Positron Emission Tomography in the Initial Staging of Esophageal Cancer

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Objective: To assess the value of positron emission tomography (PET) compared with computed tomography (CT) in the initial staging of esophageal cancer.

Design: Case series.

Setting: Tertiary care veterans hospital.

Patients: Patients with newly diagnosed esophageal cancers from January 1996 through May 2001 who underwent both CT and PET scanning within 4 weeks were included in the study (n = 24). Only patients who underwent pathological or radiographic follow-up were included.

Main Outcome Measures: The sensitivity, specificity, and negative and positive predictive values of CT and PET were determined based on a criterion standard of pathological staging in 16 patients (67%) and follow-up imaging in 8 patients (33%).

Results: For staging regional lymph node involvement, CT and PET scans showed no statistically significant difference in sensitivity (57% and 71%, respectively) and specificity (71% and 86%, respectively). For detection of metastatic disease, CT and PET showed no significant difference in sensitivity (83% and 67%, respectively) and specificity (75% and 92%, respectively). There was no significant difference in clinical decision making when the results of both tests were discordant.

Conclusions: There was no significant difference between the 2 imaging modalities in the initial staging of esophageal cancer. The CT scan was a sensitive indicator of distant metastases, whereas PET was more specific. It is unclear what additional role PET scanning should have in the initial screening of patients.

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The incidence of esophageal cancer continues to increase in the United States. In 2002, it is estimated that there will be 13,100 new cases and 12,600 deaths. Treatment can include a number of options, such as surgery, neoadjuvant treatment with chemotherapy and radiation therapy, photodynamic therapy, radiation therapy alone or in combination with chemotherapy, and stent placement. Treatment planning for individual patients should be based on the physician’s ability to correctly define the extent of local, regional, and distant disease. The question facing both the clinician and the patient is who achieves the most benefit from which therapy. The role of surgical treatment in palliation is limited, and it is reserved for those patients who may derive some curative benefit from the intervention. The only patients who are candidates for resection are those with no evidence of metastatic disease.

The development of neoadjuvant chemotherapy and radiation therapy protocols has influenced the drive for more accurate staging. Esophageal cancer staging encompasses 3 areas: the primary tumor (T stage), regional lymph nodes (N stage), and distant disease (M stage). The current staging modalities include computed tomography (CT), endoscopic ultrasonography (EUS), and positron emission tomography (PET). All 3 modalities give anatomic information; in addition, PET scanning detects metabolically active cancer tissue based on glucose metabolism. The potential to aggressively treat someone with extensive locoregional disease (T3 and/or N1) prior to an operation is an attractive concept. Some clinical trials have demonstrated a possible survival benefit for this type of treatment over surgical treatment alone. More accurate initial staging of the extent of the disease can identify possible candidates for neoadjuvant protocols, which could improve survival in this chal-
lenging group. Therefore, other staging modalities, such as EUS and PET, may have an increasing role in the initial staging of esophageal cancer.

Each modality has different advantages, depending on which component of the staging is being evaluated. Clearly, primary T stage is the least important for clinical decision making, unless patients are going to be offered neoadjuvant protocols for advanced T3 or T4 lesions; EUS has clearly been shown to be superior at defining the depth of wall invasion, with a sensitivity of 85% to 95% compared with 50% for CT. and PET can show whether primary tumors are present but cannot give the depth of wall invasion. The assessment of regional nodal disease (N stage) is more confusing. Prior studies suggest that CT has limitations, with a sensitivity of only 60% to 87%, whereas EUS is thought to perform better, with a sensitivity of 70% to 80%. A wide range of sensitivity (28%-52%) has been reported for PET. Identification of distant metastases (M stage) is the single most important component of the initial staging. At the time of presentation, it is estimated that 30% to 50% of patients will have advanced (stage IV) disease. In the American Joint Commission on Cancer (AJCC) Cancer Staging Manual, celiac, cervical, and supraclavicular nodal disease, in addition to other distant sites, have been designated as metastatic disease and upstage patients to stage IV. Therefore, accurate staging of patients is critical to identify the subset that will derive the most benefit from surgical resection. The development of PET scanning and its ability to detect metabolically active tumor sites in addition to the anatomic information derived by imaging such as EUS and CT make this an attractive new option. Initial reports demonstrated that CT missed metastases that were then identified by PET. A wide range of sensitivity (28%-52%) has been reported for PET. Identification of distant metastases (M stage) is the single most important component of the initial staging. At the time of presentation, it is estimated that 30% to 50% of patients will have advanced (stage IV) disease. In the American Joint Commission on Cancer (AJCC) Cancer Staging Manual, celiac, cervical, and supraclavicular nodal disease, in addition to other distant sites, have been designated as metastatic disease and upstage patients to stage IV. Therefore, accurate staging of patients is critical to identify the subset that will derive the most benefit from surgical resection. The development of PET scanning and its ability to detect metabolically active tumor sites in addition to the anatomic information derived by imaging such as EUS and CT make this an attractive new option. Initial reports demonstrated that CT missed metastases that were then identified by PET. A wide range of sensitivity (28%-52%) has been reported for PET.

