Evolving Technology

Integrated computed tomography–positron emission tomography in patients with potentially resectable malignant pleural mesothelioma: Staging implications

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Background: Integrated computed tomography–positron emission tomography imaging with coregistration of anatomic and functional imaging data may improve the accuracy of malignant pleural mesothelioma staging. We evaluate the use of integrated computed tomography–positron emission tomography in patients with malignant pleural mesothelioma who are being considered for extrapleural pneumonectomy.

Methods: Twenty-nine patients with malignant pleural mesothelioma who were judged to be candidates for extrapleural pneumonectomy after clinical and conventional radiologic evaluation underwent whole-body integrated computed tomography–positron emission tomography and pathologic staging. Two reviewers blinded to the results of clinical and pathologic staging retrospectively evaluated computed tomography, positron emission tomography, and coregistered computed tomography–positron emission tomography images. Staging was performed according to the International Mesothelioma Interest Group TNM staging system. Histopathology and/or results of further radiologic evaluation or follow-up served as the reference standard.

Results: Integrated computed tomography–positron emission tomography provided additional information in 11 of 29 patients that precluded extrapleural pneumonectomy. The overall tumor stage was correctly classified in 21 of 29 patients. The tumor stage was correctly determined in 15 of 24 patients, 6 of whom had T4 (nonresectable) disease. The node stage was accurately determined in 6 of 17 patients. Extrathoracic metastases not identified by routine clinical and conventional radiologic evaluation were detected in 7 of 29 patients and were found to be diffuse (n = 2) or solitary (n = 5).

Conclusions: Integrated computed tomography–positron emission tomography increases the accuracy of malignant pleural mesothelioma staging and is important in determining the appropriate therapy in patients being considered for extrapleural pneumonectomy.

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Malignant pleural mesothelioma (MPM) is an uncommon neoplasm arising from mesothelial cells of the pleura with an annual incidence of approximately 2500 to 3000 cases in the United States.[1,2] Advances in the management of MPM have occurred during the past few years, including the

adoption of an internationally accepted staging system, new active chemotherapeutic regimens, novel targeted agents, improved approaches for local control, and decreased morbidity and mortality in patients who undergo extrapleural pneumonectomy (EPP).[3-8] However, there is not a universally accepted standard therapy for MPM, and the prognosis remains poor. Failure of single-modality therapy has resulted in the use of multimodality regimens combining chemotherapy, radiotherapy, immunotherapy, and surgery, with an increasing tendency to perform surgical resection in cases of limited disease.[4,5,6,9-11] EPP is the surgical procedure of choice for patients with MPM who present with resectable disease.[5,9] In an attempt to distinguish these patients from those requiring palliative treatment, the International Mesothelioma Interest Group staging system for MPM, accepted by the American Joint Committee on Cancer and the International Union Against Cancer, describes the anatomic extent of disease according to a traditional TNM system.[3,12] A consequence of the increasing use of TNM staging is that accurate determination of the anatomic extent of disease is important in selecting patients for potentially curative resection. Computed tomography (CT) is usually performed to assess the extent of local chest wall and mediastinal invasion and presence of nodal and lung metastases in patients with MPM.[13,14] However, CT often fails to predict resectability. The use of positron emission tomography (PET) with [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) in the evaluation of patients with MPM has been reported.[15-20] Most of these studies were small, though, and the poor spatial resolution of PET when compared with that of CT often precluded assessment of the presence and extent of local tumor invasion.

The recent use of integrated CT-PET imaging with coregistration of anatomic and functional imaging data may improve the localization of regions of increased FDG uptake and accuracy of staging in patients with MPM. However, the role of FDG-PET and integrated CT-PET imaging in the staging of MPM has not been fully elucidated. Therefore, in this article, we report on the role of CT-PET imaging in patients with MPM who are being considered for EPP.

