Role of Integrated 18-Fluorodeoxyglucose Position Emission Tomography-Computed Tomography in Patients Surveillance after Multimodality Therapy of Malignant Pleural Mesothelioma

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Introduction: To investigate the role of 18-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG-PET-CT) in the surveillance of patients after multimodality treatment of malignant pleural mesothelioma.

Methods: Retrospective study of patients who had chemotherapy, radical surgery, extrapleural pneumonectomy or pleurectomy/decortication, and radiotherapy for mesothelioma in our unit. PET-CT was performed after multimodality therapy to evaluate response to treatment or when disease recurrence was suspected. 18-FDG-PET scans were acquired from skull base to upper thigh with low-dose CT scans for attenuation correction and image fusion.

Results: Forty-four patients had extrapleural pneumonectomy (21) or pleurectomy/decortication (23) between January 2004 and July 2008. Twenty-five patients had PET-CT performed after multimodality therapy. This was performed in 11 patients in whom disease recurrence was suspected at a median of 9 (range, 6–16) months after treatment. PET-CT correctly diagnosed recurrent disease in eight patients and missed microscopic recurrence in one. Surveillance PET-CT was performed in 14 asymptomatic patients at a median of 11 (range, 7–13) months after treatment. It showed unsuspected recurrences in four patients. The standard uptake value max of recurrent mesothelioma was 8.9 ± 4.0 (4–18.4). PET-CT had a sensitivity of 94%, a specificity of 100%, and the positive and negative predictive values of 100 and 88%, respectively.

Conclusions: 18-FDG-PET-CT is useful in diagnosing disease recurrence after multimodality therapy for malignant pleural mesothelioma. We propose a prospective study to fully assess its value in this group of patients.

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The incidence of malignant pleural mesothelioma (MPM) in Great Britain and Europe is rising as predicted[1,2] but treatment options remain limited and controversial. The chance of cure is rare with most deaths occurring within 1 to 2 years of diagnosis. Radical surgery or extrapleural pneumonectomy (EPP) on its own has not been associated with any demonstrable increase in survival,[3] and it is now most often being offered with chemotherapy and radiotherapy.[4,5] A less-extensive surgical resection, also known as pleurectomy/decortication (P/D) may be performed to strip away the tumor without removing the underlying lung.[6] The objective of radical P/D is to achieve complete macroscopic clearance of the tumor with resection of pericardium and diaphragm, if necessary. However, in patients with more extensive disease, P/D may only involve removal of the tumor bulk to allow re-expansion of the underlying lung and relieve symptoms of breathlessness and pain.[7] Only a small proportion of patients with mesothelioma are deemed suitable candidates for multimodality therapy that includes chemotherapy, radical surgery, and radiotherapy.

Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) has established an important role in the diagnosis and staging of MPM,[8,9] and therefore, it is a useful tool in the assessment of patients when considering multimodality therapy. It may be useful to help characterize pleural lesions, direct biopsy, and assess the extent of tumor involvement, in particular to detect extrathoracic metastasis. Integrated 18-FDG-PET-CT combines anatomic and metabolic information in a single imaging procedure and has been shown to be a reliable tool in the staging and assessment of patients with MPM who are candidates for radical treatment.[10] Preliminary reports using 18-FDG-PET-CT to monitor tumor response to chemotherapy and radiotherapy have been published.[11–13] The use of PET/PET-CT to identify recurrent disease after radical surgery has not been well studied.[14] The aim of this

study was to investigate the potential role of PET-CT using 18-FDG in the surveillance of patients who have undergone multimodality therapy for MPM.

PATIENTS AND METHODS

Patients with a diagnosis of MPM who have been treated with chemotherapy, radical surgery, and radiotherapy were identified retrospectively from our departmental database. Radical surgery involved either EPP or P/D. Patients undergoing EPP were given induction chemotherapy consisting of three cycles of cisplatin and gemcitabine or pemetrexed. After EPP, they received radical hemithoracic radiotherapy (54 Gy in 30 fractions). Those undergoing P/D received adjuvant chemotherapy within 8 weeks of surgery on the premise that induction chemotherapy can make P/D technically more difficult. Adjuvant chemotherapy consisted of four to six cycles of cisplatin and pemetrexed. In addition, patients who underwent P/D had prophylactic radiotherapy to wound and chest drain sites (21 Gy in three fractions).

All patients were followed up regularly in the outpatient clinic till death. They were seen initially at 1 month after surgery, then 3 to 6 monthly thereafter.

