Prognostic Value of FDG PET Imaging in Malignant Pleural Mesothelioma

François Bénard, Daniel Sterman, Robin J. Smith, Larry R. Kaiser, Steven M. Albelda and Abass Alavi

Division of Nuclear Medicine, Department of Radiology; Division of Pulmonary and Critical Care, Department of Medicine; Division of Thoracic Surgery, Department of Surgery; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Despite several attempts at treating malignant pleural mesothelioma with various modalities, mortality remains high, with median survival between 12 and 18 mo. This disease may have a highly variable clinical course, with occasional long-term survivors. The purpose of this study was to assess whether tumor metabolic activity, as assessed by fluorodeoxyglucose (FDG) PET imaging, correlates inversely with survival. **Methods:** Twenty-eight patients with suspected mesothelioma underwent FDG PET scanning between September 1995 and May 1997. A diagnosis of mesothelioma was confirmed in 22. Fully corrected scans with attenuation correction of the entire chest were available in 17 patients with sufficient follow-up for survival analysis. Standardized uptake values (SUVs) were determined from the most active tumor site in each patient. **Results:** Seven patients died during follow-up, at a median period of 5.3 mo after FDG PET scanning. Follow-up information was available on the remaining 10 patients for a median period of 15.6 mo after the PET study. The mean SUV of the deceased patients was 6.6 ± 2.9, compared with 3.2 ± 1.6 among the combined survivors. The deceased patients had tumor SUVs that were highly correlated with duration of survival after the PET study ($r = 0.87$, $P < 0.05$). The cumulative survival estimate by the Kaplan-Meier product limit method was 0.17 at 12 mo for the patients with tumor SUVs greater than the median value and 0.86 for those with lower SUVs. The survival distribution of the high SUV group showed significantly shorter survivals compared with the low SUV group ($P < 0.01$). **Conclusion:** Patients with highly active mesotheliomas on FDG PET imaging have a poor prognosis. High FDG uptake in these tumors indicates shorter patient survival.

Key Words: fluorodeoxyglucose; PET; mesothelioma; survival

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Malignant pleural mesothelioma is an uncommon cancer of the mesothelial lining of the thorax that has been strongly associated with asbestos exposure. The course of the disease usually is one of inexorable progression, with a median survival of 12–18 mo after diagnosis (*1*). Various treatment options are available, ranging from palliative care to aggressive multimodality regimens, but treatment algorithms remain highly controversial (*2*). Several factors have been shown to correlate with survival: intrathoracic lymph node metastases, distant metastatic disease and the initial extent of pleural involvement (*3*). Patients with mesotheliomas of the epithelial subtypes tend to survive longer than those with mixed or sarcomatoid subtypes. However, the natural course of the disease is highly variable, with the occasional patient achieving long-term survival.

The use of PET scanning with ^{18}F-fluorodeoxyglucose (FDG) in patients with malignant disease has grown significantly (*4*). There are now many established indications for clinical FDG PET scanning in brain tumors, lung cancer and many other malignancies. In a small series of patients, we recently demonstrated the high sensitivity of FDG PET imaging in detecting malignant mesothelioma and assessing the extent of tumor involvement (*5*).

The FDG PET method allows investigators to estimate the tissue metabolic activity by measuring the fraction of the injected dose incorporated per unit of volume at the tumor sites. The standardized uptake value (SUV), despite its limitations (*6*), allows simple measurements of tissue activity to be made without having to resort to complex kinetic modeling requiring arterial blood sampling (*7*). In malignant mesothelioma, despite a relatively good demarcation between malignant and benign disease, the dispersion of SUV measurements among patients can be quite large (Fig. 1). There is a trend toward lower FDG uptake in mesotheliomas of the epithelial subtype, generally thought to be a less aggressive form of the disease (*5*). This observation led us to hypothesize that tumor metabolic activity could correlate with patient survival, as has been shown in other malignancies (*8–12*). The purpose of this study was to assess whether increased tumor metabolic activity (as measured by the SUV) can provide information about patient survival in malignant mesothelioma.