RESULTS

There were 24 patients, all men, with a mean ± SD age of 65.9 ± 10.9 years. Twenty-one patients were white, 2 were African American, and 1 was Latino. Tumor location was in the lower thoracic esophagus (40 cm from incisors) in 19 patients (79%) and the midthoracic (32 cm from upper incisors) in 5 (21%). Tumor histologic diagnosis was adenocarcinoma in 15 (63%), squamous cell in 7 (29%), and other cell types (small cell and sarcoma) in 2 (8%). A total of 21 patients (88%) had invasive cancer, and 3 (13%) had carcinoma in situ.

STAGING

Regional Lymph Node Involvement (N Stage)

Twenty-one patients (88%) were evaluated for regional lymph node involvement. Of these 21 patients, 7 (33%) had involved regional nodes, and 14 (67%) had nodes that were not involved. The CT scan was correct in 14 patients (67%) and incorrect in 7 patients (33%).
Of the 7 for whom the scans were incorrect, 4 would have been upstaged and 3 downstaged by CT. The PET scan was correct in 17 patients (81%) and incorrect in 4 patients (19%). Of those 4, 2 would have been upstaged and 2 downstaged incorrectly. Overall, PET had a higher sensitivity and specificity than CT (71% and 86% vs 57% and 71%, respectively) (Table 1). These differences did not reach statistical significance. Based on an observed regional lymph node involvement prevalence of 33%, both tests had higher negative predictive values (PET, 86%; CT, 77%) than positive predictive values; PET had a better positive predictive value than CT (71% vs 50%), but this difference was not statistically significant.

**Metastatic Disease (M Stage)**

All 24 patients could be evaluated for distant metastases (Table 2). There were 12 patients (50%) with metastatic disease; 8 had their metastases confirmed by histologic examination, and 4 had metastases confirmed by imaging studies. Nineteen patients (79%) were correctly staged by CT, and there were 2 false-negative and 3 false-positive results. Nineteen patients (79%) were also correctly staged by PET, and there were 4 false-negative and 1 false-positive results. In 2 patients (8%), CT failed to identify metastatic disease (cervical lymph node in 1 patient and celiac lymph node in another patient) but correctly identified 3 patients (13%) with metastatic disease missed by PET (lung nodule in 1 patient, para-aortic node in a second patient, and celiac lymph node in a third patient). In 4 patients (17%), PET failed to identify metastatic disease (celiac lymph nodes in 2 patients, abdominal lymph node in a third patient, and a lung nodule in a fourth patient) but correctly identified 1 patient with metastatic disease missed by CT (cervical lymph node). Three patients were incorrectly identified by CT as having metastatic disease (lymph nodes in all 3 patients: 1 patient with sarcoidosis and 2 with lymph nodes with no histologic abnormalities). Only 1 of the 3 patients also had a false-positive result on PET. One patient was incorrectly identified by PET as having metastatic disease (colon), but the results of CT were also false positive in this patient (distal node). Overall, CT had a higher sensitivity than PET for identifying patients with metastatic disease (83% vs 67%) but a lower specificity (75% vs 92%). Based on a 50% prevalence of metastatic disease, CT had a lower positive predictive value than PET (77% vs 89%) but a higher negative predictive value (82% vs 73%). None of the differences between CT and PET were statistically significant.
LESION ANALYSIS

Liver

Only 1 patient was found to have a hepatic lesion. This was correctly imaged on both CT and PET scans and was confirmed by subsequent imaging that demonstrated an increase in lesion size and number. This site represents 8% of all metastatic disease.

