Published in final edited form as:

Gastroenterol Clin North Am. 2009 March ; 38(1): 105–ix. doi:10.1016/j.gtc.2009.01.007.

The Role of FDG-PET and Staging Laparoscopy in the Management of Patients with Cancer of the Esophagus or Gastroesophageal Junction

Harry H. Yoon, MD, MHS^{a,*}, Val J. Lowe, MD^b, Stephen D. Cassivi, MD, MSc^c, and Yvonne Romero, MD^{d,e}

^aDivision of Medical Oncology, Department of Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

^bDivision of Nuclear Medicine, Department of Radiology, Mayo Clinic, Rochester, MN 55906, USA

^cDivision of General Thoracic Surgery, Department of Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

^dDivision of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

^eDepartment of Otolaryngology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Keywords

PET; CT; Esophageal cancer; Staging laparoscopy; Treatment response; Staging; Gastroesophageal junction cancer; Prognosis

Prognostically, esophageal cancer is characterized by high rates of local or distant recurrence following primary therapy, with death occurring soon after. Further darkening this grim prognosis is the observation that patients may spend their final months enduring and trying to recover from primary therapy, which often includes a potentially toxic combination of chemotherapy, radiation, and surgery.

The high failure rate is partly due to inadequacies in staging, which ideally would distinguish curable from incurable disease at the outset. Ideal staging selects patients for therapy according to the likelihood of clinical benefit—patients with local or locally advanced disease could receive local or multimodality therapy, whereas those with distant metastases could be spared aggressive and futile interventions.

For years, CT was the first-line method to detect distant metastases; however, major US trials enrolling patients thought to have resectable disease after CT with or without endoscopic ultrasonography (EUS) yielded noncurative resections in as many as 15% to 30% of patients and 1-year disease-free and overall survival rates of only 30% to 48% and 58% to 72%, respectively.^{1,2} In recent years, CT has been reported to have a sensitivity and specificity for detecting distant metastases of 41% to 81% and 82% to 83%, respectively.^{3,4}

When EUS was introduced, it became the most reliable method for determining T stage and identifying cancerous regional lymph nodes. EUS with fine-needle aspiration (FNA) enabled selective aspiration of echographically suspicious nodes, including those at the celiac axis; however, even when combined with CT, EUS has a reported sensitivity for detecting involved lymph nodes of only 11% to 54% and a specificity of 90% to 95%.⁴ Moreover, EUS is limited in esophageal obstruction, which impedes adequate passage of the endoscope and accurate detection of the depth of invasion and metastatic disease.

While tremendous attention has focused on developing effective therapies in all stages of disease, another line of investigation has been to improve initial staging. Modalities that have received attention or become standard at some institutions include 2-deoxy-2-[¹⁸F]fluoro-D-glucose positron emission tomography (FDG-PET) scanning, staging laparoscopy, and EUS.

PET has emerged as an important, increasingly common staging tool, particularly for the detection of distant metastases. Its routine use is recommended by the National Comprehensive Cancer Network in staging patients lacking M1 disease on CT and EUS. PET has also been studied to assess therapeutic response and to prognosticate, a role that is still investigational. Meanwhile, staging laparoscopy has been evaluated for the detection of peritoneal disease, particularly in patients with disease involving the gastroesophageal junction. Its acceptance has been less widespread. The role of EUS is discussed in detail elsewhere in this issue.

This article primarily reviews the data on the role of PET in staging and restaging esophageal cancer and in assessing the response to therapy. It also discusses the potential role of laparoscopy as a staging tool. Because of the dominance of adenocarcinoma in the United States and other Western countries, and because it appears to be a distinct clinical entity from squamous cell carcinoma, this discussion of the current literature draws attention to studies focusing on this histologic subtype.

POSITRON EMISSION TOMOGRAPHY IN INITIAL STAGING

CT and EUS provide anatomic visualization, whereas PET measures metabolic processes. PET can potentially determine quantitative information on blood flow, receptor status, and metabolic processes, depending on the radiopharmaceutical selected. Many of the early studies of PET in esophageal cancer were performed with “PET only” imaging. The advent of PET scanners with integrated CT scanners in recent years has allowed for direct comparison of metabolic information with anatomy with the added benefit of shorter imaging times for patients. This integration has led to an improvement in diagnostic accuracy from PET imaging; therefore, all state-of-the-art PET imaging is currently performed with integrated CT (PET/CT). The FDG is a glucose analogue that emits positron radiotracer. It is transported intracellularly and phosphorylated to FDG-6-phosphate via the same pathways as glucose. Because it is highly polarized, it is trapped in the cell. FDG-6-phosphate accumulates in tumors following injection and provides a signal of high glycolytic tissue activity in the body. Malignant tumors in most organ systems, except the brain and urinary tract, are frequently detected by FDG-PET.