MATERIALS AND METHODS

FDG PET imaging was performed in 28 patients with clinically suspected mesothelioma between September 1995 and May 1997. This population was described in a previous report (*5*). A diagnosis of malignant mesothelioma was confirmed histologically in 22 patients. Quantitative analysis of the data could be performed in 17 patients who had adequate follow-up for survival analysis. Fol-

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For correspondence or reprints contact: Abass Alavi, MD, Division of Nuclear Medicine, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

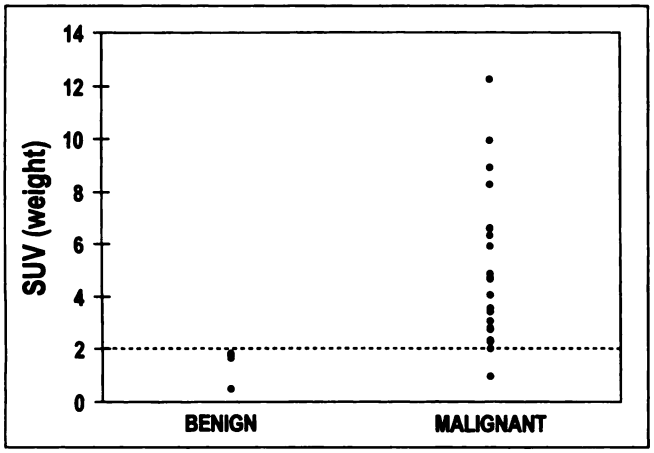

FIGURE 1. Distribution of SUVs in patients with benign and malignant pleural thickening, showing wide variability in SUV measurements in patients with malignant disease. Dotted line indicates optimal SUV (2.0) for differentiating benign from malignant pleural disease.

low-up information was obtained from the medical records or by phone contact with the treating physician to obtain the date of death or status at last follow-up.

PET imaging was performed in all patients after a fast of at least 4 h. FDG was injected intravenously at a dose of 4.218 MBq/kg, and scanning was initiated 60–90 min after injection. Multiple partially overlapping scans of 12.8 cm were obtained over the chest and abdomen, using a PENN-PET 240H scanner (UGM Medical Systems, Inc., Philadelphia, PA). This scanner operates without septa and has a resolution of 5.5 mm in all three planes at the center of the field of view (*13*). At the end of the study, transmission scans were obtained for nonuniform attenuation correction over the chest, according to previously described techniques (*14,15*). The images were reconstructed using the ordered subset expectation maximization algorithm. Attenuation-corrected scans were available in all cases. An SUV measurement was obtained at the most active tumor site, drawing a region of interest (ROI) around the lesion at a threshold of 50% of the maximal tumor activity. This ensured consistent and reliable ROI placement to maximize reproducibility. The average counts within the ROI were used for comparison with the survival data. The SUV was normalized by using the actual body weight.

Survival curves were calculated using the Kaplan-Meier product limit method. Patients were assigned to two groups on the basis of SUV measurements. Patients with tumor uptake equal to or below the median value were placed in the low SUV category, whereas those with uptake above the median value were placed in the high SUV group. The survival distributions in each group were compared using the log-rank test.

RESULTS

The patient data are reported in Table 1. This population included 14 men and 3 women (median age 62 y, range 48–78 y). Seven patients died during follow-up, at a median time of 5.3 mo after FDG PET scanning. Six of these patients died of disease progression, and 1 patient died of pulmonary edema a few days after extrapleural pneumonectomy. Ten patients were alive at the time of data analysis. Follow-up for these patients was available for a median period of 15.6 mo after the PET study. The mean SUV of the deceased patients was 6.6 ± 2.9, compared with 3.2 ± 1.6 among the combined survivors. The overall median SUV was 4.03, and this was chosen as a cutoff to establish two survival curves (low SUV and high SUV groups).