Methods

Thirty-three patients with biopsy-proven MPM were referred to The University of Texas M.D. Anderson Cancer Center for possible enrollment in an institutional review board-approved phase II study investigating the feasibility of EPP followed by intensity-modulated radiation therapy. Patients with mesothelioma of all histologic subtypes were eligible for this study. All patients underwent whole-body integrated CT-PET before surgical staging consisting of bronchoscopy, mediastinoscopy to exclude contralateral mediastinal nodal metastases, and/or laparoscopy with peritoneal lavage to rule out abdominal involvement. Four patients were excluded from the study group because of medical comorbidity. The final study group consisted of 29 patients (26 men and 3 women; mean age 63 years [range, 44-77 years]).

CT-PET Imaging Parameters

An integrated CT-PET scanner (Discovery ST-8; General Electric Medical Systems, Milwaukee, Wis) was used. PET images were acquired during shallow breathing in the 2-dimensional mode for 3 minutes per bed position 60 to 90 minutes after intravenous administration of 555 to 740 MBq of FDG. Non–contrast-enhanced CT images were acquired in helical mode (speed, 13.5 mm/rotation) from the base of the skull to the mid-thighs during suspended mid-expiration at a 3.75-mm slice thickness, 140 kVp, and 120 mA.

CT-PET Imaging Interpretation

Two reviewers experienced in CT and PET interpretation retrospectively reviewed the CT-PET scans. Both reviewers were blinded to the results of mediastinoscopy, laparoscopy, and surgery. The findings were recorded by consensus. The PET and CT images were reviewed on a Xeleris workstation (General Electric Medical Systems). CT, PET, and coregistered CT-PET images were available for review in all standard planes. PET scans were analyzed visually and quantitatively. FDG uptake was considered to be abnormal on visual analysis when it was substantially greater than the mediastinal blood pool activity on the attenuation-corrected images. A pixel region of interest was also outlined within regions of increased FDG uptake and measured on each slice. The highest recorded FDG uptake was semiquantitatively analyzed according to the following formula: maximum standardized uptake value (SUV) = decay-corrected activity (millicuries/milliliter)/injected FDG dose (millicuries)/body weight (gram).

Surgical Procedures

All surgical staging procedures and EPPs were performed by experienced thoracic surgeons. Laparoscopy consisted of direct visualization of the diaphragm with biopsy analysis of any visible abnormalities as well as peritoneal lavage. Mediastinoscopy was used to evaluate the mediastinal nodes, and specimens were classified according to the American Thoracic Society mapping system.[21] Because patients with N2 disease were eligible for EPP, mediastinoscopy was only performed to evaluate for N3 disease that would have precluded surgery.

Staging Considerations

Disease in the patients was staged according to the International Mesothelioma Interest Group TNM staging system by combining the information obtained from the CT and PET scans.[12] In our protocol, patients with stage I to III MPM (T1-3 N1-2 M0) were eligible for EPP, whereas those with stage IV MPM (any T4, any N3, any M1) were not. FDG-avid lymph nodes on PET, regardless of size on CT, were interpreted as positive for metastasis. Because patients with N2 nodes were eligible for EPP, PET information was used to direct invasive sampling in patients with FDG-avid N3 nodes. In terms of extrathoracic PET positive foci, if CT showed anatomic abnormalities suspicious for metastases, patients were excluded from surgery and underwent palliative therapy. The decision to obtain pathologic confirmation of metastatic disease was at the discretion of the treating physician.