Lung

Three patients were found to have lung metastases. The CT scan identified metastatic lung disease in 3 of 3 patients, and the PET scan identified metastasis in only 1 of 3. The numbers are too small for statistical comparison. Lesion confirmation was by analysis of a biopsy specimen in 2 patients and subsequent imaging in 1 patient. This site represents 23% of metastatic disease.

Adrenal

Both CT and PET scans correctly identified the 1 patient with an adrenal metastasis. Lesion confirmation was by analysis of a biopsy specimen. This site represents 8% of all metastatic disease.

Bone

Two patients were positively identified as having bone metastases. The PET scan was the only imaging modality that identified both. One patient had a biopsy specimen that was positive for metastasis, and the other had further imaging with a bone scan and magnetic resonance imaging to confirm the lesion. This site represents 15% of all metastastic disease.

Distant Lymph Node

Six patients were proven to have involved distant nodes. Both CT and PET correctly identified 4 of 6 patients. Nodal involvement was confirmed by histologic examination in 5 patients and by subsequent imaging in 1 patient. This site represents 46% of all metastatic disease.

CLINICAL DECISION MAKING

The CT and PET scans had concordant findings in 14 of 24 patients. Both PET and CT were correct in 12 patients and incorrect in 2 patients (Table 3). There were 10 cases in which the CT and PET scan findings were discordant. The PET scan was correct in 5 of the 10 discordant cases, 3 of which were for regional node (N stage) disease and 2 for distant (M stage) nodal disease. The CT
scan was correct in 3 of 10 discordant cases, all 3 of which were in identifying M stage disease: 1 pulmonary metastasis and 2 distant lymph nodes. In the other 2 discordant cases, both tests incorrectly staged the disease. In analyzing whether CT or PET findings influenced clinical decision making, it is clear that in 4 cases the results of a discordant study did influence management. The CT and PET scans both changed clinical management in 2 cases.

Accurate initial staging of esophageal cancer is of vital importance in treatment planning for individual patients. Patient stratification into those with early-stage disease, advanced local disease, and metastatic disease mirrors the relative benefit of operative therapy in each group. Clearly, only those patients with early-stage disease have any chance for a long-term cure. Those with advanced local disease (T3 and/or N1) may benefit from neoadjuvant treatment, followed by restaging to rule out disease progression, and then resection if no metastases have developed. Lastly, those who present with distant disease are incurable, and the focus should be on palliation and maximizing the remaining quality of life.

This retrospective, nonrandomized study compares the abilities of 2 different imaging modalities to stage the initial cancer. The criterion reference standard had been defined as pathological staging in 67% of cases or follow-up imaging analysis in the other 33%. The 2 most common reasons why patients were not included in the analysis were that no PET scan had been obtained or no pathological or follow-up imaging study was available for comparison. Most likely, these patients underwent initial screening with CT, were found to have obvious metastatic disease, and therefore were never referred for PET scanning. Documentation from the cancer registry demonstrates that for this period 51% of newly diagnosed cancers were stage IV. In this study sample, 50% of patients had stage IV disease, and we feel it is a representative sampling of available cases. Because this was a nonprospective case series, we recognize that the data may have some selection bias; it is possible that patients with earlier-stage disease were not included because a PET scan was not performed. We recognize the possible influence on our results but feel that the patients most likely to not have had PET scans ordered were those with CT evidence of stage IV disease.

