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Positron emission tomography predicts survival in malignant pleural mesothelioma

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Objectives: Recent studies suggest that standard uptake value on fluorodeoxyglucose positron emission tomography scan can predict mediastinal lymph node status in malignant pleural mesothelioma. Because mediastinal nodal metastasis is known to be associated with poor prognosis, we hypothesized that standard uptake value on fluorodeoxyglucose positron emission tomography might independently predict survival.

Methods: Patients with pathologically proven mesothelioma underwent fluorodeoxyglucose positron emission tomography scanning. Patients fasted and received a minimum of 10 mCi of F18-fluorodeoxyglucose. Whole-body emission studies were acquired, followed by whole-body transmission scans with iterative reconstruction. On the basis of the maximal chi-square method, a standard uptake value of 10 was chosen to classify patients as low versus high standard uptake value. Survival probabilities for both standard uptake value groups were estimated by the Kaplan-Meier method. A Cox proportional hazards model assessed the joint influence of standard uptake value, histology, and stage on survival.

Results: From 1998 to 2005, 137 patients with malignant pleural mesothelioma underwent positron emission tomography scans. The median follow-up for all surviving patients was 24 months. Median survivals were 9 and 21 months for the high and low standard uptake value groups, respectively ($P = .02$). In a multivariable analysis, high standard uptake value tumors were associated with a 1.9 times greater risk of death than low standard uptake value tumors ($P < .01$). Mixed histology carried a 2.9 times greater risk of death than epithelioid histology ($P < .01$), and stages III and IV had a 1.8 times greater risk of death than stages I and II ($P = .05$).

Conclusions: Standard uptake value greater than 10, mixed histology, and stages III and IV are poor risk factors in malignant pleural mesothelioma. These findings suggest that fluorodeoxyglucose positron emission tomography can be used to stratify patients for treatment and clinical trials.

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Malignant pleural mesothelioma (MPM) is a rare disease for which there is no universally accepted therapy. Treatment varies from observation alone to complex multimodality therapy consisting of surgery, radiation, and chemotherapy. To direct treatment and to stratify patients for clinical trials, predictors of survival are needed. Currently, histology and tumor stage are the best predictors of survival. Computed tomography (CT) and magnetic resonance imaging, the most widely used methods of clinical staging, frequently fail to stage disease accurately at the time of diagnosis.[1] Approximately 25% of patients who undergo surgical exploration for resection are found to have unresectable tumors because of locally advanced (T4) disease undetected by imaging studies.[2]

We previously investigated positron emission tomography (PET) as a preoperative staging tool and found that it identified occult distant metastasis in 10% of

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Abbreviations and Acronyms
CT = computed tomography
FDG = fluorodeoxyglucose
MPM = malignant pleural mesothelioma
PET = positron emission tomography
SUV = standard uptake value

patients, but that it did not predict T4 disease identified at surgery.[3] However, a high PET standard uptake value (SUV) did correlate with the presence of N2 disease at the time of resection in MPM. Because SUV seems to reflect the tumor biology of MPM, we hypothesized that maximum PET SUV independently predicts survival in MPM.

The objectives of this study were to determine whether PET SUV predicted survival and to identify an SUV cutoff value that stratifies patients into high- and low-risk groups.

Methods

Patients

From April 1998 to January 2005, all patients with MPM who underwent fluorodeoxyglucose (FDG)-PET scanning were identified from an institutional database. Clinical data were also obtained from a prospective institutional database. Data acquisition and analysis were approved by our institutional review board. The pathologic diagnosis of mesothelioma was confirmed by histologic review, relevant immunohistochemical analysis, and electron microscopy when necessary. All patients were considered for surgery if they had potentially resectable lesions identified by CT scan of the chest and upper abdomen and adequate cardiopulmonary function.

PET Evaluation

PET scans were acquired on dedicated BGO-based systems, including the GE Advance (Munich, Germany, Siemens HR+, and Siemens Biograph scanners (Erlangen, Germany). All patients were instructed to fast for 6 hours before the administration of FDG. After a minimum of 45 minutes post-injection of at least 10 mCi of FDG, whole-body emission scans were performed, with rod source-based transmission scans to allow for iterative reconstruction with segmented attenuation correction.

Patients were clinically staged by PET with the American Joint Commission on Cancer and the Union Internationale Contre le Cancer staging system.[4,5] The SUV was calculated according to standard methods based on the uptake of FDG in grams per milliliter corrected for the injected dose of FDG adjusted for the patient's weight. To calculate the maximal SUV in the tumor, we electronically threshholded the images so that only the hottest voxel of tumor was seen. A region of interest was drawn around the hottest voxel on the transaxial slice of the iteratively reconstructed images, and the SUV maximal value, corrected for body weight, was recorded.