PET images are analyzed qualitatively and quantitatively. The intensity of FDG uptake characterized as a standardized uptake value (SUV) within specific lesions is calculated as follows:

$$\text{SUV} = \frac{\text{mean activity in the region of interest (mCi/mL)}}{\text{injected dose of (mCi) / body wt (g)}}$$

Assessing T Stage

PET/CT has limited use in T staging, although tumor invasion into adjacent organs (T4) can sometimes be detected. Signs of invasion into adjacent organs include blurring of periesophageal fat, loss of intervening fat planes, and a large concave interface.⁵ After neoadjuvant radiotherapy, loss of normal tissue planes due to radiation-induced fibrosis and necrosis makes repeat evaluation of the T classification difficult with all imaging modalities, and local organ invasion may not be detected until esophagectomy.⁵

Key studies evaluating PET in the initial staging of patients with adenocarcinoma of the esophagus or gastroesophageal junction are shown in Table 1. The sensitivity of PET for detecting primary esophageal tumors has been reported in prospective studies to be 91% to 95%.^{3,6} In one study of 75 esophageal cancer patients, PET correctly assessed T status in 43% of cases, understaged status in 29%, and over-staged status in 29%.³ Given the limited spatial resolution of PET imaging devices (about 5–8 mm), it is generally believed that lesions smaller than 1 cm, particularly early stage cancers, may not be detected.

Assessing N Stage

Locoregional lymph nodes (eg, gastrohepatic ligament) are generally considered resectable (N1), whereas the resectability of celiac axis nodes is more controversial (M1a). Most studies indicate that PET, with or without CT, has limited use in assessing locoregional lymph node status (see Table 1). FDG uptake within periesophageal nodes close to the primary tumor is difficult to differentiate from uptake within the esophageal tumor itself due to the limited spatial resolution of PET. Further limiting the interpretation of nodes is the observation that FDG uptake can occur in benign disease such as granulomatous inflammation (eg, sarcoidosis), aspiration pneumonitis, or other inflammatory/infectious conditions.

A meta-analysis of 12 studies (n = 490) that examined the diagnostic accuracy of PET in preoperative staging of esophageal cancer reported sensitivity and specificity for detecting locoregional node involvement of 51% and 84%, respectively.⁷ The studies in the meta-analysis were heterogeneous in methodologic quality, in whether preoperative EUS was incorporated, and in whether PET images were fused with images from CT.

A Belgian study⁴ included in the meta-analysis reported the accuracy of PET in detecting local versus regional-distant nodal involvement (n = 74) and found accuracy rates to be similar between nodal regions. Local nodes were defined as those located within 3 cm from the primary tumor. Regional and distant nodes comprised all other nodes, including those in mediastinal, supraclavicular, and retroperitoneal areas. The sensitivity and specificity of PET were similar in the two nodal groups: 33% and 89% for local nodes and 46% and 90% for regional-distant nodes, respectively.

Subsequent to the meta-analysis, the authors reported the results of a prospective study at their institution comparing the accuracy of PET, CT, and EUS in the initial staging of patients with esophageal cancer (n = 75).³ In contrast to other data, the sensitivity of PET was found to be higher and the specificity of PET lower for detecting nodal metastases, that is, 82% and 60%, respectively.

Our reported specificity was probably lower because, unlike in other reports, EUS operators in the study were initially blinded to PET and CT results. After finishing TNM staging and sampling of visualized nodes, the EUS operator opened a sealed envelope to learn whether PET and CT had identified additional nodes or metastatic foci that could be assessed. If so, the operator sampled these areas, allowing histopathologic evaluation of all detected nodes in all modalities. Such pathologic confirmation could lead to a higher false-positivity rate (or lower specificity) attributed to PET or CT than reported elsewhere.

The sensitivity rate reported in our study was higher possibly because (1) we included both unresectable and resectable cases following CT evaluation, whereas other studies⁸ excluded unresectable cases, and (2) we performed PET with attenuation correction, which is known to improve sensitivity.⁹

Changing Management: Evaluating Distant Disease (M Stage)

The crucial test for incorporating a diagnostic modality in staging work-up is the degree to which it rationally alters clinical management. In esophageal cancer, two anatomic-pathologic checkpoints can most affect clinical management. The first checkpoint is distinguishing T2 (submucosa) from T3 (serosa) lesions. T1-2 lesions may be cured with surgery alone, whereas T3 lesions are commonly managed with trimodality therapy. As discussed previously, PET contributes minimally in this regard. The second checkpoint is distinguishing potentially resectable, locally advanced disease (T3-4N0, N1, perhaps M1a) from distant disease (M1b, perhaps M1a). Patients properly diagnosed with distant disease would receive more accurate prognostic information and palliative chemotherapy and would be spared combined chemoradiation and esophagectomy. For these patients, PET may be most helpful.

In their discussion, the investigators of the meta-analysis observed that patient management was altered in 3% to 20% cases due to the addition of PET in the preoperative work-up.⁷ The large range is explained in part by differences in entry criteria, the rigor with which pathologic verification (gold standard) was obtained, the study design, and criteria for resectability.

In prospective studies with clear reporting and rigorous attempts at pathologic confirmation that distinguished between M1a and M1b disease, M1b disease was detected by PET and missed by CT (with or without EUS) in 5% to 7% of cases.^{6,10} The addition of preoperative PET would have spared these patients unnecessary surgery.

One study reported that PET indicated M1b disease in an additional 10% of patients, but pathologic confirmation was not obtained.⁶ The investigators clarified that these PET-avid M1b lesions were unlikely to be malignant, because many of the unconfirmed findings were noted in patients who subsequently underwent surgical resection and had no evidence of recurrence or progression at 6 months.