The status of regional lymph node involvement is only clinically relevant if patients are being considered for neoadjuvant treatment protocols. Otherwise, treatment decisions will be based solely on the determination of M stage status. The 57% and 71% sensitivity of detection of regional lymph node involvement by CT and PET were within the range reported by other investigators. The ability of PET scans to accurately detect involvement of regional lymph nodes has been thought to be limited by the poor spatial resolution of PET scans in which the primary tumor cannot be distinguished from regional nodes. In a study by Rankin et al, the sensitivity for regional node identification was better in CT than in PET. They concluded that PET scans might not have been interpreted in combination with CT scans. In our report, PET scans were most often interpreted with full knowledge of and access to the CT scans. This may account for the higher sensitivity and specificity for PET in detection of regional lymph node involvement. The CT sensitivity and specificity reported here are much better than those reported by Flamen et al. In their extensive study, they report no regional lymph node detection by CT when compared with pathological material from resections. One of the problems with this analysis is that sensitivity was computed by comparing CT data with the actual number of positive nodes found during pathological examination of the esophagectomy specimen. Clinically, this may not be as relevant as determining the global regional nodal status, N1 vs N0, not how many regional nodes are involved. The majority of studies agree that EUS has the highest sensitivity for regional lymph node detection (70%-80%), and its specificity can be improved by combining it with fine-needle aspiration of suspicious nodes if that information is important to treatment planning.

In the most important aspect of this analysis, identification of metastatic disease, CT performed better than in other series, with a sensitivity of 83% compared with 41% in the series by Flamen et al and 46% in the series by Luketich et al. The 75% specificity rate is within the range reported in these series. The sensitivity and specificity of the PET scan (67% and 92%, respectively) are within the performance range reported in other studies. Most interesting, we did not find the expected 20% of patients in whom PET scans changed clinical management, primarily by detecting novel sites of metastatic disease. In this series, PET identified a single patient (4%) with a metastasis not identified on CT scan. In contrast, CT identified 3 patients (13%) who had metastases that were not detected on the PET scan. There are some possible explanations for the lack of increased benefit of PET scans in our series. In this series, even though 50% of patients had metastatic disease, the most frequent site was nodal, not hepatic, metastasis, as expected in 35% of new patients. This may represent some selection bias in our institution as to who was referred for PET scanning. In addition, supraclavicular lymph node metastases have been a common site where CT has not demonstrated lesions. In the study by Flanagan et al, 5 of 7 patients with metastatic disease had supraclavicular nodes as the distant site, none of which were identified by CT but all of which were visible on PET scans. These lymph node beds may not be captured by CT imaging because the neck is not included in routine CT scans. These nodes are also accessible on physical examination, and none of these studies remark on whether the nodes that were identified on PET scan were palpable. In this series, none of our patients had disease in supraclavicular nodes. Another factor in comparing these results is whether the total number of metastases has been used for calculations of sensitivity and specificity. This can result in higher values when compared with calculations based on the presence or absence of any distant disease. The one clear advantage in this study and others is the ability of a PET scan to identify bone metastases. In this series, 15% of patients had documented bone metastases.
involvement, and PET was the only imaging modality to identify the metastases. Bone has been recognized as a site for distant disease in up to 15% of patients with esophageal cancer.

An interesting observation of our series is that only one third of patients had involved regional nodes in contrast with 50% of patients who presented with M1 disease. Of those who had M1 disease, half had metastases in distant lymph nodes. This illustrates some of the problems in interpreting the literature concerning accuracy in detection. Studies use a variety of definitions of what is considered a regional lymph node. Luketich et al13 defined distant lymph nodes as those more than 10 cm from the primary lesion. Block et al11 defined nodes as either being “adjacent” or “nonadjacent” by proximity to the primary tumor. Data definition and interpretation also influence how PET scans have been evaluated for detection of distant disease. Many centers have adopted a lesion-specific type of analysis comparing how many specific metastases in each patient were identified by each technique. We chose to address a more binary question in this analysis: Is distant disease present or not? We have adopted this approach because that is the clinically relevant information. Once a patient has been diagnosed with metastatic disease, curative surgical treatment is not an option. We are not sure of the clinical relevance of whether a test shows 3 vs 5 lesions once it demonstrates the presence of any distant spread. Therefore, in this analysis we have applied the AJCC definitions of regional nodes and distant metastases to standardize definitions and recreate scenarios of clinical decision making. With such disparate definitions of regional or distant nodes, it is difficult to compare our data with those of other institutions. We would also encourage strict adoption of the AJCC staging criteria because this is a standard nomenclature that has been used to determine which patients are considered for neoadjuvant or other treatment protocols. We recognize the limitations of this type of retrospective analysis. In a recent editorial about PET scanning, Brennan10 called for surgeon-run trials to prospectively evaluate new technology to avoid unrealistic expectations based on early reports. We look forward to the prospective American College of Surgeons Oncology Group trial to define the role of this exciting new imaging modality for esophageal cancer staging. In conclusion, we recommend that initial staging continue to be performed with CT scanning. In those patients with no obvious metastases who are candidates for operations, consider performing a PET scan with prospective data collection to evaluate this technology within your own center.

