al.*, early metabolic responders had improved survival (P=0.011) and significant histopathologic response was more common than in nonresponders (44% and 21%, respectively; P=0.0055). It is important to be aware that radiation therapy can induce inflammation that may cause false overestimation of true uptake in actual tumor during treatment (96). Preclinical data suggest that ^{18}F-FLT PET may allow for better differentiation between inflammation and residual tumor during neoadjuvant therapy (97,98).

The phase II MUNICON (metabolic response evaluation for individualisation of neoadjuvant chemotherapy in esophageal and esophagogastric adenocarcinoma) trial evaluated the feasibility of using early ^{18}F-FDG PET response to guide therapy (50). Patients classified as metabolic responders, defined by a ≥35% reduction in metabolic activity between pretreatment imaging and imaging performed 14 days after initiation of therapy, continued with neoadjuvant therapy prior to surgery. However, metabolic nonresponders proceeded directly to surgery in an attempt to spare these patients from chemotherapy-related toxicity. After a median follow-up of 2.3 years, median event-free survival (EFS) and OS in the nonresponders were 14.1 and 25.8 months, respectively. For metabolic responders, median event-free survival was 29.7 months and median OS was not reached, both of which were significantly higher than for metabolic nonresponders. Significant pathologic treatment effect (<10% residual tumor) was noted in 58% of responders, whereas no such effect was seen in the nonresponders. Metabolic responders who also achieved a major histologic response had significantly higher EFS

[hazards ratio (HR) 3.03 (1.28-7.16); P=0.006] and OS [HR 4.55 (1.37-15.04); P=0.004] than the 21 metabolic responders who did not achieve a significant histologic response.

The MUNICON II trial was devised to determine whether metabolic nonresponders would have improved outcomes with the addition of salvage neoadjuvant CRT when <35% decrease in SUV uptake was identified on an ^{18}F-FDG PET scan obtained at day 14 (55). Metabolic nonresponders switched from neoadjuvant chemotherapy to concurrent cisplatin and 5-fluorouracil and radiation therapy (32 Gy in 1.6-Gy fractions given twice a day). Metabolic responders continued to receive neoadjuvant chemotherapy for 3 months prior to surgical resection and did not receive radiation therapy. The primary endpoint was to increase the margin negative resection (R0) rate for metabolic nonresponders from 74% to 94%. Although R0 resections were obtained in 82% of the metabolic responders and 70% of the metabolic nonresponders, the primary endpoint was not met. One-year progression-free survival was higher among responders than nonresponders (74% and 57%, respectively; P=0.035). Median OS was lower in the nonresponders than in the whole group (18.3 and 38.3 months, respectively), and the median OS had not been reached for responders. The authors noted that although the radiation dose of 32 Gy was relatively low, a major histopathologic response was observed in 26% of the metabolic nonresponders who underwent CRT. As mentioned previously, none of the metabolic nonresponders in the first MUNICON trial had a major histopathologic response after chemotherapy alone, raising the possibility of cell killing as a factor in a subset of patients who received CRT. The authors concluded that salvage neoadjuvant CRT led to local remissions in a select group of patients; however, systemic disease continued to influence clinical outcomes and survival.

A recent Cancer and Leukemia Group B 80302 phase II trial (NCT00316862) is looking at whether giving induction chemotherapy of cisplatin and irinotecan followed by CRT therapy will have any influence on pathologic complete response rate at time of surgery. One of the secondary objectives is to evaluate for potential response or progression of disease during induction chemotherapy with ^{18}F-FDG PET. Thus, patients will receive ^{18}F-FDG PET imaging at baseline, 15-19 days after the start of induction chemotherapy, and within 7 days before beginning chemoradiotherapy. The results of this study are not yet available, but could potentially provide additional information about treatment response related to pathologic response.

^{18}F-FDG PET and response after treatment

Although assessment of response during treatment is promising, the utility of posttreatment ^{18}F-FDG PET imaging has been more thoroughly studied. Most of these studies are single-institution retrospective reports with fairly small patient numbers, but they collectively suggest that uptake on ^{18}F-FDG PET after neoadjuvant treatment is associated with long-term outcomes and histopathologic outcomes (99-102) (*Table 2*). A recently published systematic review of 26 studies including 1,544 esophageal and GEJ cancer patients who received neoadjuvant therapy suggested that posttreatment ^{18}F-FDG PET can effectively predict long-term outcomes (63). In fact, the pooled HR for complete metabolic response compared to no response was 0.51 for OS (95% CI, 0.4-0.64; P<0.0001) and 0.47 for DFS (95% CI, 0.38-0.57; P<0.0001).

As previously discussed, investigators have questioned whether ^{18}F-FDG PET metrics other than SUV_{max} are more useful for evaluating treatment response after neoadjuvant therapy. A recent study from the University of Maryland extracted comprehensive spatial-temporal ^{18}F-FDG PET features from pre- and post-CRT PET scans in an attempt to predict pathologic tumor response in 20 esophageal patients (4). An area under receiver operating characteristic curve (AUC) value was used to quantify the ability of each feature to predict pathologic tumor response. In addition to SUV_{max} decline, two PET intensity features (mean SUV decline and skewness) and three PET texture features (inertia, correlation, and cluster prominence) were significant predictors of pathologic response. These novel PET features either had the same or higher AUCs than SUV_{max}. Recent data published by the same group using a support vector machine and logistic regression models suggest that these spatial-temporal ^{18}F-FDG PET features may more accurately predict pathologic tumor response when combined with conventional PET/CT measures and clinical parameters (93).