TABLE 1. Patient data

Patient No.	Age	Sex	Histology	Tumor SUV	Tumor R/L	Procedure	CT-PET TNM	Reference standard TNM	CT-PET stage	Reference standard stage
1	58	M	E	8.9	R	EPP	T2 N3 M0	T2 N0 M0	IV	II
2	61	M	M	3.0	R	EPP	T2 N0 M0	T2 N0 M0	II	II
3	66	M	E	10.0	R	EPP	T1 N1 M0	T2 N0 M0	III	II
4	63	M	E	11.0	R	EPP	T3 N0 M0	T2 N1 M0	III	III
5	62	M	E	8.7	R	EPP	T1 N0 M0	T2 N2 M0	I	III
6	60	M	M	20.0	L	EPP	T3 N0 M0	T3 N0 M0	III	III
7	57	M	M	6.4	L	EPP	T3 N0 M0	T3 N0 M0	III	III
8	64	M	M	8.5	R	EPP	T2 N3 M0	T3 N1 M0	IV	III
9	65	F	M	11.4	R	EPP	T3 N2 M0	T3 N1 M0	III	III
10	60	M	E	8.0	R	EPP	T3 N1 M0	T3 N2 M0	III	III
11	77	M	S	12.0	R	EPP	T3 N0 M0	T3 N2 M0	III	III
12	58	F	E	11.2	L	EPP	T4 N0 M0	T3 N2 M0	IV	III
13	44	M	E	7.9	L	EPP	T3 N0 M0	T3 N2 M0	III	III
14	51	M	E	12.9	R	EPP	T2 N3 M0	T3 N2 M0	IV	III
15	58	M	E	16.0	L	EPP	T3 N2 M0	T3 N2 M0	III	III
16	73	M	M	11.5	R	EPP	T4 N2 M0	T4 N2 M0	IV	IV
17	58	M	E	10.5	R	ET	T4 N0 M0	T4 N0 M0	IV	IV
18	73	M	S	9.8	L	ET	T4 N2 M0	T4 NX M0	IV	IV
19	65	M	E	12.0	L	Lap	T4 N0 M0	T4 NX M0	IV	IV
20	61	M	E	5.6	R	Lap	T2 N0 M0	T4 NX M0	II	IV
21	60	M	E	10.5	R	Lap	T2 N2 M0	T4 NX M0	III	IV
22	65	M	S	10.5	R	Lap	T4 N0 M0	T4 NX M0	IV	IV
23	68	M	S	16.0	R	Lap	T4 N0 M1	T4 NX M1	IV	IV
24	64	M	E	11.6	R	Lap	T3 N3 M1	T4 NX M1	IV	IV
25	62	M	E	11.8	L	Bx	T3 N2 M1	TX NX M1	IV	IV
26	70	M	E	10.5	L	*	T3 N3 M1	TX NX M1	IV	IV
27	67	F	E	4.4	L	*	T2 N1 M1	TX NX M1	IV	IV
28	64	M	E	15.0	L	*	T3 N2 M1	TX NX M1	IV	IV
29	66	M	S	10.0	R	*	T4 N0 M1	TX NX M1	IV	IV

E, Epithelial; *S,* sarcomatoid, *M,* mixed; *EPP,* extrapleural pneumonectomy; *ET,* exploratory thoracotomy; *Lap,* laparoscopy; *Bx,* abdominal node biopsy; *SUV,* standardized uptake value; *CT-PET,* computed tomography–positron emission tomography. *No invasive procedure. M1 disease confirmed by imaging follow-up; TNM: X, not confirmed.

Although many institutions use magnetic resonance imaging in the preoperative assessment of patients with MPM, particularly to evaluate for diaphragmatic involvement, our institution does not because of the limitation of this modality in detecting subtle transdiaphragmatic invasion. Instead, laparoscopy to directly visualize the undersurface of the diaphragm and detect small volume disease as well as peritoneal lavage was performed in our study patients.

Statistical Analysis

Statistical analysis was performed with the SPSS version 11 software program (SPSS Inc, Chicago, Ill). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT-PET imaging in TNM staging were determined. The SUV of the primary tumor on PET was compared with histology using the 1-way analysis of variance.