M1 disease of any type (M1a or M1b) was detected by PET and missed by CT (with or without EUS) in 6% to 15% of patients.^{4,6,10} The minimal contribution of PET in detecting M1 disease in our study (1%) is perhaps explained by the fact that EUS detected M1a and some adjacent hepatic lesions with substantially greater sensitivity than reported elsewhere.^{3,4,10}

Limitations and Risk of Positron Emission Tomography

A potential downside to the routine use of PET in staging is the burden imposed by false-positive findings. The specificity of PET for M1a or M1b disease has been reported consistently to be high (90%–98%).^{3,4,7,10,11} Nevertheless, as with any diagnostic modality, false-positive findings lead to futile, potentially harmful work-up.

This problem is most aptly illustrated in the ACOSOG trial, one of few studies that reported adverse events stemming from the use of PET. In that trial, 4% of patients had negative confirmatory procedures. One patient underwent an adrenalectomy for a false-positive PET suggesting an adrenal metastasis. In addition to requiring a surgical procedure, the patient also required subsequent therapy for adrenal insufficiency. Another patient experienced a grade 3 adverse event for a wound complication after a confirmatory procedure for a false-positive finding.

REPEAT POSITRON EMISSION TOMOGRAPHY DURING OR AFTER NEOADJUVANT THERAPY AS A RESTAGING TOOL AND PROGNOSTIC MARKER

Based on the cumulative evidence of several underpowered trials, one standard therapy for resectable, locally advanced esophageal cancer in the United States has evolved to include chemotherapy concurrent with radiation (before surgery). Likewise, some parts of Europe have adopted neoadjuvant chemotherapy alone (followed by surgery). Both preoperative approaches have improved outcomes modestly at best and with considerable toxicity; therefore, investigators have sought ways to improve the selection of patients for therapy.

In this context the value of obtaining a repeat PET scan during or after neoadjuvant therapy has been studied as a restaging tool and as a prognostic marker. Three clinical scenarios have received the most attention in their potential for PET to alter and improve patient management (Table 2): (1) during neoadjuvant therapy for prognostication, (2) after neoadjuvant therapy and before surgery for restaging, and (3) after neoadjuvant therapy and before surgery for prognostication.

The scenario with the most straightforward implications is the use of PET after the completion of neoadjuvant therapy as a restaging tool before anticipated surgery (scenario two, see Table 2). Identifying the interval development of unresectable disease on repeat PET would disqualify the patient from surgery or other aggressive therapies. The treatment paradigm would shift to palliation. Because CT is commonly used to assess response, PET or PET/CT would need to add substantially to CT alone for integration after neoadjuvant therapy.

This particular question has not been extensively studied. One study prospectively enrolled 48 patients with esophageal cancer (85% adenocarcinoma) who were staged with CT, EUS-FNA, and PET/CT before and after neoadjuvant chemoradiation.¹² Patients with tissue confirmation of persistent nodal or metastatic disease who did not undergo complete resection were also included. Tissue biopsy was required to document M1b disease. Regarding the detection of M1b disease after chemoradiation, integrated PET/CT correctly identified four cases, falsely identified four cases, and missed two cases. CT performed similarly to PET/CT, correctly identifying three cases, falsely identifying three cases, and missing three cases. In this small study, PET/CT was superior to CT alone in finding evidence of distant disease, but at the price of a higher false-positive rate.

In another study, medical records were reviewed of patients scheduled to receive trimodality therapy who underwent PET/CT and esophagogastroduodenoscopy/EUS at baseline and after neoadjuvant treatment.¹³ Neoadjuvant therapy consisted of induction chemotherapy followed by chemoradiation, or chemoradiation alone. Among 88 patients who fit this profile, repeat PET/CT detected the interval development of M1b disease alone in three patients (3.4%). A fourth patient had M1a disease alone, and a fifth patient had both M1a and M1b disease. Of the three patients with M1b disease, two (2%) had metastases in skeletal muscle or bone marrow confirmed by biopsy or follow-up PET/CT. These disease sites are certainly outside the range of CT.

The sparse data that exist do not demonstrate substantial superiority of PET/CT over CT alone in the interval detection of unresectable disease after neoadjuvant therapy. In addition, one must consider the potential, albeit rare, risk of complications following confirmatory procedures, especially when the PET/CT abnormality may ultimately be deemed to reflect a false-positive finding. The use of PET/CT in this setting should not be considered mandatory until further data emerge. Balancing the substantial potential harm associated with an aborted esophagectomy due to metastases found at the time of laparotomy or, worse, a completed

esophagectomy without survival benefit compared with the low likelihood of serious harm from pursuing a false-positive PET/CT abnormality, our multidisciplinary practice has increasingly employed PET/CT to detect the interval development of distant disease following neoadjuvant chemoradiation.

By contrast, a clinical time point that has been reported more extensively and with intriguing findings is the use of PET 2 to 3 weeks after initiating neoadjuvant therapy (scenario one, Tables 2 and 3). In a single-arm, single-institution study, a German group enrolled 65 patients with resectable, locally advanced adenocarcinoma of the gastroesophageal junction.¹⁴ All patients were scheduled to receive chemotherapy alone followed by surgery. A PET scan was obtained at baseline and 2 weeks after the initiation of chemotherapy. Patients were classified as metabolic responders if the metabolic activity of the primary tumor had decreased by more than 35% at the time of the second PET and as nonresponders otherwise. Outcome variables were the presence of a histopathologic “response” (ie, less than 10% tumor cells in the resected specimen) and overall survival.

