Neoplasms of the Esophagus and Stomach

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Esophageal cancer is one of the most lethal of all neoplasms. During the last two decades, there have been significant changes in the epidemiology and treatment of esophageal cancer. The incidence of adenocarcinoma is increasing whereas that of squamous cancer is decreasing. Surgery, the mainstay of treatment of esophageal cancer, has been used with neoadjuvant chemoradiotherapy to improve prognosis in patients with localized disease. Accurate staging is essential for selection of the best mode of therapy and to predict prognosis. In addition, with widespread use of neoadjuvant therapy, accurate assessment of response to therapy has become very important because responders have better a prognosis than nonresponders. Anatomical imaging methods, such as computed tomography and endoscopic ultrasonography, that are commonly used to evaluate esophageal cancer have shortcomings in demonstrating the true extent of disease and in assessing or predicting response to therapy. Positron emission tomography (PET) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) has been shown to be a useful adjunct to anatomical imaging methods. For initial staging of esophageal cancer, the combination of PET and endoscopic ultrasonography with fine-needle aspiration biopsy has been suggested to be the most effective strategy. For restaging and monitoring response to therapy, FDG-PET has been shown to be superior to conventional imaging. The incidence of gastric cancer is decreasing worldwide, but it is also a highly lethal cancer. Similar to esophageal cancer, noninvasive staging of this cancer is unsatisfactory. Approximately one-third of the patients thought to have limited disease and to be candidates for surgery by conventional staging methods, are found to have advanced disease at surgery. Only a few published studies have evaluated gastric cancer with FDG-PET. These studies suggest that FDG-PET may be useful in evaluating gastric cancers of intestinal type and nonmucinous tumors.

ESOPHAGEAL AND GASTRIC CANCERS are aggressive malignancies with a dismal prognosis. In the United States, it is estimated that nearly 37,000 patients will be diagnosed in 2004 with esophageal or gastric cancer and that approximately 25,000 of these patients will die as a result of these cancers (4.4% of all cancer-related deaths).[1] There has been a major shift in the histology and location of these cancers in Western countries; the most common location is in the distal esophagus and gastroesophageal junction and the most common histology is adenocarcinoma.

There are several approaches to treating esophageal and gastric cancers, including surgical, nonsurgical, and multimodality therapies. Surgery alone is potentially curative when a complete resection can be achieved. Nonsurgical therapy can be palliative in patients with advanced disease or be potentially curative in patients with small-volume disease that has not spread locally or distantly. There is evidence that multimodality therapy, consisting of neoadjuvant chemoradiotherapy followed by surgery, is superior to other treatment regimens in patients with resectable disease.[2]

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0001-2998/04/3403-0004$30.00/0
doi:10.1053/j.semnuclmed.2004.03.005

The TNM staging system is used for staging of both esophageal and gastric cancers. This classification considers that a cancer grows locally (T), spreads to regional lymph nodes (N), and finally spreads to distant sites (M), and there is diminishing survival with progression of disease. However, the TNM staging system does not take into account nonanatomical factors, such as histopathologic type and grade and the presence or absence of various biomarkers that may be important determinants of prognosis. Thus, future refinements in staging will likely incorporate such nonanatomical factors and should permit prognosis to be more reliably determined for individual patients.

ESOPHAGEAL CANCER

The incidence and prevalence of esophageal cancer are increasing in the Western World. Whereas the incidence of squamous cell carcinoma is stable or decreasing, that of adenocarcinoma of the esophagus and gastroesophageal junction is increasing. Cancer of the esophagus is asymptomatic in its early stages; most cases are diagnosed at an advanced stage, when tumor has spread beyond the esophagus, which is the main reason for the overall poor prognosis of this cancer. Because of the inaccuracy of clinical methods for distinguishing potentially curable from incurable disease, both local and distant recurrences are common, even after complete primary tumor resection and extensive lymphadenectomy or after multimodality treatment.

Accurate staging is essential to guide therapy and to predict prognosis and is particularly important in selecting those patients likely to benefit from intensive (and expensive) multimodality therapy. The current staging of esophageal cancer typically includes imaging by

computed tomography (CT), by endoscopic ultrasonography (EUS) and, increasingly, by positron emission tomography (PET). Magnetic resonance imaging (MRI) may be useful in selected patients but generally does not provide additional staging information by comparison with CT. Each of these modalities has advantages and disadvantages and, thus, the combined use of all three modalities is often needed for initial staging of esophageal cancer.

The primary role of EUS is to determine whether the tumor is localized and can be treated with surgery alone or locally advanced requiring treatment with chemoradiotherapy with or without surgery. The accuracy of EUS for assessing T and N status has been reported to be 85% and 75%, respectively, whereas the sensitivity has been reported to be in the range of 85-95% and 70-80%, respectively.[3,4] However, complete EUS staging is not possible in all patients because of esophageal obstruction, thus preventing passage of the endoscope beyond the tumor. Also, because of its limited field of view, EUS is not useful for staging distant metastatic disease.

The sensitivity of CT for staging T and N disease has been reported to be about 50% and 60-87%, respectively.[4] Detection of advanced disease (stage IV) is very important. If distant disease is present, locoregional staging has little importance. It is estimated that 30-50% of patients have advanced (stage IV) disease at presentation and that this distant disease is missed in 18-29% of patients staged conventionally.[4]

In this review, the role of PET in diagnosing, staging, and monitoring response to therapy, as well as evaluating recurrent disease will be discussed. In particular, the impact of the addition of PET with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) to the current imaging techniques will be discussed.