When a patient undergoes esophagectomy, PET/CT is often used to monitor for recurrent or metastatic disease. Local disease recurrence most commonly occurs near the anastomotic site and may be a subtle finding on CT alone (*Figure 3*). In addition, PET can often detect distant metastatic disease, which can occur in 8-17% of patients on restaging imaging, before disease becomes apparent

Table 2 Retrospective studies evaluating metabolic response during or after neoadjuvant treatment in esophageal cancer patients

Study	No.	Tumor histology	Timing of 2nd PET	Chemo	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response *vs.* nonresponders	P value	Survival of metabolic responders *vs.* nonresponders	P value
Swisher *et al.*, 2004 (103)	103	90 AC, 13 SCC	3-5 wk post CRT	CRT or induction [irinotecan + taxotere + 5FU] then CRT	50.4 Gy	Post-CRT SUV <4	SUV ≥4 had highest accuracy for predicting pathologic nonresponse: 76%	NR	18-mo survival: 77% *vs.* 34%	0.01
Konski *et al.*, 2007 (71)	81	18 AC, 7 SCC	4-6 wk post CRT	At discretion of medical oncologist	Preop: median 45 Gy, (7.2-50.4 Gy); Definitive: median 50.4 Gy (7.2-62.08 Gy)	Percent SUV change >32.3%	25% with pCR for total group	NS difference found between mean % SUV dec in pCR *vs.* no pCR	Median OS for trimodality therapy: 16.7 mo *vs.* definitive CRT: 5.2 mo	NR
Mamede *et al.*, 2007 (104)	25	22 AC, 3 SCC	22.3±14.5 d	Depended on clinical trial (cis + irinotecan, cis + irinotecan + cetuximab, cis + others)	50.4 Gy	Average percent SUV change >32.3%	Sensitivity of pathologic response 75% and specificity 62.5%	AUC 0.64	PostCRT SUV_{max} ≤4.35 progression-free survival not yet reached *vs.* 16.2 mo	0.0196
Monjazeb *et al.*, 2010 (105)	163: 88 trimodality therapy, 75 definitive CRT	122 AC, 42 SCC	Post CRT but exact time NR	Varied: 5FU + platinum, carboplatin/ taxol, FU alone, capecitabine	Median: 50.4 Gy	Post CRT SUV ≤3	53% *vs.* 33%	NS	Median OS: 29.7 *vs.* 15.9 mo	0.01
Sharma *et al.*, 2011 (106)	40	26 AC, 14 SCC	4-6 wk post CRT	At discretion of medical oncologist	Median: 50.4 Gy	Decrease in postCRT SUV	NR	NR	DFS: HR 1.3, 95% CO =1.03-1.6	0.03
Jayachandran *et al.*, 2012 (107)	37	27 AC, 10 SCC	Median 32 d after completing CRT (range 2-58 d)	At discretion of medical oncologist	Median: 50.4 Gy	$MTV_{2.5Post}$ ≤7.6 *vs.* >7.6 cm^3 $rMTV_2$ ≤0.39 *vs.* >0.39	71% pCR for total group of resected patients: 67% pCR in SCC, 39% pCR in AC	$MTV_{2.5Post}$ P=0.01; $TGA_{2.5Post}$, P=0.025	2-y OS $MTV_{2.5Post}$ ≤7.6 cm^3 84% *vs.* 29% >7.6 cm^3; $rMTV_2$ ≤0.39 77% *vs.* 37% for $rMTV_2$ >0.39, P=0.04	$MTV_{2.5Post}$ P=0.007; $rMTV_2$ ≤0.39 P=0.04

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma; 5FU, 5-fluorouracil; cis, cisplatin; RT, radiation therapy; CRT, chemoradiation therapy; SUV, standard uptake value; OS, overall survival; NR, not reported; CSS, cancer-specific survival; pCR, pathologic complete response; DFS, disease-free survival; NS, not significant; mCR, metabolic complete response; HR, hazard ratio; AUC, area under curve; MTV, metabolic tumor volume; rMTV, ratio of $MTV_{PostCRT}/MTV_{PreCRT}$; TGA, total glycolytic activity.

on standard anatomic imaging (83,88). Although disease recurrence after esophagectomy has a poor prognosis, therapy can be tailored toward palliation to improve patient symptoms and quality of life. Those who develop local or distal disease may be candidates for palliative therapy, including CRT, if adjuvant therapy has not been previously administered.

Conclusions

Advances in molecular imaging have led to dramatic improvements in care for esophageal cancer patients, ranging from diagnosis at an earlier and more manageable stage to altering treatment based on the degree of treatment response. Although ^{18}F-FDG PET is the most widely used molecular imaging technique, its optimal utilization in esophageal cancer management is still unclear. The Cancer and Leukemia Group B 80302 trial may provide addition information about how to best incorporate ^{18}F-FDG PET at various time points in the treatment of esophageal cancer.

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