Nine patients were excluded because baseline FDG uptake was too low ($n = 8$) or blood glucose was too high at repeat PET ($n = 1$). Of the remaining 56 patients, 6 experienced disease progression and the other 50 reached surgery. Of the 50, 41 patients underwent surgery with cancer-free margins.

The investigators found that metabolic responders when compared with nonresponders were more likely to have a histopathologic response (44% versus 5%, $P = .001$) and to live longer (3-year overall survival rate of 70% versus 35%, $P = .01$). Furthermore, multivariate modeling revealed that a metabolic response predicted risk independently (hazard ratio [HR] for death, 0.34, when comparing responders with nonresponders). This finding held true when limiting analysis to patients who reached operation. It also held true when assessing disease-free survival among patients with cancer-free resection margins.

Although these results are intriguing and warrant further testing, they should be interpreted with caution in their clinical implementation. First, simple associations with outcome are insufficient evidence to rationally affect clinical management. What is necessary are predictive values or likelihood ratios followed by validation studies. The investigators reported positive and negative predictive values with regard to histopathologic response and clinical response. The former is perhaps the strongest prognosticator of overall outcome, but neither factor has been demonstrated to be a valid surrogate of meaningful clinical outcome. Overall survival was not assessed with regard to PET findings.

Second, subjects in the study may be highly selected and not reflect those in the general population. The median survival in this cohort far exceeded that reported in patients in the combined chemotherapy/surgery arms of large randomized trials (32 versus 15–17 months).^{1,15} One can speculate that survival in the general population is worse.

Third, the generalizability of the findings is further limited because 14% of subjects enrolled were excluded from analysis, mostly due to insufficient uptake on their baseline PET.

Fourth, further diminishing generalizability is the fact that treatment consisted of chemotherapy alone and not chemoradiation. Metabolic response and PET interpretation (eg, determining threshold cutoff values) may differ between patients who receive chemotherapy versus chemoradiation.

Lastly and perhaps most problematic is the fact that, without a randomized trial, the appropriate triage of nonresponders (or responders) is unknown. It has been suggested that nonresponders be sent down a variety of therapeutic paths, all mutually exclusive, as follows: (1) immediate

surgery (under the rationale that chemotherapy adds only modest benefit to surgery anyway, and for nonresponders will only add toxicity), (2) palliation alone (under the rationale that neither chemotherapy nor surgery will help), or (3) the use of a new chemotherapy agent followed by surgery (under the rationale that surgery alone has been demonstrated to have poor outcomes and that response to a new agent may be better).

To clarify these issues, a randomized phase II trial (MUNICON) was led by the same German group. Patients with locally advanced gastroesophageal cancer ($n = 119$) were enrolled to assess the metabolic response as a means to guide subsequent therapy. PET was obtained at baseline and after 2 weeks of chemotherapy. Metabolic responders (using a $>35\%$ decrease in SUV as the cutoff) continued with chemotherapy and then underwent surgery. Nonresponders discontinued chemotherapy and underwent immediate surgery. One hundred ten patients were evaluable for metabolic response, half of whom were responders. Patients were followed up for a mean of 2.3 years.

The most important finding was that the overall survival of nonresponders (26 months) who were denied chemotherapy did not appear to be lower than that of historical controls who received chemotherapy and surgery (15–18 months).^{1,14,15} Nevertheless, again, the cohort as a whole appears to have been highly selected, because their overall survival exceeded that in other trials.

In addition, the correct allocation of responders or nonresponders is still unknown. Whether responders would perform just as well without further chemotherapy, and whether nonresponders would have performed better with further chemotherapy remain unanswered. Until these questions are addressed in a randomized trial, assessing the PET response during induction therapy should be considered investigational.

Assessing treatment response by PET has also been studied following the completion of neoadjuvant therapy (scenario three, see Tables 2 and 3). The outcomes that PET has been assessed against include the pathologic response (ie, complete absence versus residual tumor in the resected specimen) and the disease-free or overall survival.

PET has been consistently demonstrated to be unreliable in predicting a pathologic complete response (pCR) after neoadjuvant chemotherapy or chemoradiation. One group retrospectively reviewed the records of patients who underwent trimodality therapy and who had PET between chemoradiation and surgery.¹⁶ Among 19 patients whose tumor was more PET avid than adjacent irradiated esophagus, suggesting residual disease, at least five had a pCR. Furthermore, among 23 patients whose tumor was less PET avid than adjacent irradiated esophagus, suggesting tumor clearance, 16 had residual (mostly microscopic) tumor.

Another study reviewed the records of patients who received neoadjuvant chemotherapy alone followed by surgery, with similar results.¹⁷ Among 13 patients who had a 100% reduction in their SUV after chemotherapy, suggesting tumor clearance, only two had a pCR. The other patients had gross ($n = 8$) or microscopic ($n = 3$) residual disease. A third study found that the positive predictive value of PET/CT for identifying a pCR was 76%, statistically similar to that found by CT (57%) or EUS-FNA (60%).