Primary Tumor Staging (T-Stage)

Esophageal cancer is silent in its early stages because of the ability of the esophagus to distend; typical symptoms of dysphagia and weight loss do not occur until the disease is advanced. The principal goal of clinical T-staging is to identify patients with tumor infiltration into mediastinal organs because these patients will not be suitable candidates for surgical resection. The best radiologic technique for detection of early esophageal cancer is the double-contrast barium study, which then will be followed by endoscopy and biopsy.[5] Once the diagnosis of esophageal cancer is established, the depth of tumor invasion, which is an important prognostic factor, needs to be determined. Clinically, the evaluation of the depth of primary tumor penetration within the wall and the invasion of periesophageal tissues is best done by EUS. However, in approximately 30% of patients, complete staging by EUS is not possible because of stenosis or obstruction of the esophageal lumen by tumor.[6] CT complements EUS in detecting gross invasion of mediastinal fat and infiltration into the adjacent organs, particularly the trachea and bronchi. CT is less efficient for detection of pericardial invasion because of the absence of a definable fat plane between the esophagus and the pericardium as a result of the significant weight loss typical in patients with esophageal cancer. The accuracy of EUS is lower for evaluation of T1 and T2 tumors than for T3 and T4 tumors, provided that the endoscope can be advanced past the tumor.[7] In addition, neither EUS nor CT is able to distinguish tumor from inflammation, so that tumor stage may be overestimated in the presence of peritumoral inflammation.

In nearly all studies, FDG-PET has been shown to detect primary esophageal cancer with a higher sensitivity than that of CT (95-100% versus 81-92%).[8-15] The exception was reported in a single study, in which PET was performed with a partial-ring scanner without attenuation correction, and was found to have a lower sensitivity than CT (84% versus 97%).[16] FDG uptake in esophageal cancer is greater than that in the normal esophagus; thus, the primary tumor can be distinguished easily from background activity in most cases.[17] In general, false-negative results are related to small tumor volume or well-differentiated tumor, especially considering the mild to moderate physiologic uptake of FDG seen in the normal esophagus. False-positive results with FDG-PET are typically related to inflammation, such as reflux esophagitis. In addition, radiation-induced esophagitis is commonly observed when the esophagus is included in a radiotherapy portal. However, esophagitis often involves a long segment of the esophagus and usually can be distinguished from esophageal cancer.

Himeno and coworkers demonstrated that FDG-PET has a sensitivity of 100% ($n = 15$) for detection of primary tumors extending to the submucosa (pT1b) or deeper. However, PET was unable to detect any ($n = 7$) of the lesions that were confined to mucosa (Tis or T1a).[18] These results likely reflect the limited spatial resolution of PET. There are conflicting results regarding the relationship of the primary tumor FDG uptake assessed by determination of the standardized uptake value (SUV) and the depth of tumor invasion (T-stage). Kato and coworkers found a significant relationship between FDG uptake and the depth of tumor invasion within the primary tumor ($P < 0.05$), but other investigators have not found any correlation between these two parameters.[15,17] No difference is reported in FDG uptake in adenocarcinomas versus squamous cell carcinomas.[17]

The two main shortcomings of all currently used imaging techniques include poor sensitivity for detecting small-volume tumors and the inability to differentiate tumor from active inflammatory disease reliably. Thus, histopathological examination of the resected specimen remains the criterion standard for T-stage determination.

Nodal Staging (N-Stage)

Regional lymph node metastasis is one of the most important prognostic factors in esophageal cancer and has a major impact on treatment selection. Patients without lymph node involvement have a better prognosis than do those with nodal involvement (5-year survival of 42-72% versus 10-12%).[7] Survival decreases with an increasing number of involved lymph nodes. In general, patients with a limited number of involved lymph nodes in the peritumoral region have a better prognosis than do those with more extensive nodal disease. The esophagus has a rich lymphatic drainage. Lymph node drainage of the esophagus extends from the neck, through the mediastinum, and to the upper abdomen including lesser curvature (gastrohepatic) and celiac nodes. Lymph node metastasis can occur anywhere within these drainage pathways, and it is not unusual for proximal esophageal tumors to metastasize to abdominal nodes or for distal esophageal tumors to metastasize to cervical nodes. A recent study has shown that lymph node size is an important prognostic factor; these investigators found that survival decreased with each millimeter increment in the size of the involved lymph nodes.[19] Among several prognostic factors (such as primary tumor size, histopathologic type, number of metastatic lymph nodes and size of metastatic lymph nodes), metastatic lymph node size was the strongest independent predictor of survival. Despite the importance of lymph node status in esophageal cancer, noninvasive lymph node staging is still less than ideal in these patients. CT and EUS are commonly used to evaluate for lymph node metastasis; EUS is found to be superior to CT for evaluation of regional nodal disease. However, EUS is operator dependent and is unable to evaluate lymph nodes distant from the esophageal wall or those located behind air-filled structures.[7] The reported accuracy of EUS for detection of mediastinal nodal metastasis is superior to that of CT (64-88% versus 45-74%).[7] However, the combined accuracy of spiral CT and EUS has been reported to be greater than that of each modality alone (70-90%).[20] The main limitations of current anatomical imaging techniques are related to their inability to detect tumor involvement in normal-sized lymph nodes, and to differentiate metastatic from inflammatory disease in enlarged lymph nodes. Thus invasive procedures such as thoracoscopy and/or laparoscopy are often used to evaluate for lymph node metastasis to select the best mode of therapy for the individual patient. However, because of their high cost and associated morbidity, the use of these procedures should be limited to those patients where a positive finding will have major therapeutic impact.