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REFERENCES


DISCUSSION

Edward A. Stemmer, MD, Long Beach, Calif.

We are all aware of the increasing incidence of adenocarcinoma of the esophagus in the past 20 years. Overall, carcinoma of the esophagus deserves its grim reputation, with fewer than 10% of its victims surviving 5 years. Operative mortality in large series cited over the last 10 years still approaches 10%; nevertheless, multimodal therapy followed by esophagectomy has increased 5-year survivals to 30% or 40% in selected patient groups. Appropriate staging could avoid the risk of operation in those who stand little chance of cure while identifying those patients who could benefit most from surgical management.

Evaluation of the accuracy of pretreatment staging has assumed great importance, and PET scanning is the most recent technique for nonoperative staging. However, in addition to being very expensive, there is a significant learning curve for accurate interpretation of a PET scan. The authors are to be commended for their efforts to determine whether or not PET scanning adds enough to the sensitivity and specificity of existing staging procedures, particularly CT, to justify the cost of the procedure.

Accurate detection and documentation of the presence of distant metastases is clearly the major concern in deciding whether or not to proceed with esophagectomy in these patients. Dr Wren’s pathologic staging documented that 12 of 24
patients had distant metastases. In 7 of the 12 patients, the metastases were detected by both CT and PET scans. In the remaining 5 patients, the metastases were detected in 3 patients by CT scanning and in 2 by PET scanning. Thus, all patients with distant metastases were detected by 1 or by both scans. It is important to recognize that the addition of PET scanning identified 2 patients, or 8% of the study group, in whom metastases might have been suspected but were not documented by more conventional staging procedures.

In the 14 patients in whom both scans agreed on the presence or absence of regional or distant metastases, the scans were correct in 12 patients but incorrect in 2 patients. In 1 of these patients, both scans were interpreted as showing distant metastases when, in fact, none were documented by pathologic staging. In the other patient, both scans failed to detect positive regional nodes.

In 10 patients the CT and PET scans disagreed on the presence or absence of regional or distant metastases. The CT scan was correct and the PET scan was incorrect in 3 of the 10 patients, while the PET scan was correct and the CT scan incorrect in 5 of the 10 patients. Both scans were incorrect in 2 patients. Two of the 10 patients were identified incorrectly as having distant metastases when they did not.

From the foregoing, it would appear that the addition of PET scanning to the pretreatment staging procedures did indeed enhance staging accuracy. Nevertheless, like all imaging studies, CT and PET scanning are not the equivalent of a tissue diagnosis. In the authors’ series, if the CT scan had been the only staging procedure employed, 3 patients might have been denied an operation because distant metastases were thought to be present when they were not. If only a PET scan had been used, 1 patient might have been denied an operation when there were no distant metastases present.

When both imaging procedures were performed, only 1 patient might have been excluded from surgical treatment when no distant metastases were present. No patient who did have distant metastases would have undergone surgery on the basis of an erroneous interpretation of 1 or both scans.

I would like to ask the authors 3 questions: (1) What are the cost, charges, and reimbursement for a PET scan? (2) Will you continue to use PET scanning based on the results of this series? If so, in what circumstances? And (3) how should a patient with newly diagnosed esophageal cancer be approached for work-up and evaluation for operation?

Bruce E. Stabile, MD, Torrance, Calif: I would like to ask about this issue of loss of sensitivity of PET scanning following neoadjuvant therapy. This is one of the recognized limitations of PET scanning in this and other malignant diseases following neoadjuvant therapy. Do you have any pathological information as to why there was loss of sensitivity for N and M staging following neoadjuvant therapy? Was it due to biological sterilization of those metastatic sites, or was it due to some other tissue effects of the therapy?