The link between metabolic response and survival has also been evaluated, often generating positive associations of important scientific interest and limited or unclear clinical relevance. One group reviewed the records of patients ($n = 83$, mostly adenocarcinoma) who received chemoradiation therapy followed by surgery, with CT, EUS, and PET performed before and after chemoradiation. After chemoradiotherapy, an SUV of four or greater on PET was the only preoperative factor that correlated with decreased survival (2-year survival rate of 33% versus 60%, $P = .01$). Multivariate analysis was not reported. In another single-institution

study, a prospective study, metabolic responders had improved disease-free (67% versus 38%) and overall (89% versus 63%) survival at 2 years when compared with nonresponders.¹⁸ Whether metabolic response was an independent predictor of outcome was not reported.

By themselves, these results do not clarify how to manage metabolic responders versus nonresponders following chemoradiation, for the same reasons it is unclear how to manage responders versus nonresponders after chemotherapy alone. We do not believe PET should be used routinely to assess the response after chemoradiation for guiding subsequent therapy. For now, the major clinical role of PET following neoadjuvant chemoradiation therapy remains the identification of distant metastases before performing esophagectomy.

Preliminary studies such as these open the way for further protocols to explore these questions, much as the MUNICON study has done. The effort to improve complete pathologic responses has led to trials in which chemoradiation and surgery are preceded by induction chemotherapy. Appropriately, studies have begun to assess the role of PET in these therapeutic contexts as well.^{19,20}

STAGING LAPAROSCOPY

Minimally invasive surgery, including laparoscopy with or without thoracoscopy, has been proposed as a way of improving staging and has yielded reports of its diagnostic superiority over EUS or CT (Table 4).^{11,21-27} Laparoscopic staging typically involves direct visualization and biopsy of abnormal findings on the peritoneal and liver surfaces. Entry into the lesser sac by incising the gastrohepatic ligament allows for potential sampling of lymph nodes adjacent to the lesser curve and celiac axis (lymph node stations 16–20).

The main potential benefit of staging laparoscopy is its ability to detect distant metastases missed by conventional imaging, thereby protecting the patient from a meaningless laparotomy. In addition, laparoscopy allows pathologic confirmation of nodal status, which could aid prognostication, help define radiation fields, and allocate unimodality versus trimodality therapy. Proponents of staging laparoscopy have pointed to other benefits, including better assessment of primary tumor size;²³ providing tissue samples to assess the prognostic ability of molecular markers;²⁵ the fact that staging laparoscopy, unlike EUS, is not prevented or limited by esophageal obstruction; and the possibility for inserting an enteral feeding tube before the stresses of anticipated chemoradiation.

Single-institution experience indicates that laparoscopy, when CT and EUS are used, substantially increases the sensitivity and specificity for detecting lymph node and distant metastases. Following CT and EUS, laparoscopy upstages nodal status in 0% to 21%²²⁻²⁵ of cases and downstages in 4% to 19%.^{22,24,25} Moreover, laparoscopy detects liver or peritoneal metastases in 7% to 20% of patients,²²⁻²⁵ in which case the therapeutic paradigm is altered toward palliation. In one series (n = 59), staging laparoscopy following CT and EUS changed the tumor diagnosis in six patients from esophageal to gastric cancer.²² Four patients with localized gastric cancer underwent gastrectomy, whereas two with advanced disease, that was otherwise occult, were treated with palliative measures only.

In the largest series to date (n = 511) of esophageal and gastric cancer patients, staging laparoscopy changed treatment primarily in patients with disease located in the lower esophagus or proximal stomach and never in the upper or mid esophagus. A major weakness of this study is that less than 10% patients (48/511) received both EUS and CT. A multicenter trial (CALGB 9380) was performed to evaluate the accuracy of staging laparoscopy, but it too was limited in that only half the patients underwent baseline EUS.²⁶ Follow-up data for that trial have not been reported (M.J. Krasna, personal communication, 2008).²⁸

Major complications have been reported in 0% to 4%^{22,23,25,26} of cases, with no reported mortality. In one series (n = 59)²² in which feeding tubes were placed, one patient had a perforation of the small bowel adjacent to the J-tube insertion site and required laparotomy with small bowel resection. A second patient experienced intraoperative pulmonary edema secondary to unexpected aortic valve stenosis, which eventually required an aortic valve replacement before esophagectomy. An older series (n = 26) reported prolonged ileus (n = 2), atelectasis (2), urinary retention (2), port site infection (2), and small bowel obstruction (1).

¹¹ Mean hospital stays lasted 2 to 3 days.^{11,22,23,26}

To date, in all reported series assessing staging laparoscopy, PET has not been included in the staging algorithm. This absence substantially limits the generalizability of the reports, because PET has reasonable accuracy for the detection of distant metastases⁷ and has become a mainstay in the staging work-up of esophageal cancer.

It is unclear whether PET would have accurately detected the metastases discovered by laparoscopy in the previous series, because the sizes of those lesions were usually not reported. Notably, one prospective study (n = 74) in which therapy consisted of surgery alone found that peritoneal carcinomatosis was missed in five patients (6.7%) by both CT and PET and was discovered only at the time of laparotomy.¹⁰ Whether this lack of sensitivity would have altered management depends on the surgical practice, because four of these patients also had PET-avid celiac or para-aortic nodes before surgery, which would have precluded resection in some centers.