TABLE 1
Patient Data

Patient no.	Age (y)	Subtype	SUV	SD*	ROI size (mL)	Stage	T stage	Status	Interval† (mo)
1	78	Epithelial	0.94	0.11	0.4	Ib	T1b	Alive	17.63
2	61	Epithelial	2.26	0.53	2.4	Ia	T1a	Alive	19.13
3	72	Epithelial	2.27	0.60	1.5	Ib	T1b	Alive	8.13
4	62	Epithelial	2.31	0.45	0.3	Ia	T1a	Alive	23.43
5	66	Biphasic	2.78	0.64	1.0	Ib	T1b	Alive	7.40
6	56	Biphasic	3.04	0.79	4.4	II	T2	Alive	26.57
7	73	Unspecified	3.39	0.71	2.0	II	T2	Alive	13.47
8	52	Unspecified	3.54	0.39	1.2	Ia	T1a	Deceased	12.23
9	69	Epithelial	4.03	0.60	0.3	IV	T4	Alive	13.17
10	61	Epithelial	4.63	0.98	1.7	II	T2	Deceased	12.37
11	67	Epithelial	4.70	1.47	1.3	Ia	T1a	Alive	18.77
12	58	Biphasic	4.84	1.08	0.8	III	T2	Deceased	10.33
13	73	Biphasic	5.88	0.40	6.0	III	T2	Deceased	5.27
14	59	Biphasic	6.56	0.55	0.6	II	T2	Deceased	0.03
15	62	Epithelial	6.59	1.96	2.3	IV	T4	Alive	7.90
16	48	Sarcomatoid	8.25	0.55	2.6	II	T2	Deceased	3.40
17	64	Biphasic	12.21	2.15	2.9	III	T3	Deceased	2.53

*Pixel-to-pixel standard deviation within the region of interest.
†Interval from the time of PET scanning to the last follow-up or time of death.
SUV = standardized uptake value; ROI = region of interest.

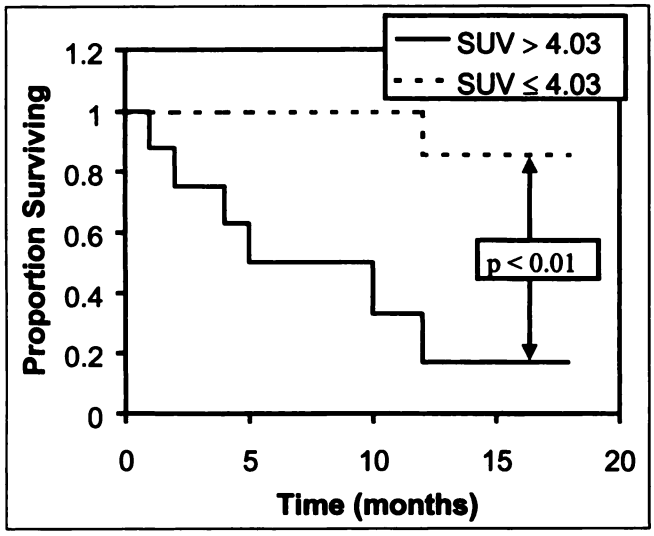

FIGURE 2. Kaplan-Meier survival curves for low (dotted line) and high (solid line) SUV patient groups, showing clear demarcation, with poor survival of subjects in high SUV group.

The survival curves for these two groups are shown (Fig. 2), indicating a much more rapid decline in the high SUV group's survival estimates. The patient with an SUV of 4.03 (equal to the median value) was included in the low SUV group; switching this patient to either group did not significantly alter the difference between the two survival curves. The cumulative survival estimate by the Kaplan-Meier product limit method was 0.17 at 12 mo for the patients with tumor SUV greater than the median value (4.03) and 0.86 for those with lower SUVs. By comparing the survival distributions using the log-rank method, the high SUV group showed significantly shorter survival times compared with the low SUV group ($P = 0.00142$). One patient died a few days after extrapleural pneumonectomy of pulmonary edema, and this death was attributable to a complication of surgery rather than disease progression. Analyzing the survival data without this patient did not alter the results significantly; the difference between the two survival curves remained statistically significant ($P < 0.05$). Excluding this patient, the deceased patients had tumor SUVs that were highly correlated with the duration of survival after the PET study (Fig. 3; $r = -0.87$, $P < 0.05$; Spearman's rho $r_s = -1.0$).