Paul Hansen, MD, Portland, Ore: This was a very nicely performed and presented paper. We have become great believers in PET scans for colorectal metastasis to the liver, and yet one of the problems we have had is a lot of our patients end up on chemotherapy at about the time they get the PET scan; that significantly influences the metabolic activity of the metastases and, therefore, whether or not they show up on PET. I presume most of your esophageal cancer patients are getting preoperative or perioperative chemoradiation, and do you have any data as to how the timing of that may have affected the results of the PET scan? Secondly, of the 3 patients who were incorrectly staged by the PET scan, did you go back and actually find out, did those patients get repeat PET scans postoperatively to find out if those areas that had lit up on the preoperative scan were still positive on the postoperative scan? In fact, maybe it was just a lymph node that was missed during the dissection.

Claude H. Organ, Jr, MD, Oakland, Calif: Could you clarify the denominators on some of your statistics? When you said 50% were metastatic, was that of the entire cohort? In other words, was the denominator 87? Secondly, is that compatible with 67% of them being node-negative? Is the denominator different? It appears from Dr Stemmer’s comments that the value of PET scanning in staging is under 5%.

1. Benjamin Paz, MD, Duarte, Calif: One of the most challenging things in the esophagus is to correctly stage the disease to decide which patient should not be operated on and to which patients you offer adjuvant therapy. It has been our practice to use EUS, which is far superior to both CT and PET scanning for correct TN staging. I agree that a CT and PET both are accurate in the staging of metastases; there are at least 4 or 5 studies in the literature that compare the 3, and basically they have shown that they are complimentary. Now, I would like to ask the authors, how will you suggest, based on your studies, to use PET scans? In our personal experience, I use PET scans in patients who have been treated with chemoradiation prior to deciding if I will do surgery following this treatment in advanced stages. I find that both CT and EUS in those patients are notoriously unsatisfactory to determine the correct staging, and I find PET superior. I don’t do PET scans at the initial diagnosis because stage II patients, for whom I offer surgery up front, rarely have distant metastasis not seen in CT. In stage III patients, we usually offer chemoradiation. We do a PET scan following the treatment.

Dr Wren: To answer Dr Stemmer’s questions first, what is the cost of a PET scan? The PET scan out-of-pocket cost for all of the materials is approximately $400. The charge is approximately $1700, and Medicare reimbursement is currently $2350, but that is dropping to $1375. That compares to about $900 for a CT scan of the chest, abdomen, and pelvis.

Your second question is, what am I going to do with this data? We have decided to continue performing PET scans but are prospectively collecting the data to see if these differences or lack of differences hold true within our institution. We also look forward to the American College of Surgeons Oncology Group’s sponsored trial specifically addressing this question about the role of PET scanning in the initial staging of esophageal cancer.

As to the third question, how would I approach a patient with esophageal cancer? The first thing is a careful physical examination and fine-needle aspiration of any suspicious lymph nodes in the cervical area. Next, a staging CT scan of the chest, abdomen, and pelvis is critical. I do believe EUS is valuable because it identifies patients with advanced local-regional disease (T3 N1) for entrance into neoadjuvant treatment protocols.

At our institution, we will obtain PET scans to prospectively collect this data. To answer Dr Stable’s question, we do have data on PET scans following neoadjuvant treatment, but I did not present that data here. There is increasing interest in using PET scans to follow response to chemotherapy and radiation.

Dr Organ, as to your question on sensitivity and specificity, the 12 (50%) of the reported 24 patients who had metastatic disease were of the 24 included, not 50% of all patients diagnosed in the institution at that point in time.

Dr Paz asked about the suggested use of PET scanning. I think that without adequate prospective trials to evaluate these new technologies, it is very difficult to comment on their use. Within our institution, we were surprised when we looked at our data. We were expecting to have PET scans detect occult disease in a greater number of patients. I think the American College of Surgeons Oncology Group is going to help answer this question for us in a definitive manner, and I look forward to that.