Several studies have compared FDG-PET with CT and/or EUS for assessment of local nodal involvement. The reported sensitivities have ranged from 22% to 76% (with one report of 92%) for PET, compared with 0-87% for CT.[8,9,11,12,14,15,20] Specificities ranged from 78% to 100% for PET, and 73% to 100% for CT.[8,9,11,12,14,15,20] Kim and coworkers compared FDG-PET with CT and histopathological results from esophagectomy and extensive lymph node dissection.[21] Forty-seven patients underwent transthoracic esophagectomy with either two-field lymph node dissection (abdominal approach and right thoracotomy or abdominal approach, right thoracotomy and cervical anastomosis) or three-field lymph node dissection (abdominal approach, right thoracotomy, cervical lymph node dissection, and cervical anastomosis). Three patients underwent transhiatal esophagectomy. The sensitivity, specificity, and accuracy for detection of metastasis to lymph node groups were 52%, 94%, and 84%, respectively, for FDG-PET and 15%, 97%, and 77%, respectively, for CT. This is the only study in literature that has compared PET and CT with the findings of extensive lymph node dissection, and it showed that FDG-PET has the same specificity but significantly greater sensitivity and accuracy than CT for assessment of nodal metastasis. EUS has been shown to be superior to PET for evaluation of N-stage. A recent prospective study by Flamen and coworkers of 74 patients with esophageal cancer demonstrated that EUS is more sensitive (81% versus 33%), but less specific (67% versus 89%) than PET for detection of regional nodal metastasis.[15] In addition, combined EUS and CT were more sensitive (62% versus 33%), but less specific (67% versus 89%) than PET in their patient population. Similar results have been demonstrated by Lerut and coworkers.[20] False-negative results with PET are mainly the result of small tumor burden (especially nodes less than 1 cm in diameter). Additionally, involved lymph nodes that lie in close proximity to the primary tumor may be obscured by intense FDG uptake in the primary tumor. As with CT and EUS, false-positive results with PET are mainly caused by inflammatory disease. In addition, heterogeneous uptake in the primary tumor simulating periesophageal nodal metastasis is another source of false-positive results with PET. Because of the relative insensitivity of FDG-PET and other imaging techniques for detecting regional nodal disease, nodal sampling is routinely used in all patients who are otherwise considered to be surgical candidates. However, the status of adjacent lymph nodes that are typically resected with the primary tumor does not usually alter management.

Distant Metastatic Disease (M Stage)

A curative surgical approach is not appropriate in patients with metastasis to distant solid organs. Because of the high morbidity and poor outcome of surgical procedures in patients with advanced disease, it is essential to identify patients who can be more safely treated with palliative nonsurgical approaches. Distant metastatic disease (stage IV) most commonly occurs in

distant lymph nodes, liver, and lung. Several studies have shown that FDG-PET is superior to CT for detection of distant metastatic disease.[8-11,22] FDG-PET detected distant disease unsuspected by conventional methods in 3-37% of patients with esophageal cancer.[8-11,22] In a prospective study, Luketich and coworkers compared PET and CT to minimally invasive staging in 91 patients (100 PET scans) with esophageal cancer.[22] In 39 patients, 70 distant metastatic lesions were confirmed clinically or by biopsy. The sensitivity and specificity of FDG-PET for detection of distant disease were 69% and 93%, respectively, for FDG-PET and 46% and 74%, respectively, for CT. Flamen and coworkers, in a recent prospective study of 74 patients with esophageal cancer found that FDG-PET was superior to CT and EUS in detection of stage IV disease.[15] The sensitivity and specificity were 74% and 90%, respectively, for FDG-PET, 41% and 83%, respectively for CT, and 42% and 94%, respectively, for EUS. In this study, FDG-PET upstaged the tumor in 11 patients (15%) by detecting unsuspected metastatic disease and downstaged five patients (7%). More recently, in a subsequent re-analysis of data in 42 of these 74 patients,[20] these investigators showed that FDG-PET had higher sensitivity (77% versus 46%) and specificity (90% versus 69%) than the combination of CT and EUS, specifically for detection of distant nodal disease. In addition, FDG-PET upstaged 12% (5 of the 42) of patients from N1 or N2 to M1 disease.

To date, no large, multicenter trials have been published to confirm the value of FDG-PET for staging of esophageal cancer. The results of one such ongoing study (American College of Surgeons Oncology Group Study Z0060) are not expected to be available until 2005. Nonetheless, FDG-PET is currently accepted as a standard staging technique along with CT and EUS in patients with esophageal cancer. The main impact of PET in these patients is a result of its improved detection of otherwise occult stage IV disease and identification of the local or distant metastatic sites that are the most accessible to confirmation by directed tissue sampling by minimally invasive procedures (Figs 1 and 2). This approach not only facilitates staging and avoids extensive unnecessary surgical procedures for staging, but it also prevents ineffective radical therapies that are associated with high cost and morbidity in patients with advanced disease. However, PET is not perfect and false-negative results because of small tumor size and false-positive results because of inflammatory or infectious processes can occur. Thus, histologic confirmation of PET findings is necessary before a patient is denied potentially curative surgery.

Although PET reveals unique functional information, it provides limited anatomical information. This limitation has recently been overcome with the introduction of combined PET/CT scanners. These scanners provide accurately fused functional and morphological data in a single examination, and this capability has been shown to significantly improve the interpretation accuracy of PET and CT in oncologic patients (Fig 3).[23,24] Presumably this improved accuracy will translate into improved patient management. There are only limited data yet available regarding the use of PET/CT in esophageal cancer. A PET/CT study of 18 patients with esophageal cancer demonstrated improved detection and characterization of 35% of suspicious lesions in 89% of patients, and affected management of 22% of patients.[25]

Wallace and coworkers recently compared the effectiveness of several different strategies for preoperative staging of patients with esophageal cancer.[26] These investigators compared the following six strategies: CT alone; CT + EUS with fine-needle aspiration biopsy; CT + thoracoscopy and laparoscopy (TL); CT + EUS with fine-needle aspiration biopsy + TL; CT + PET + EUS with fine-needle aspiration biopsy; and PET + EUS with fine-needle aspiration biopsy. The model was based on a third-party payer perspective and incorporated the following: the test characteristics for each staging technique; prevalence of local, regional, and distant disease; life expectancies and cost associated with the treatment for patients with local, regional, and distant disease; and probability of death for patients undergoing TL and those undergoing resection. They found that the combination of PET + EUS with fine-needle aspiration biopsy is most effective strategy.[26]