The volumes of the ROI used for SUV calculations were not significantly different in the two groups (1.5 ± 1.3 mL in the low SUV group and 2.3 ± 1.7 mL in the high SUV group; 2-tailed t test, $P = 0.33$) and were not correlated with the SUV ($r = 0.32$). However, as seen in Table 1, patients with lower SUVs tended to be at a lower stage than those with high SUVs. As expected, the extent of primary tumor involvement (T stage) also tended to be lower in the patients with the longest survival. This was also apparent on visual interpretation of the FDG PET studies, on which most long-term survivors tended to have much less conspicuous disease (Fig. 4).

DISCUSSION

FDG is becoming a widely used radiopharmaceutical in nuclear oncology. Its properties make it a tremendously useful agent to study many organs and systems, and its use is expected to grow in oncology for many years. We recently showed that FDG PET imaging could be of value as an adjunct to conventional methods in diagnosing and staging malignant mesothelioma (*5*). Patronas et al. (*8*) established that hypermetabolism in brain tumors was associated with poor survival, an observation that was confirmed by others (*9*). Since then, FDG uptake has been associated with poor prognosis in lymphoma (*10*), pancreatic cancer (*11*) and head and neck tumors (*12*). In lung cancer, the level of FDG uptake has been correlated with tumor doubling time (*16*).

Although many mechanisms have been postulated to explain the incorporation of FDG in tumors, a unified model remains elusive. Tumor cells with high glycolytic rates have been shown to have high levels of enzymes that control glycolysis, such as hexokinase, phosphofructokinase and pyruvate dehydrogenase (*17,18*). Increased membrane glucose transporter levels (*19*), macrophage infiltration (*20,21*) and tumor hypoxia (*22*) have also all been implicated to various degrees. Regardless of the precise mechanism of uptake, it is likely that rapidly growing tumors in vivo have increased metabolic demands, tend to be hypoxic as a result of the slower relative growth of neovasculature and may shed more antigens than slowly progressive lesions, producing a local inflammatory response. All these factors will increase the uptake of FDG in tumor tissue.

Pleural mesothelioma is a malignancy in which the prognostic information provided by FDG PET imaging could be of value. This disease often coexists with pleural effusion and benign diffuse pleural thickening from asbestos exposure, rendering the evaluation of the extent and size of the primary tumor difficult with CT. In addition, there is a wide variability in survival among patients afflicted with this disease. Although the therapeutic options are currently limited outside formal clinical trials, the prognostic informa-

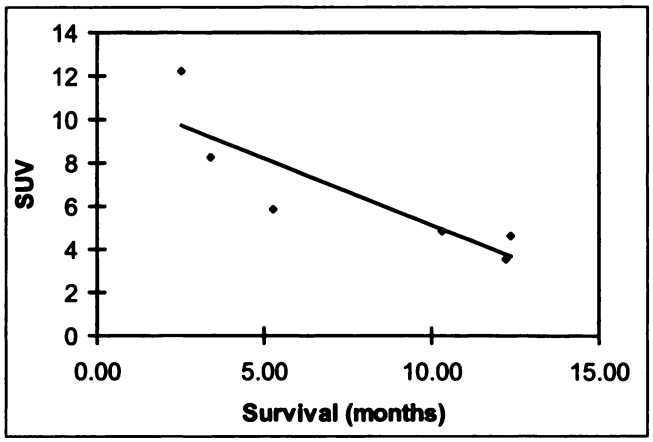

FIGURE 3. Correlation between survival times of deceased subjects and tumor SUV measurements.