After multimodality therapy, PET-CT was performed as part of routine surveillance. Patients were scanned in the fasting state 90 minutes after injection of 350 MBq of FDG on Discovery ST PET-CT cameras (General Electric Healthcase, Milwaukee, WI). Images were acquired from skull base to upper thighs at 5 minutes per 15-cm bed position. Low-dose noncontrast CT scans were performed for attenuation correction and image fusion. Images were reconstructed using iterative reconstruction. PET and CT datasets were reported on a dedicated workstation by two independent readers. In patients reported as having active tumor, a region of interest was drawn around the tumor on the axial plane with the "hottest" uptake to calculate the maximum SUV (SUVmax) according to the formula:

$$\text{Max SUV} = \text{maximum activity concentration (MBq/ml)} \times \text{body weight (g)/injected activity (MBq)}$$

RESULTS

A total of 44 patients underwent multimodality therapy between January 2004 and July 2008 for MPM. There were 40 men and four women and their median age was 62 years (range, 45–74 years). EPP was performed in 21 patients and P/D in 23. Twenty-six patients had right-sided disease and 18 had left-sided disease. All patients who had EPP and 14 who had P/D had R0-R1 resection. Epithelioid mesothelioma was confirmed histologically in 29 patients, biphasic in 13 patients, and sarcomatoid in two patients.

Twenty-five of 44 patients had PET-CT scans after multimodality therapy. The remaining 19 consisted of patients who died unexpectedly after treatment, patients who clearly had recurrence diagnosed on CT or who were referred for radical surgery as a part of the Mesothelioma and Radical Surgery trial[15] but were then followed up with CT locally. A few patients were too ill to travel to attend for a PET-CT performed in London.

PET-CT was performed when disease recurrence was suspected or as a part of routine surveillance. Disease recurrence was suspected clinically when patients exhibit symptoms of weight loss, cough, chest pain, or increasing breathlessness, or when there was a follow-up chest radiograph that was abnormal or showed possible disease progression. In 11 patients, PET-CT was performed when disease recurrence was suspected at a median of 9 (range, 6–16) months postoperatively. PET-CT correctly identified recurrent disease in eight patients but missed microscopic recurrence in one. Prior CT scan was performed in six of the 11 patients, four of them were felt to be diagnostic of recurrent disease. In the other two patients, recurrent disease was suspected on CT scan but was not diagnostic. A subsequent PET-CT confirmed local recurrent disease was identified in one patient and in the other no evidence of recurrence was found. The latter patient was diagnosed to have constrictive pericarditis from which he later died.

The other 14 patients were asymptomatic and underwent PET-CT as a part of surveillance at a median of 11 (range, 7–13) months postoperatively. PET-CT showed unsuspected recurrence in nine patients. Eleven of the 14 patients had undergone prior CT scan, three of them were felt to be diagnostic of recurrent disease. In six of the 11 patients, no evidence of recurrent disease was seen on CT scan, but PET-CT subsequently showed recurrence in four, all with local intrathoracic disease. In addition, peritoneal disease was also identified by PET-CT in two of the four patients. In two of the 11 patients, CT scan was suspicious for recurrence, but PET-CT showed no FDG uptake in these suspicious areas, indicating no evidence of recurrent disease.

Patients with recurrence identified by PET-CT all had local intrathoracic disease, but in addition, PET CT identified recurrence in the contralateral lung in two patients, metastatic peritoneal disease in four patients, bone metastasis in two patients (Fig. 1), and metastasis to a supraclavicular node in one patient.

PET-CT failed to identify recurrence in one patient who had developed a small contralateral pleural effusion 12 months after left EPP. She went on to have video-assisted thoracoscopy where multiple small nodules on the visceral and parietal pleura were seen (Fig. 2). Biopsies confirmed these to be recurrent mesothelioma.

The mean SUVmax of recurrent disease was measured at 8.9 ± 4.0 (range, 4–18.4). Histologic confirmation of recurrent disease was obtained in all patients where recurrence was suspected on PET-CT. The absence of disease was established by clinical and radiologic follow-up; mean follow-up was 18 (range, 6 to 39) months. PET-CT correctly identified recurrent mesothelioma in 17 of the 18 (sensitivity 94%) patients and correctly identified seven of the seven as having no residual disease (specificity 100%). Positive and negative predictive values were 100 and 88%, respectively. Six of the seven patients with no disease seen on PET or histologically are still alive. The other patient died 18 months after EPP from constrictive pericarditis, confirmed at postmortem examination. Ten of the 17 patients with recurrent disease identified by PET are still alive.