Assessment of Prognosis With FDG-PET

Several tumor characteristics of esophageal cancer at presentation have been found to be predictive of prognosis. Among these is the intensity of FDG uptake in the primary esophageal tumor. Fukunaga and coworkers reported that patients with a tumor standardized uptake value (SUV) > 7.0 had a worse prognosis than did those with lower values.[17] They also found a good correlation between hexokinase activity, assessed histochemically in the resected tumor specimens, and preoperative evaluation of tumor FDG uptake by means of SUV and k3, the rate constant for phosphorylation of FDG. In addition, FDG-PET demonstration of local or distant metastatic disease at initial presentation was highly predictive of survival.[22] Luketich and coworkers reported that the 30-month survival of patients with PET evidence of local disease only ($n = 64$) was 60%, compared with 20% for patients with PET evidence of distant disease ($n = 27$, $P = 0.01$). However, no statistically-significant correlation was found between CT stage of the tumor and survival in this study: the 30-month survival of patients with CT evidence of local disease only ($n = 58$) was 52% compared with 38% for patients with CT evidence of distant disease ($n = 33$).[22]

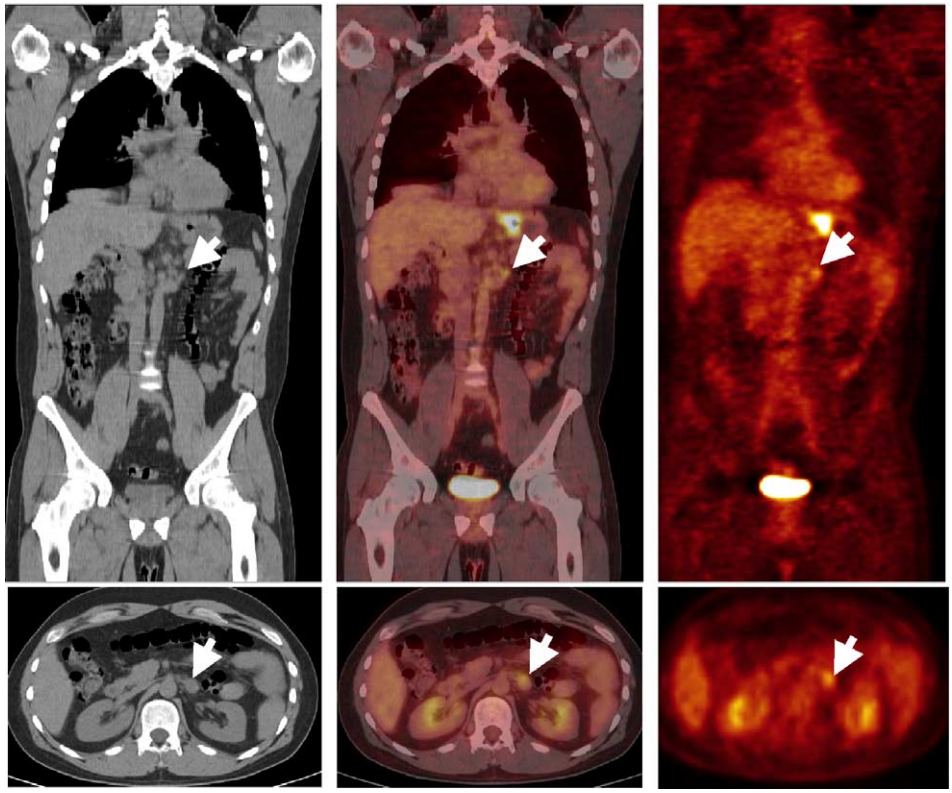

Fig 1. Staging esophageal cancer in a 35-year-old man with adenocarcinoma of distal esophagus. Coronal (top) and transaxial (bottom) computed tomography, positron emission tomography/computed tomography fusion, and positron emission tomography images demonstrate intense FDG uptake within the thickened distal esophagus, consistent with primary esophageal cancer. No lymph node enlargement was observed except for an enlarged left periaortic lymph node (1.9 × 1.8 cm) at the midrenal level (arrows), which showed increased FDG uptake (arrows), suspicious for metastatic disease. Endoscopic biopsy of this lymph node was positive for metastatic disease. (Color version of figure is available online.)

Assessment of Response to Therapy

Management of esophageal cancer is by one or more of the following: surgery, radiotherapy, and chemotherapy. For localized disease, neoadjuvant chemoradiotherapy before esophagectomy has shown promising results. The goal of neoadjuvant therapy includes improvement of local tumor control, prevention of distant disease, and decreased tumor burden locally to allow for higher rates of complete resection. Nonresponsiveness to neoadjuvant therapy seems to be associated with a worse prognosis.[27] Complete macroscopic and microscopic resection of the primary tumor is a strong independent prognostic factor. Patients with locally advanced disease (T3-4) with complete resection have a 20 to 31% chance of 5-year survival, whereas with incomplete resection there is no chance of 5-year survival.[7]

At the present time, most patients with esophageal cancer receive chemoradiotherapy in the neoadjuvant or adjuvant setting, but chemoradiotherapy is also used as definitive therapy in patients with localized disease who are not medically fit for surgery and as palliative therapy in patients with distant disease. Response to chemoradiotherapy is not uniform; whereas some tumors respond well to therapy, others progress during therapy. Not surprisingly, nonresponders have a poorer prognosis than do responders. This in part may be related to therapy-induced side effects and to delay in surgical treatment. Thus it is important to distinguish responders from nonresponders early in the course of therapy to avoid the cost and toxicity of unnecessary therapy in nonresponders. CT, MRI, and EUS have been used to assess response to therapy; however, these modalities are not reliable in differentiating residual viable tumor from post-therapeutic changes such as inflammation or scar, and a delay of several weeks after completion of therapy is necessary for evaluating response. In addition, no significant correlation has been found between these anatomical imaging modalities and pathological response[28]

Several studies have evaluated the use of FDG-PET for predicting response shortly after initiation of therapy or to assess response following completion of therapy in