Some investigators who appear to favor staging laparoscopy have acknowledged that the standard use of PET limits the role of laparoscopy to situations in which PET, CT, and EUS fail or are not feasible. Such situations would include that of a suspicious lymph node that is either inaccessible for biopsy or yields a negative or ambiguous pathologic reading on FNA.²⁶

Furthermore, a cost-effectiveness analysis evaluating CT, EUS-FNA, PET, thoracoscopy/laparoscopy, and combinations thereof found that CT plus EUS-FNA was the least expensive strategy and offered more quality-adjusted life-years than all other strategies with the exception of PET plus EUS-FNA.²⁸ The latter was slightly more effective but more expensive. The investigators recommend PET plus EUS-FNA as the staging procedure for patients with esophageal cancer unless resources are scarce or PET is unavailable.

At the authors' center, EUS-FNA and integrated PET/CT are incorporated as the standard in the initial staging of all patients with esophageal cancer. We initially use a dedicated CT scan of the chest and abdomen because of its better anatomic definition to evaluate the extent of local invasion and screen for distant metastases. If none are found, PET/CT is used for further evaluation. If distant metastases are suggested by these imaging modalities, tissue confirmation is obtained. Only in cases in which no distant disease is suspected and curative resection remains a treatment option do we pursue EUS-FNA. Laparoscopy and thoracoscopy are reserved for situations in which the findings from history, physical examination, EUS-FNA, or PET/CT are equivocal and evidence of M1b disease would alter the planned treatment. Laparoscopy for staging is also performed at the time of placement of a laparoscopic feeding jejunostomy if one is required before esophagectomy. In the PET/CT era, we have not yet found a sufficient diagnostic or prognostic benefit for the patient to support the routine addition of laparoscopy in the staging of esophageal cancer.

SUMMARY

At the authors' center, patients with biopsy-proven submucosally invasive cancer of the esophagus or gastroesophageal junction routinely undergo the following staging work-up: CT

of the chest and abdomen, integrated PET/CT scan and EUS-FNA, and other testing targeted to specific findings elicited on the history and physical examination. We do not perform routine staging laparoscopy or thoracoscopy and reserve these modalities for specific situations in which the testing results are equivocal and different findings would alter the treatment options. Localized early stage esophageal cancer is treated with esophagectomy alone, whereas locally advanced resectable disease is treated by neoadjuvant chemoradiation followed by surgery. Following chemoradiation, repeat CT is performed to identify interval development of unresectable disease. Among our oncology providers, the use of PET/CT to detect the interval development of distant disease is currently physician dependent. At present, the use of PET/CT to assess treatment response and influence subsequent therapy is investigational.

REFERENCES

1. 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;339(27):1979–84. [PubMed: 9869669]
2. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19(2):305–13. [PubMed: 11208820]
3. Lowe VJ, Booya F, Fletcher JG, et al. Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. *Mol Imaging Biol* 2005;7(6):422–30. [PubMed: 16270235]
4. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000;18(18):3202–10. [PubMed: 10986052]
5. Bruzzi JF, Munden RF, Truong MT, et al. PET/CT of esophageal cancer: its role in clinical management. *Radiographics* 2007;27(6):1635–52. [PubMed: 18025508]
6. Meyers BF, Downey RJ, Decker PA, et al. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg* 2007;133(3):738–45. [PubMed: 17320575]
7. van Westreenen HL, Westertep M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 2004;22(18):3805–12. [PubMed: 15365078]
8. Kneist W, Schreckenberger M, Bartenstein P, et al. Positron emission tomography for staging esophageal cancer: does it lead to a different therapeutic approach? *World J Surg* 2003;27(10):1105–12. [PubMed: 12917769]
9. Rice TW. Clinical staging of esophageal carcinoma: CT, EUS, and PET. *Chest Surg Clin N Am* 2000;10(3):471–85. [PubMed: 10967751]
10. Heeren PA, Jager PL, Bongaerts F, et al. Detection of distant metastases in esophageal cancer with (18)F-FDG PET. *J Nucl Med* 2004;45(6):980–7. [PubMed: 15181133]
11. Luketich JD, Schauer P, Landreneau R, et al. Minimally invasive surgical staging is superior to endoscopic ultrasound in detecting lymph node metastases in esophageal cancer. *J Thorac Cardiovasc Surg* 1997;114(5):817–21. discussion: 21–3. [PubMed: 9375612]
12. 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* 2005;129(6):1232–41. [PubMed: 15942562]
13. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109(1):125–34. [PubMed: 17146785]
14. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24(29):4692–8. [PubMed: 16966684]

15. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002;359(9319):1727–33. [PubMed: 12049861]
16. Erasmus JJ, Munden RF, Truong MT, et al. Preoperative chemoradiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. *J Thorac Oncol* 2006;1(5):478–86. [PubMed: 17409902]
17. Port JL, Lee PC, Korst RJ, et al. Positron emission tomographic scanning predicts survival after induction chemotherapy for esophageal carcinoma. *Ann Thorac Surg* 2007;84(2):393–400. [PubMed: 17643605]
18. 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;21(3):428–32. [PubMed: 12560430]
19. Ribi K, Nitzsche E, Schuller J, et al. 2007 ASCO Annual Meeting Proceedings Part I. *Journal of Clinical Oncology* June 20;2007 25(Supplement):4587. PET scanning and patient reported dysphagia before and after chemotherapy (CT) for prediction of pathological response after CT and chemoradiotherapy (CRT) in patients with locally advanced esophageal cancer (EC): a multicenter phase II trial of the Swiss. [PubMed: 17925553]
20. Gea, KU. Phase II trial of preoperative cisplatin/irinotecan and radiotherapy for locally advanced esophageal cancer: PET scan after induction therapy may identify early treatment failure. ASCO Gastrointestinal Cancers Symposium. [Accessed September 23, 2008]. 2007 Available at: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=45&abstractID=10131
21. de Graaf GW, Ayantunde AA, Parsons SL, et al. The role of staging laparoscopy in oesophagogastric cancers. *Eur J Surg Oncol* 2007;33(8):988–92. [PubMed: 17344017]
22. Heath EI, Kaufman HS, Talamini MA, et al. The role of laparoscopy in preoperative staging of esophageal cancer. *Surg Endosc* 2000;14(5):495–9. [PubMed: 10858480]
23. Kaiser GM, Sotiropoulos GC, Fruhauf NR, et al. Value of staging laparoscopy for multimodal therapy planning in esophagogastric cancer. *Int Surg* 2007;92(3):128–32. [PubMed: 17972466]
24. Kaushik N, Khalid A, Brody D, et al. Endoscopic ultrasound compared with laparoscopy for staging esophageal cancer. *Ann Thorac Surg* 2007;83(6):2000–2. [PubMed: 17532386]
25. Krasna MJ, Jiao X, Mao YS, et al. Thoracoscopy/laparoscopy in the staging of esophageal cancer: Maryland experience. *Surg Laparosc Endosc Percutan Tech* 2002;12(4):213–8. [PubMed: 12193812]
26. Krasna MJ, Reed CE, Nedzwiecki D, et al. CALGB 9380: a prospective trial of the feasibility of thoracoscopy/laparoscopy in staging esophageal cancer. *Ann Thorac Surg* 2001;71(4):1073–9. [PubMed: 11308139]
27. Patel AN, Buenaventura PO. Current staging of esophageal carcinoma. *Surg Clin North Am* 2005;85(3):555–67. [PubMed: 15927651]
28. Wallace MB, Nietert PJ, Earle C, et al. An analysis of multiple staging management strategies for carcinoma of the esophagus: computed tomography, endoscopic ultrasound, positron emission tomography, and thoracoscopy/laparoscopy. *Ann Thorac Surg* 2002;74(4):1026–32. [PubMed: 12400740]
29. Block M, Patterson GA, Sundaresan RS, et al. Improvement in staging of esophageal cancer with the addition of positron emission tomography. *Ann Thorac Surg* 1997;64:770–7. [PubMed: 9307472]
30. Luketich JD, Schauer PR, Meltzer CC, et al. Role of positron emission tomography in staging esophageal cancer. *Ann Thorac Surg* 1997;64(3):765–9. [PubMed: 9307471]
31. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007;8(9):797–805. [PubMed: 17693134]
32. 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 chemoradiation in patients with esophageal carcinoma. *Cancer* 2004;101(8):1776–85. [PubMed: 15386332]

Table 1
Studies evaluating PET in initial staging of esophageal adenocarcinoma

Study	Institute	Design	Number of Patients	Other Modalities	AC/SCC (%)	N		M	
						Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Block 1997 ²⁹	Washington University	Unclear	58	CT	59/40	–	–	–	15
Luketich 1997 ³⁰	University of Pittsburgh	Retro	35	EUS, bscan, CT, Ls or Ts	71/26	97	45	100	93 ^a
Lowe 2005 ³	Mayo	Prosp	75	CT, EUS	90/10	–	82	60	91
Flamen 2000 ⁴	Gathuisberg, Belgium	Prosp	74	CT, EUS	72/28	95	39	97	74
Meyers 2007 ⁶	ACOSOG	Prosp	189	CT	NR	91	–	–	5%–10% Upstaged to M1b 3% Falsely upstaged to M1b
Heeren 2004 ¹⁰	Groningen, Netherlands	Prosp	74	CT, EUS	84/16	95	55	71	98
									7

Abbreviations: AC, adenocarcinoma; ACOSOG, American College of Surgeons Oncology Group; bscan, bone scan; EUS, endoscopic ultrasound; Ls, laparoscopy; M, metastasis; M1b, stage IV M1b denoting distant organ metastases; N, node; NR, not reported; PCM, PET changes management based on identification of M1b or otherwise unresectable disease missed by other modalities; Prosp, prospective; Retro, retrospective; SCC, squamous cell carcinoma; T, tumor; Ts, thoracoscopy.

^aSensitivity for identifying primary tumor. Specificity for detecting tumor was not assessed in most studies because inclusion criteria required the presence of primary esophageal tumor.

^bDash denotes results reported in a way that did not permit simple cross-study comparison.

^cDistant metastases refers to M1b disease.