Results

T Staging

All patients had increased FDG uptake in their primary tumor (mean SUV, 10.5 [range, 3-20]). There was no statistically significant correlation ($P = .727$) between the SUV of FDG uptake in the primary tumor and histology: epithelioid (n = 18; mean, 10.4 [range, 4.4-16.0]), sarcomatoid (n = 5; mean SUV, 11.7 [range, 9.8-16.0]), and mixed (n = 6; mean SUV, 10.1 [range, 3.0-20.0]). Evaluation of T staging with CT-PET was based on patients in whom the T stage was verified histopathologically after EPP (n = 16) or exploratory thoracotomy (n = 2) and laparoscopy (n = 24). T stage could not be determined in 5 of the 29 patients because these patients were precluded from surgery when M1 disease was detected on CT-PET. The T stage was accurately determined on CT-PET in 15 of the 24 patients (63%) (T1, n = 0; T2, n = 2; T3, n = 7; T4, n = 6) (Table 1). Of the 6 patients with T4 MPM, 4 had transdiaphragmatic extension of the tumor into the peritoneum.

CT-PET overstaged T disease in 2 patients (8%). One of these patients was determined by CT-PET to have T4 disease because of transmural pericardial involvement; surgi-

cal resection revealed nontransmural involvement of the pericardium (T3 disease). The second patient was determined to have nontransmural pericardial involvement (T3 disease) that was not confirmed at surgical resection.

CT-PET understaged T disease in 7 patients (29%). In 3 patients CT-PET did not detect transdiaphragmatic tumor extension into the peritoneum (T4 disease) diagnosed at laparoscopic evaluation. Peritoneal involvement was diagnosed by biopsy analysis of small (<5 mm) focal nodules on the inferior diaphragmatic surface in 2 of these patients and by peritoneal lavage in 1 patient. The remaining 4 patients had focal chest wall, lung, and/or diaphragmatic invasion revealed at surgical resection that was not detected by CT-PET. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT-PET for T4 disease were 67%, 93%, 86%, 82%, and 83%, respectively.

N Staging

Evaluation of N staging by CT-PET was based on resection of lymph nodes at EPP (n = 16) and exploratory thoracotomy (n = 1). Correlation of the CT-PET findings with N staging was only possible in 17 patients who underwent complete staging by lymph node dissection. The findings of node evaluation by CT-PET were not compared with those of mediastinoscopy, because biopsy analysis was only performed to detect contralateral or nonresectable (N3) disease. The N stage was accurately determined in 6 of the 17 patients (35%: N0, n = 4; N1, n = 0; N2, n = 2; N3, n = 0) (Table 1).

CT-PET overstaged the nodal involvement in 5 patients (29%). Two patients were determined to have N0 and N1 disease by CT-PET; surgical resection showed N1 and N2 disease, respectively. Three patients were determined to have contralateral mediastinal and/or supraclavicular nodal metastases (N3 disease); mediastinoscopy and surgical resection revealed N0, N1, and N2 disease in these 3 patients.

CT-PET understaged the nodal involvement in 6 patients (35%). Five patients were determined to have N0 disease by CT-PET; surgical resection revealed N1 disease in 1 patient and N2 disease in 4 patients. The sixth patient was determined to have N1 disease; surgical resection revealed N2 disease. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT-PET in lymph node staging in patients with N2 disease were 38%, 78%, 60%, 58%, and 59%, respectively.

M Staging

In 7 of the 29 patients (24%), CT-PET detected extrathoracic metastases that were not suspected after routine clinical and conventional radiologic evaluation (Table 1). Histopathologic analysis in these patients revealed epithelial (n = 5) and sarcomatoid (n = 2) tumors. Two patients had diffuse metastases (lung, bone, adrenal, abdominal nodes, and/or abdominal wall), and 5 had a solitary metastasis (bone, n = 1; abdominal lymph nodes, n = 4). Evaluation of M staging by CT-PET was based on further radiologic evaluation or follow-up (n = 6) and abdominal lymph node biopsy analysis (n = 1). In the 4 patients with abdominal nodal metastasis, the lymph nodes (mean diameter, 1.4 cm [range, 1.0-1.5 cm]; mean SUV, 6.9 [range, 4.5-9.3]) were located in the region of the celiac axis (n = 3) or the retroperitoneum (n = 1).