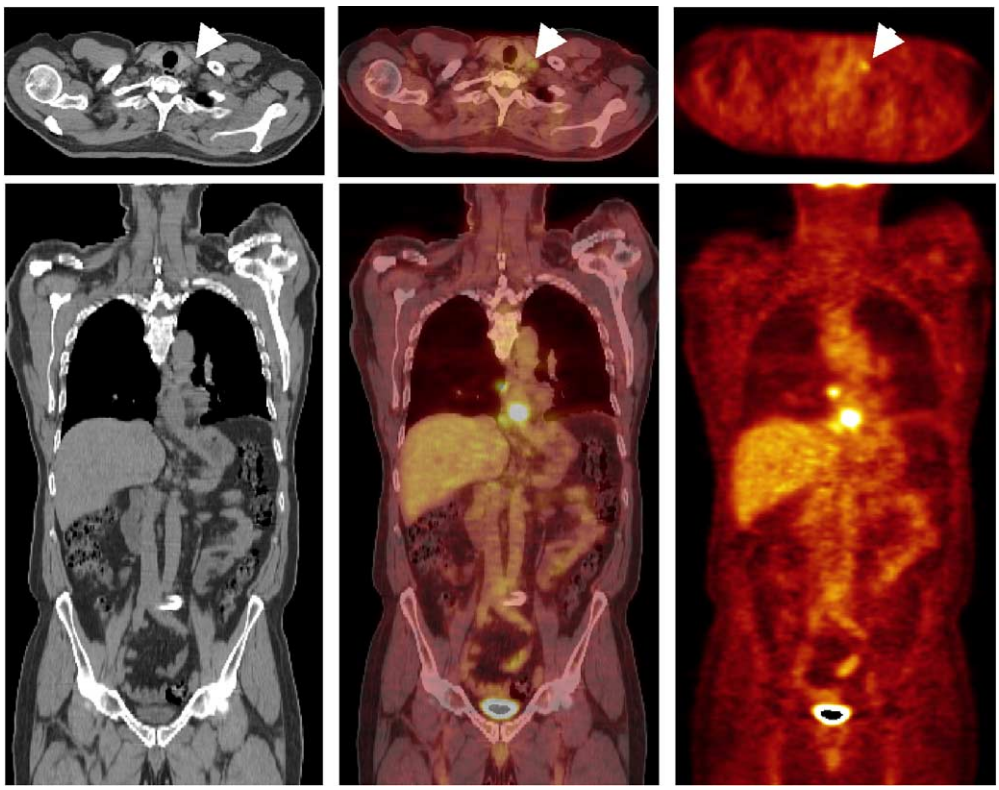

Fig 2. Staging esophageal cancer in a 54-year-old man with adenocarcinoma of the distal esophagus. Transaxial (top) and coronal (bottom) computed tomography, positron emission tomography/computed tomography fusion, and positron emission tomography images demonstrate intense FDG uptake within the primary tumor mass and several peri-esophageal and mediastinal lymph nodes. Intense FDG uptake also was observed in a normal-size left supraclavicular lymph node (arrows), which was the most easily accessible lymph node to confirm inoperable disease. (Color version of figure is available online.)

patients with esophageal cancer who underwent neoadjuvant therapy. Weber and coworkers have shown that FDG-PET has the potential to distinguish responders from nonresponders shortly after beginning induction therapy.[29] Forty patients with adenocarcinoma of the gastroesophageal junction were studied by FDG-PET before and 14 days after initiation of neoadjuvant chemotherapy. Patients were evaluated for clinical response, defined as reduction in tumor length and wall thickness by $>$ 50% using endoscopy and conventional imaging, 3 months after completion of therapy, and those patients who underwent surgery were evaluated for histopathologic response. They found that, 14 days after induction therapy, responders had a significantly greater decrease (mean $\pm$ standard deviation) in tumor FDG uptake ($-54\% \pm 17\%$) compared with nonresponders ($-15\% \pm 21\%$). A reduction of FDG uptake of 35% was found to be an accurate cutoff value for distinguishing responders from nonresponders. This cutoff value predicted clinical response with a sensitivity of 93% and specificity of 95%. Eight of the 15 patients (53%) with metabolic response and only one of the 22 (5%) patients without metabolic response had complete or subtotal histopathological tumor regression. The latter had significantly shorter disease-free and overall survival ($P = 0.01$ and $P = 0.04$, respectively). Thus, the use of FDG-PET to predict response to neoadjuvant therapy may facilitate identification of patients who are benefiting from preoperative therapy.

Several studies have evaluated FDG-PET in assessment of response following completion of neoadjuvant therapy. Generally, a decrease in tumor FDG uptake is seen with effective therapy whereas no significant decrease or even an increase is noted with ineffective therapy (Fig 4). Downey and coworkers studied 24 patients with esophageal cancer who received induction therapy before esophagectomy.[30] FDG uptake, as measured by SUV, in the primary tumor decreased (median of 59%; range, 13-88%). The 2-year disease-free survival after induction therapy and esophagectomy was significantly longer in patients with a decrease in tumor FDG uptake by more than 60% than in patients with lesser decreases in FDG uptake (67% versus 38%, $P < 0.05$). However, there was no significant correlation