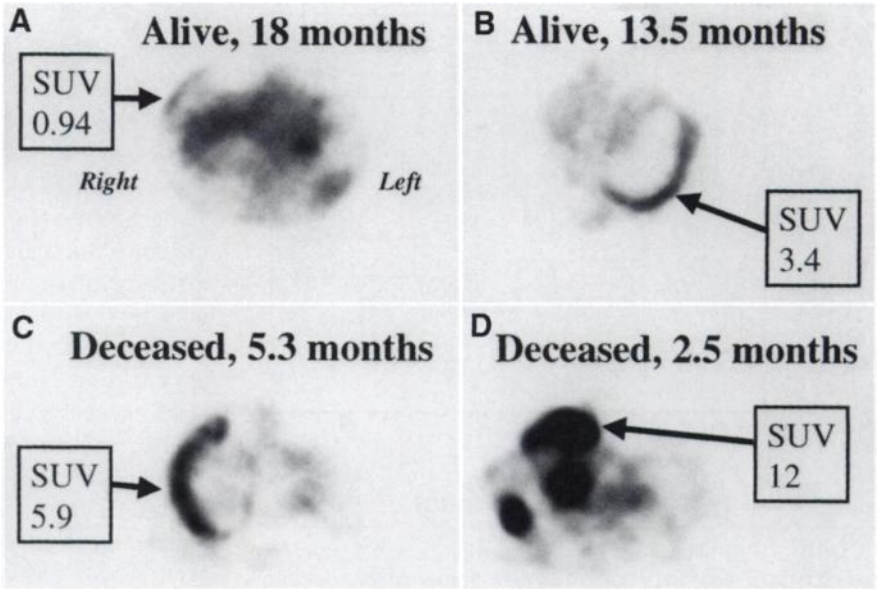

FIGURE 4. Typical appearance of FDG PET studies in malignant mesothelioma. Transaxial slices were taken from four patients. Patient A, with tumor SUV of 0.94, was alive 18 mo after PET scan. Patient B (SUV 3.4) was alive 13.5 mo after PET. Patients C (SUV 5.9) and D (SUV 12) died shortly after PET scan, at 5.3 and 2.5 mo, respectively.

tion provided by FDG PET imaging could be of value in determining whether to pursue an aggressive approach. The excellent sensitivity of FDG PET in detecting and staging malignant mesothelioma, combined with the prognostic information provided by this method, can make this imaging modality a useful adjunct to conventional evaluation.

In this series, it is unlikely that the results of FDG PET scanning had an influence on the outcome of the disease. This test was not part of the routine algorithm to select treatment, and current regimens have limited efficacy compared with palliative care. This study clearly demonstrates that increased FDG uptake in mesotheliomas is associated with an unfavorable prognosis. However, because this malignancy is uncommon and the study population is small, meaningful multivariate analysis was not possible. Therefore, we could not establish whether FDG contributes as an additional independent prognostic factor from the staging method proposed by the International Mesothelioma Interest Group (*3*). In fact, tumors with low FDG uptake tended to be at an earlier stage than those with high uptake (Table 1). This raises the issue of whether FDG uptake reflects an inherent biologic characteristic of these tumors or simply relates to the size of the primary disease. Mesotheliomas can involve very diffusely the parietal pleura with a thin layer of malignant cells, making detection with any imaging modality challenging. We did not perform any correction to obtain quantitative recovery of counts from small tumors due to partial-volume averaging effects (*23*). This can be done easily in small spherical tumors but is challenging in irregular sheet-like lesions of uncertain thickness wrapping around the lung. In addition, normalization to actual body weight rather than body surface area and the variable sampling interval (60–90 min after injection) may increase the interpatient variability of this measurement. However, the results do demonstrate that high FDG uptake in malignant mesothelioma is unequivocally associated with a poor prognosis.

CONCLUSION

Increased tumor metabolic activity as assessed by the uptake of FDG in tumor tissue is associated with a poor prognosis in malignant pleural mesothelioma. Although the independent predictive value of FDG PET is not established compared with current staging systems, this information may be useful clinically. Patients with high FDG uptake on PET scanning tend to have significantly shorter survival.

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