International Mesothelioma Interest Group Tumor Staging

CT-PET correctly assigned the overall stage of MPM in 21 of the 29 patients (72%) initially judged to be candidates for surgical resection after clinical and CT evaluation (stage I, n = 0; stage II, n = 1; stage III, n = 8; stage IV, n = 12). CT-PET accurately detected stage IV disease in 12 of 14 patients (86%). Of these 12 patients, 5 had a locally advanced, technically unresectable tumor, 2 had a technically unresectable tumor and metastatic disease, and 5 had extrathoracic metastases that were not suspected after routine clinical and conventional radiologic evaluation. One of the patients deemed as having an unresectable tumor underwent EPP. This patient had transdiaphragmatic extension of the tumor into the peritoneum (T4 disease) that was diagnosed by CT-PET. However, because laparoscopy and peritoneal lavage were negative for malignant cells, the patient then underwent surgery. Histopathologic analysis of the resected tumor revealed transdiaphragmatic extension of the tumor.

CT-PET overstaged the overall stage of MPM in 5 patients. Four of these patients were incorrectly considered to have nonresectable disease because of involvement of contralateral mediastinal or supraclavicular nodes (n = 3) or transmural pericardial involvement (n = 1). All 5 patients underwent EPP. Also, CT-PET understaged the overall stage of MPM in 3 patients. All 3 patients were initially considered to have potentially resectable disease. However, 2 patients were found to have nonresectable disease after laparoscopic detection of small (<5 mm in diameter) foci of peritoneal tumor.

Discussion

The results of this study show that integrated CT-PET with coregistration of anatomic and functional imaging data improves the accuracy of MPM staging and is important in determining the appropriate therapy in patients being considered for EPP. Specifically, integrated CT-PET was the most important component in determining the patients' eligibility for EPP. EPP would have been precluded because of CT-PET findings in 12 of the 29 patients (41%). Seven of these 12 patients had extrathoracic metastases detected by CT-PET that were not identified by routine clinical and conventional radiologic evaluation (Figures 1 and 2).

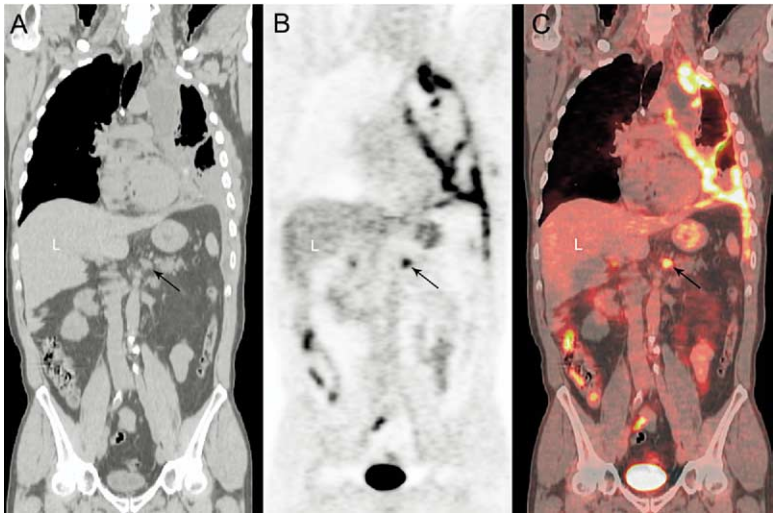

Figure 1. Coronal computed tomography (CT) (A), positron emission tomography (PET) (B), and integrated CT-PET (C) show diffuse uptake of [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) in primary left pleural tumor and focal area of increased uptake in the abdomen (*arrow*) localized to an abdominal lymph node. Biopsy confirmed nodal metastasis, precluding patient from extrapleural pneumonectomy (EPP). *L*, Liver.