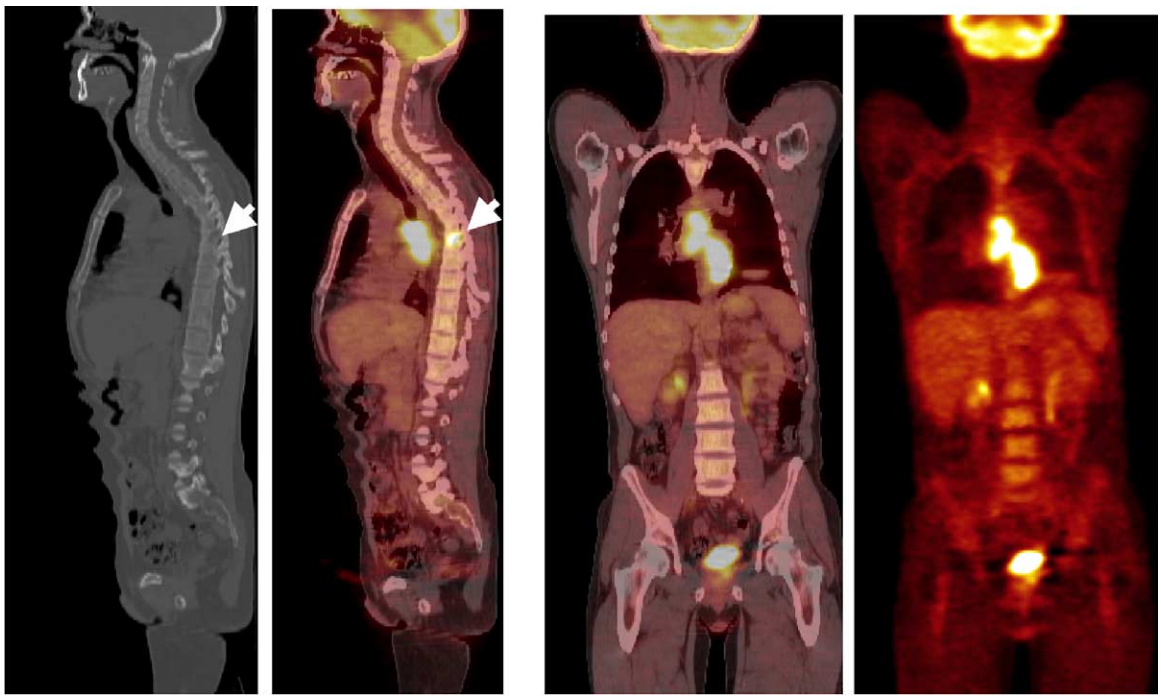

Fig 3. Staging esophageal cancer in a 39-year-old man with adenocarcinoma of mid and distal esophagus. Sagittal (left) bone-window computed tomography and positron emission tomography/computed tomography fusion images and coronal (right) positron emission tomography/computed tomography fusion and positron emission tomography images demonstrate intense FDG uptake within the primary tumor mass. In addition, intense FDG uptake was seen in T7 (arrows), consistent with advanced disease. No osseous destruction was noted on bone window images of the computed tomography scan. (Color version of figure is available online.)

between the 2-year overall survival and changes in tumor FDG uptake after induction therapy (89% versus 63%, $P = 0.88$).[30] Similar results have been reported by others.[31-33] Brücher and coworkers demonstrated a greater decrease in FDG uptake in responders in comparison to nonresponders ($-72\% \pm 11\%$ versus $-42\% \pm 22\%$) after chemoradiotherapy.[34] Nonresponders had a worse prognosis than responders. At a cutoff value of a 52% reduction in tumor FDG uptake, PET predicted response with a sensitivity of 100% and a specificity of 55%. The poor specificity of FDG-PET in this study is likely related to posttherapy inflammation that may persist for several weeks after completion of therapy. The patients in this study underwent FDG-PET 3 weeks after completion of therapy ($P < 0.0001$). Posttreatment esophagitis is a common finding in patients with esophageal cancer. Increased FDG uptake in inflamed tissue makes evaluation of response to cancer therapy by FDG-PET difficult. We were unable to differentiate residual tumor from chemoradiation-induced esophagitis by using a quantitative PET measurement technique in a recent study of 24 patients[35] with esophageal cancer. The time interval between chemoradiation therapy and PET follow-up should be carefully selected in future prospective studies.

Detection of Recurrent Disease

Despite aggressive therapy for patients with esophageal cancer, long-term survival remains poor. Recurrence is common despite presumed curative resection, mainly due to micrometastatic disease; thus, recurrence at distant sites is more common than local recurrence. Patients with recurrent disease have a poor prognosis, and the survival benefit of early detection of recurrent disease is uncertain. However, aggressive therapy of local recurrence may prolong disease-free survival or occasionally be curative. While anatomical imaging modalities are limited in differentiating scar from recurrent disease, FDG-PET has the ability to detect and differentiate recurrent disease from posttherapy changes when disease has altered metabolism without any structural changes. Thus, PET is more suitable for early detection of recurrent disease.

Only a few studies have evaluated the role of FDG-PET in detecting recurrent esophageal cancer. Fukunaga and coworkers studied 13 patients with suspected recurrent esophageal cancer. Increased FDG uptake was noted