Table 2
Rationale for obtaining repeat PET scan: three scenarios

Timing of Repeat PET	PET Features Assessed for Predictive Value	Outcomes Examined	Implication for Clinical Management
During neoadjuvant therapy	1. Change in FDG uptake (baseline versus repeat)	Pathologic response ^a or overall survival	Nonresponders: ^b alter chemotherapy agent or undergo immediate surgery Responders: ^c continue neoadjuvant chemo and subsequent surgery
After completion of neoadjuvant therapy, before potential surgery	2. Presence of unresectable disease in repeat PET scan	NA	Cancel surgery; palliative therapy
	3. Change in FDG uptake (baseline versus repeat)	Pathologic response ^a or overall survival	Nonresponders: ^b alter chemotherapy agent or undergo immediate surgery Responders: ^c forego or undergo surgery

Abbreviation: NA, not applicable.

^a Assessed at surgery.

^b Patient with persistent or progressive hypermetabolic activity on repeat PET scan.

^c Patient with decreased hypermetabolic activity on repeat PET scan.

Table 3
Studies evaluating metabolic response (repeat versus baseline PET) as prognostic marker in esophageal adenocarcinoma

Treatment Modality	Study	Institute	Number of Patients	Design	Timing of Repeat PET	Cutoff in SUV Decrease (%) to Denote Metabolic Responder	Association Between Metabolic Response and Outcome (Responder Versus Nonresponder)				
							Pathologic Response ^a	DFS or TTP		OS	
								UV (m)	MV (HR)	UV (m)	MV
C/S	Ott 2006 ¹⁴	Munich	65	Prosp, 1-arm	During ^b	>35	44% versus 5%	>42 versus 10	0.22	>32 versus 18	NS
	Port 2007 ¹⁷	Cornell	62	Retro	After ^c	>50	24% versus 4%	35 versus 18	2.4 ^d	NR	NR
	Lordick 2007 ³¹	Munich	110	Prosp, 2-arm (PET guided)	During	>35	58% versus 0%	30 versus 14	NR	>27 versus 26	NR
CRT/S	Downey 2003 ¹⁸	MSKCC	24	Prosp, 1-arm	After	>60	NR	67% versus 38% (2 y) NS	NR	89% versus 63% (2 y) NS	NR
	Swisher 2004 ³²	MD Anderson	83	Retro	After	Post-CRT SUV <4	–	NR	NR	60% versus 33% (2 y)	NR
C/CRT/S	Ribi 2007 ¹⁹	Swiss	56	Prosp, 1-arm	After C, before CRT	>40	–	NR	NR	NR	NR
	Ku 2007 ²⁰	MSKCC	55	Prosp, 1-arm	After C, before CRT	>35	–	41 versus 9	NR	HR 0.9	NR

Abbreviations: C/S, chemotherapy followed by surgery; CRT/S, chemoradiation followed by surgery; C/CRT/S, induction chemotherapy followed by chemoradiation followed by surgery; DFS, disease-free survival; HR, hazard ratio for death; m, months (median); MSKCC, Memorial Sloan Kettering Cancer Center; MV, multivariate; NA, not applicable; NR, not reported; NS, statistically nonsignificant at alpha 0.05; OS, overall survival; Prosp, prospective; Retro, retrospective; TTP, time to progression; UV, univariate; y, year.

^aPercent of patients with absence, near absence, or with presumed decrease of tumor cells in resected specimen.

^bDuring neoadjuvant therapy.

^cFollowing the completion of neoadjuvant therapy.

^dHR for death comparing nonresponder with responder statistically significant at alpha 0.05.

Table 4

Studies assessing staging laparoscopy in esophageal cancer^a

Study	Institution	Number of Patients	Design	Results			
				N (%up, down)	M (%up, down)	Management Change (%) ^b	Days in Hospital
Krasna 2002	University of Maryland ²⁵	76	Prosp	21, 9	7, ^d	NR	NR
Kaiser 2007	Essen, Germany ²³	70	Retro	17, –	20, 0	20	3
Kaushik 2007	Pittsburgh ²⁴	47	Retro	0, 4	17, 6	–	NR
Krasna 2001	CALGB ²⁶	113	Prosp	14, NR	2, NR	NR	3
Heath 2000	Hopkins ²²	59	Prosp	2, 19	≤7, NR	17	2
deGraaf 2007 ^e	Nottingham, England ²¹	416	Retro	–	–	20	NR
Luketich 1993 ^f	Pittsburgh ¹¹	26	Prosp	11, 1	4, –	–	1.8

Abbreviations: Down, downstaged after laparoscopy; M, metastatic stage; N, nodal stage; NR, not reported for esophageal cancer or laparoscopy specifically; Pro, prospective; Retro, retrospective; Up, upstaged after laparoscopy.

^a All studies except Krasna, 2001²⁶ and deGraaf, 2007²¹ performed CT and endoscopic ultrasound in more than 70% of patients before laparoscopy.

^b Results of staging laparoscopy changed clinical management.

^c “Major” complication due to laparoscopy.

^d Dash denotes results that were unclearly reported or did not permit simple cross-study comparison.

^e Includes noncardia gastric cancer patients.

^f Thoracoscopy performed with laparoscopy.