Schneider and colleagues[18] have also reported the usefulness of PET in detecting occult metastases in 2 of 18 patients with MPM who were precluded from surgery by PET. Others have reported that distant metastasis may be the initial site of relapse after EPP, and this could reflect limitations in conventional staging with CT.[22] Our findings suggest that distant MPM metastases that develop soon after EPP are likely present at the time of surgery but are not detected by conventional staging. Improvement in the accuracy of M staging with CT-PET may lead to more appropriate selection of patients for EPP and decrease the number of patients with early recurrence of MPM.

The International Mesothelioma Interest Group staging system for MPM emphasizes the importance of local tumor invasion in determining resectability.[12] However, the qualifications for T staging are postoperative pathologic descriptors that are often difficult to determine by CT and MR imaging. In our study, the sensitivity of CT-PET in detecting T4 disease was 67% compared to 19% using PET alone reported by Flores and colleagues.[17] Similar limitations in T staging were also reported by Schneider and colleagues[18] when PET failed to detect chest wall and transdiaphragmatic invasion in 2 of 18 patients with MPM. The inaccuracy of CT in assessing transdiaphragmatic extension of MPM is because of its inability to detect microscopic invasion and the inherent limitation of axial imaging to delineate the diaphragm from primary tumor. In our study, the use of whole-body CT-PET capable of high-resolution multiplanar reconstruction allowed for more optimal evaluation of the diaphragm with sagittal and coronal images (Figure 3). Diaphragmatic T4 disease was confirmed pathologically in all 4 patients identified on CT-PET as having transdiaphrag-

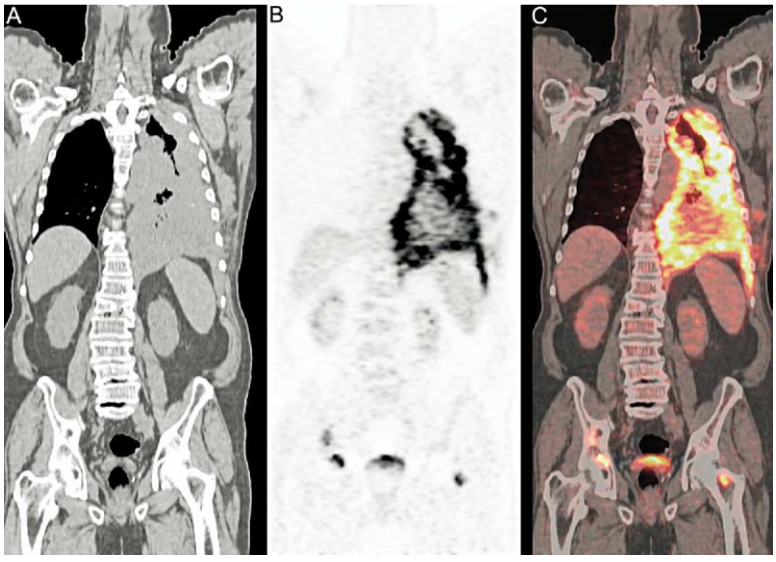

Figure 2. Coronal CT (A), PET (B), and integrated CT-PET (C) show diffuse uptake of FDG in primary left pleural tumor and focal areas of increased uptake in the pelvis localized to right iliac bone and left femoral neck. These occult metastases were not detected on conventional staging evaluation.