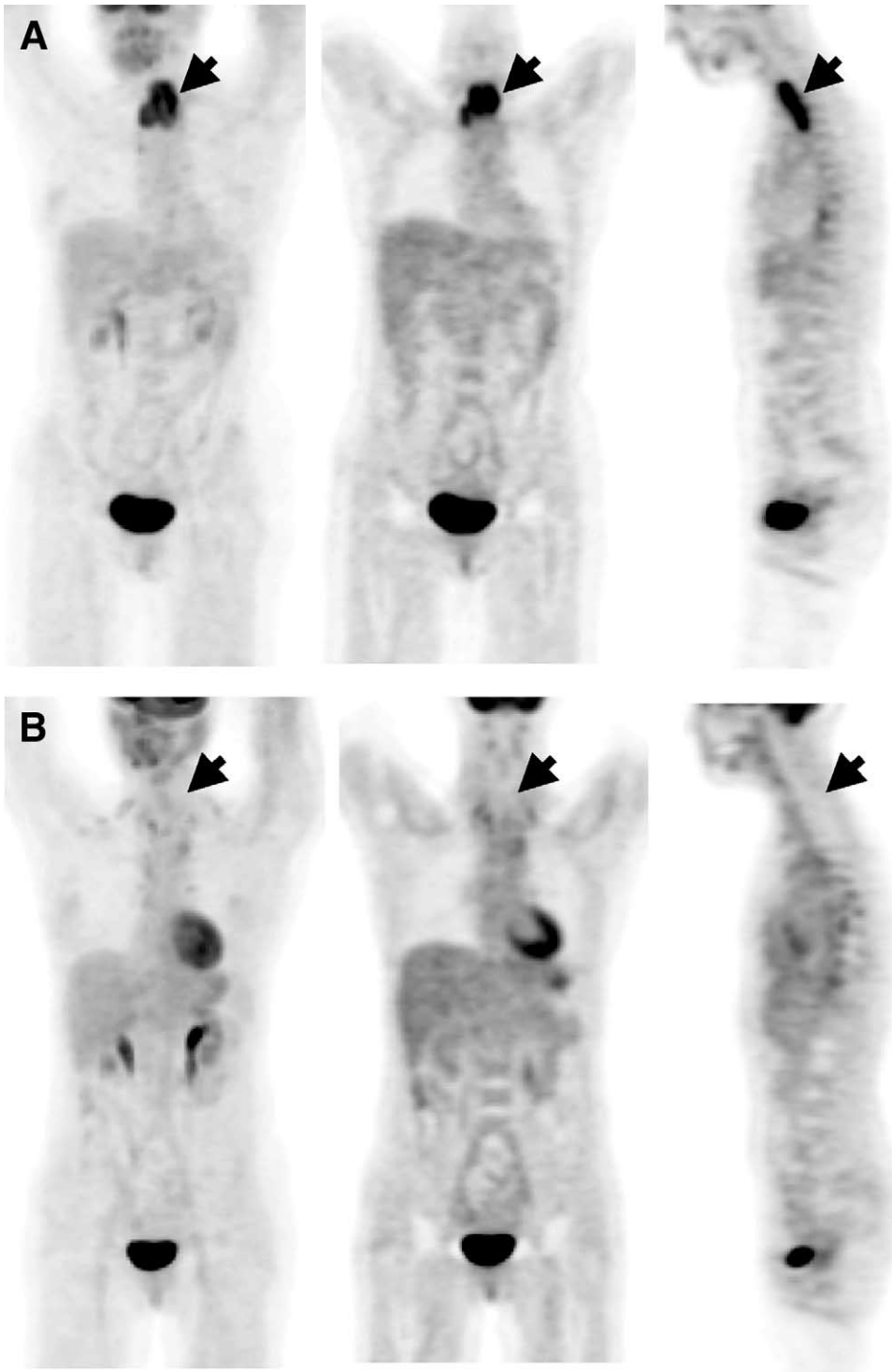

Fig 4. Response to therapy in a 50-year-old woman with esophageal cancer in the cervical esophagus. A, Anterior maximum-pixel-intensity reprojection (left), coronal (middle), and sagittal (right) FDG-PET images of the torso obtained before treatment demonstrate markedly increased FDG accumulation within a large lobulated proximal esophageal cancer (arrows). B, Approximately 8 weeks after completion of chemoradiation, similar images show no abnormally increased FDG accumulation in previously noted primary esophageal cancer (arrows). There is decreased FDG uptake in the cervical spine, consistent with post radiation changes. Esophagectomy revealed no residual tumor.

in 6 of 7 patients with proven recurrent disease, whereas no significant FDG uptake was seen in the 6 patients who did not have recurrence.[36] Flamen and coworkers studied 41 patients with clinical or radiological suspicion of recurrent disease.[37] Recurrent disease was present in 33 patients (80%). Conventional imaging was slightly, but not significantly, better than FDG-PET in detecting recurrence around the esophagogastric anastomosis; the sensitivity, specificity and accuracy were 100%, 57%, and 74%, respectively, for FDG-PET and 100%, 93% and 96%, respectively, for conventional imaging. However, PET was slightly, but not significantly, better than conventional imaging for detecting recurrent disease in the operative field (regional) and distant recurrence; the sensitivity, specificity and accuracy were 94%, 82% and 87%, respectively, for FDG-PET and 81%, 82%, and 81%, respectively, for conventional imaging. On a patient basis, FDG-PET provided additional information in 11 of 41 patients (27%), detected disease in five patients with equivocal or negative clinical findings, detected unsuspected distant recurrent disease in five patients with documented local disease, and excluded disease in one patient.

GASTRIC CANCER

Despite a universal decrease in the incidence and mortality of gastric cancer, it remains the second most common cause of cancer-related death in the world. The overall 5-year survival rate of gastric cancer is less than 25%.[38] One of the important predisposing factors for the development of gastric cancer is repeated infection with *H. pylori*. Gastric cancer is classified based on its macroscopic appearance or histologic characteristics. There are two major subgroups; the intestinal type that predominantly involves the distal stomach and is found most commonly in Asian patients, and the diffuse or signet ring type that tends to involve the proximal stomach and is found in Western patients. Gastric cancer initially spreads locally through the gastric wall and then to regional lymph nodes. However, when it reaches the serosal surface of the stomach, it also spreads intraperitoneally. Distant metastatic disease is typically seen in patients with advanced locoregional disease. Gastric cancer is defined as early-stage disease when the tumor is confined to the mucosa or submucosa, irrespective of the local lymph node status. This type of gastric cancer has a favorable prognosis, but can be easily missed, as the symptoms are very mild and nonspecific. Unfortunately, gastric cancer is all too often detected when the tumor is advanced and unresectable.

The TNM staging system also is used to stage patients with gastric cancer. Typically CT and EUS are used to determine the depth of involvement and presence of local and distant disease. In addition, staging laparoscopy is performed in patients who are thought to have resectable tumors or have imaging findings that are indeterminate for resectability, to avoid surgery in patients with nonresectable tumor. The primary mode of curative therapy is surgery. Treatment of early gastric cancer includes resection of the primary tumor and adequate lymphadenectomy. Endoscopic mucosal resection is suitable when the primary tumor is small (<2 cm) and limited to the mucosa. Patients with early gastric cancer who are treated surgically have an excellent 5-year survival rate of approximately 90%.[38] Treatment of advanced disease is palliative and is focused on relief of symptoms. The best palliative therapy is excision of the primary tumor. Advanced disease is treated with neoadjuvant chemotherapy, and has a very poor prognosis; the 5-year survival rate in the United State is reported to be poor at 3-13%.[38] The addition of neoadjuvant chemotherapy is aimed toward downstaging the tumor and may improve the results of surgery. Unlike esophageal cancer, preoperative radiation has not been found to be helpful in gastric cancer.

The role of FDG-PET in gastric cancer is not fully known, and only a few published studies are available. An early study by Yeung and coworkers of 23 patients with gastric cancer demonstrated that FDG-PET has a sensitivity of 93% (12/13) for detection of gastric cancer.[39] PET correctly excluded local recurrence in all 6 patients (specificity of 100%) who were found to be free of disease. For detection of metastatic disease in intra-abdominal lymph node stations, FDG-PET had a high specificity (97%), but a low sensitivity (22%). FDG-PET correctly identified distant metastatic disease in 4 patients, and was falsely negative in 4 additional patients who had peritoneal tumor spread.

To assess the relationship of FDG uptake and the histopathologic characteristics of gastric carcinomas, Stah and coworkers studied 40 patients with locally advanced gastric carcinoma.[40] FDG-PET detected 60% (24 of 40) of gastric cancers with higher detection rates in the intestinal type compared with the nonintestinal type (83% versus 41%, $P = 0.01$). The mean SUV was significantly greater in the intestinal type than in the nonintestinal type (6.7 ± 3.4 versus 4.8 ± 2.8, $P = 0.03$). In addition, the mean SUV was significantly greater in nonmucinous tumors than in the mucin-containing tumors (7.2 ± 3.2 versus 3.9 ± 2.1, $P < 0.01$). A similarly, greater FDG uptake was seen in grade 2 than in grade 3 tumors (7.4 ± 2.3 versus 5.2 ± 3.3, $P < 0.02$); all of the nonintestinal type and 10/18 of the intestinal type tumors were grade 3. Also, a significantly greater fraction of nonintestinal type tumors (77%) contained extracellular or intracellular mucin versus 11% for intestinal type lesions ($P < 0.01$). The survival was not significantly different among patients with PET-detectable tumors versus those with nondetectable tumors. Thus, FDG uptake in gastric cancers appears to be inversely dependent on the presence of mucin. FDG-PET is not optimal for evaluation of tumors with high mucin content; these results in mucinous gastric carci-

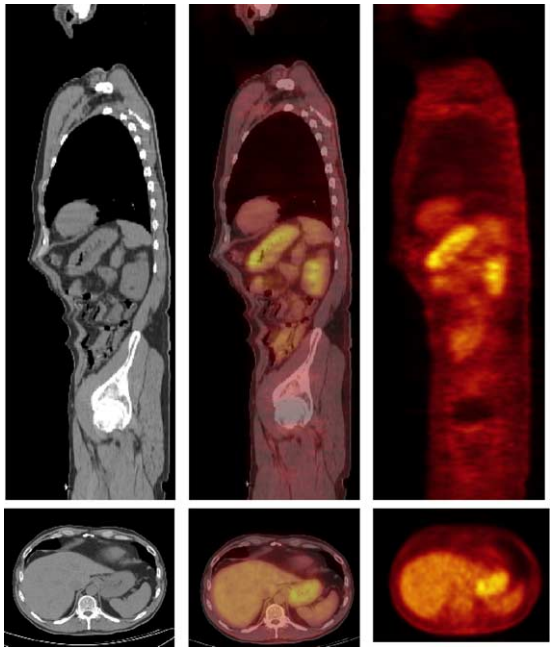

Fig 5. Staging of gastric cancer in a 62-year-old woman with poorly differentiated adenocarcinoma with signet ring features. Sagittal (top) and transaxial (bottom) computed tomography, positron emission tomography/computed tomography fusion, and positron emission tomography images of the torso demonstrate moderately increased FDG uptake in the anterior wall of the stomach. The uptake was less intense than that typically expected in a poorly differentiated carcinoma. At surgery, the patient was found to have metastatic involvement of several perigastric lymph nodes that had not been detected by positron emission tomography. (Color version of figure is available online.)

noma confirm those we have reported for mucinous carcinomas generally.[41] In another recent study, Yoshioka and coworkers found greater FDG uptake in well differentiated adenocarcinomas than in poorly differentiated adenocarcinomas and signet ring cell carcinomas (SUV 13.2 ± 6.6 versus 7.7 ± 2.6, $P < 0.05$; Fig 5).[42] They also reported that FDG-PET was very useful in detecting metastatic disease in the liver, lung and lymph nodes, but not for detection of osseous metastases and peritoneal or pleural carcinomatosis.

De Potter and coworkers[43] studied 33 patients with clinical suspicion for recurrent gastric carcinoma following surgical treatment with curative intent. Sensitivity, specificity, positive-predictive and negative-predictive values of FDG-PET for detection of recurrent disease were 70% (14/20), 69% (9/13), 78% (14/18), 60% (9/15), respectively. Longer survival was found in the patients with negative PET than those with positive PET (21.9 ± 19.0 months versus 9.2 ± 8.2 months, $P = 0.01$).

Although only a limited number of studies have evaluated the role of PET in gastric cancer, limitations similar to those encountered in imaging of other gastrointestinal cancers are evident. Overall, there is poor sensitivity for detection of mucinous carcinomas, low-grade tumors and small-volume disease. In addition, the normal, moderately intense physiologic FDG uptake in the stomach may obscure tumors that have low-level uptake. Accordingly, FDG-PET should be used as a problem-solving tool in selected patients with gastric cancer, but there are insufficient data to recommend its routine use for staging, restaging, or treatment monitoring of this disease.

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