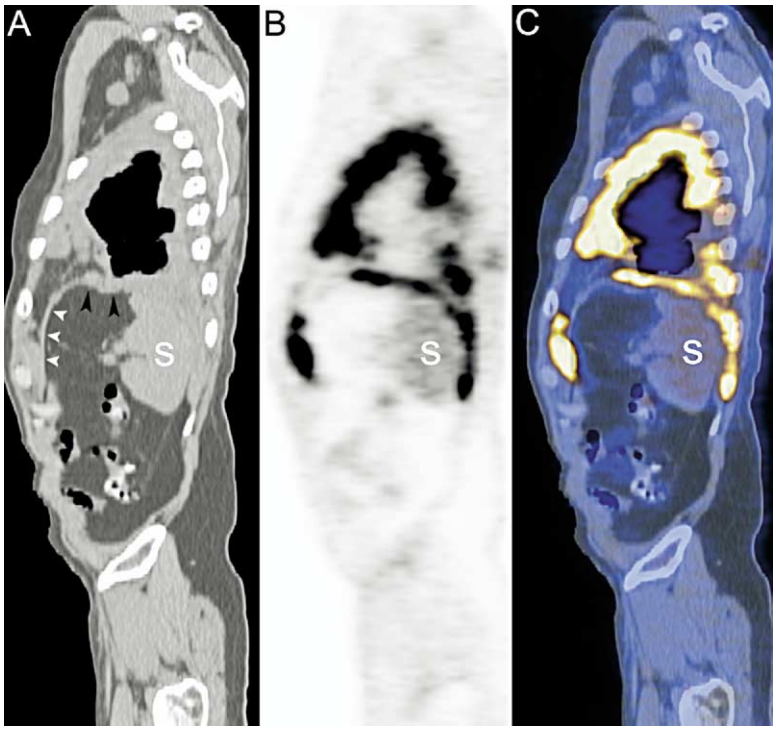

Figure 3. Sagittal CT (A), PET (B), and integrated CT-PET (C) show diffuse uptake of FDG in malignant pleural mesothelioma (MPM). Multiplanar reconstruction is useful in evaluating diaphragm and shows normal diaphragmatic contour *(white arrowheads)* and focal lobular irregularity *(black arrowheads)* suspicious for transdiaphragmatic extension of tumor. Laparoscopic biopsy confirmed T4 disease. *S,* Spleen.

matic extension. It is important to note that PET alone lacks the spatial resolution to detect transdiaphragmatic extension of tumor and in our study would have precluded fewer patients from EPP than CT-PET.

Two patients with potentially resectable disease were found to have T4 disease (transdiaphragmatic peritoneal involvement) by laparoscopy and peritoneal biopsy analysis. Their tumor implants were small (<5 mm in diameter) and would not have been detected by conventional imaging. Preoperative laparoscopy is not the standard of evaluation of MPM, because many institutions use magnetic resonance imaging to evaluate for suspected diaphragmatic invasion. However, because of the morbidity and mortality associated with EPP, we recommend laparoscopic evaluation in all patients considered for EPP.

Recently, researchers have reported better survival in patients who undergo EPP for epithelial MPM after complete local resection and an absence of nodal metastases.[5,22] PET may have a role in the evaluation of nodal metastases, particularly those not accessible by mediastinoscopy. PET has been reported to detect nodal MPM metastases in small studies.[15,18,19] A study by Benard and colleagues[19] in 1998 reported a sensitivity of 83% of PET for nodal metastases. However, a more recent study reported a sensitivity of only 11%.[17] Our study shows that CT-PET is inaccurate in evaluating nodal MPM metastases. CT-PET did not detect the metastases in the 3 patients with pathologic N1 disease because of the presence of confluent adjacent primary tumor or absence of increased FGD-uptake in the hilum. Also, CT-PET detected the metastases in only 2 of the 8 patients with N2 disease. Although this may affect prognosis, it did not affect surgical management. Furthermore, CT-PET inaccurately staged MPM as N3 (nonresectable) disease in 3 patients. In 2 of these patients, false-positive increased FDG uptake in the N3 nodes was attributable to inflammation on histopathologic examination. Because of the implications for management, we advocate sampling of all FDG-avid N3 nodes in patients with MPM. In addition, N3 lymph nodes that are enlarged according to CT criteria and are not FDG avid should be sampled in patients considered for surgery.

In summary, the use of integrated CT-PET in patients with MPM increases the accuracy of overall staging and significantly improves the selection of patients for EPP. Our study suggests that whole-body integrated CT-PET should be the preferred modality for staging in patients with MPM.

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