Statistical Methods

A Wilcoxon test was used to compare the median SUV of the epithelioid and non-epithelioid tumor types. A hazard function plotting SUV versus predicted median survival time was constructed to visualize the functional relationship between SUV as a continuous variable and survival. The maximal chi-square method was used to identify an optimal SUV cutoff that separated patients into high- and low-risk groups.[6] Kaplan-Meier analysis was first performed on patients grouped by the accepted predictors of survival (stage and histologic subtype) and then performed on patients grouped by low and high SUV. Finally, Kaplan-Meier survival probabilities were assessed on patients with epithelioid tumor histology for all the 4 possible categories by using SUV as a dichotomous variable (high and low), as well as stages I and II and stages III and IV.

A Cox proportional hazard analysis was used to identify predictors of survival. The initial model was performed including all known predictors of survival. Insignificant variables were then dropped using a stepwise procedure, thus yielding the final model.

TABLE 1. Positron emission tomography standard uptake value in relation to tumor histology

Histology	n	Median SUV
Epithelioid	106	6.2
Mixed	27	7.8
Sarcomatoid	4	3.8

SUV, Standard uptake value.

Results

Demographic Information

A total of 137 consecutive patients with biopsy-proven, previously untreated MPM underwent FDG-PET scanning as part of their initial staging evaluation. These patients included 96 men and 31 women with a median age of 67 years (range 35-85 years). Some 106 patients (76%) had tumors of epithelioid histology, 27 of mixed subtype and 4 of sarcomatoid subtype. Three patients had stage I disease, 21 patients had stage II disease, 47 patients had stage III disease, and 56 patients had stage IV disease. Seventy patients underwent extrapleural pneumonectomy, 17 patients underwent pleurectomy/decortication, 31 patients underwent exploratory thoracotomy without resection, and 19 patients did not undergo any surgical procedures. The median follow-up of surviving patients was 24 months.

Standard Uptake Value in Relation to Tumor Histology

The median SUV of the epithelioid tumors was 6.2, which was not significantly different from tumors of mixed histology for which the median SUV was 7.8 ($P = .9$). Four sarcomatoid tumors had a median SUV of 3.8 (Table 1).

Standard Uptake Value in Relation to Survival

The estimated median survival for each value of SUV is shown in Figure 1.[7] The function demonstrates a near linear correlation of increasing SUV with poor survival. The max-

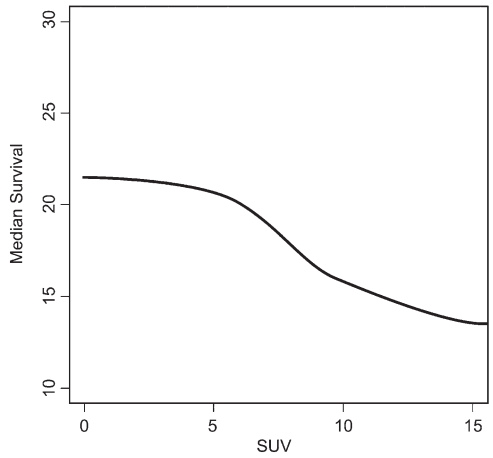

Figure 1. Hazard function plotting predicted median survival by SUV. *SUV*, Standard uptake value.

imal chi-square method selected an SUV of 10 as the best threshold to dichotomize patients into good or poor prognosis groups.

Survival Analysis

Known prognostic factors were assessed by the Kaplan-Meier survival method. Patients with epithelioid tumors had a significantly better overall survival than those with other tumor histology (median survival of 24 months vs 9 months, $P < .01$) (Figure 2). The survival of patients with stage I and II tumors was compared with that of patients with stage III and IV tumors. The median survival was 41 months for patients with stage I and II tumors and 17 months for stage III and IV tumors ($P = .02$) (Figure 3).

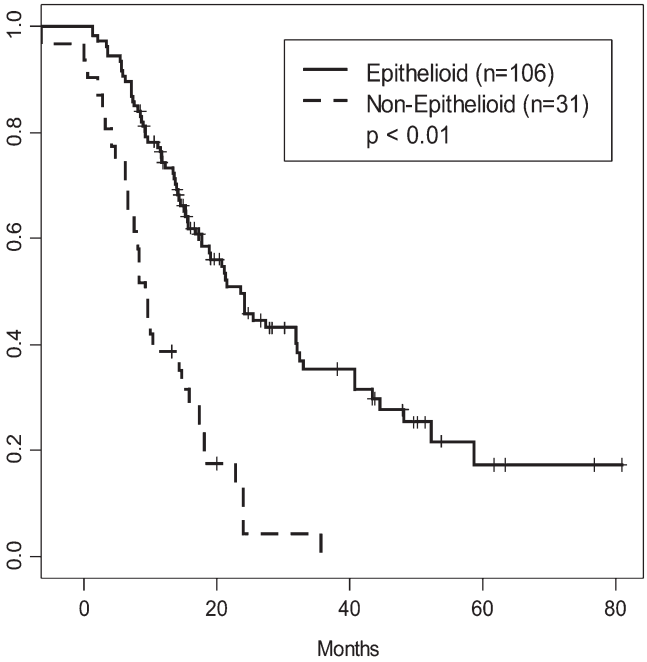

Figure 2. Overall survival by histology.

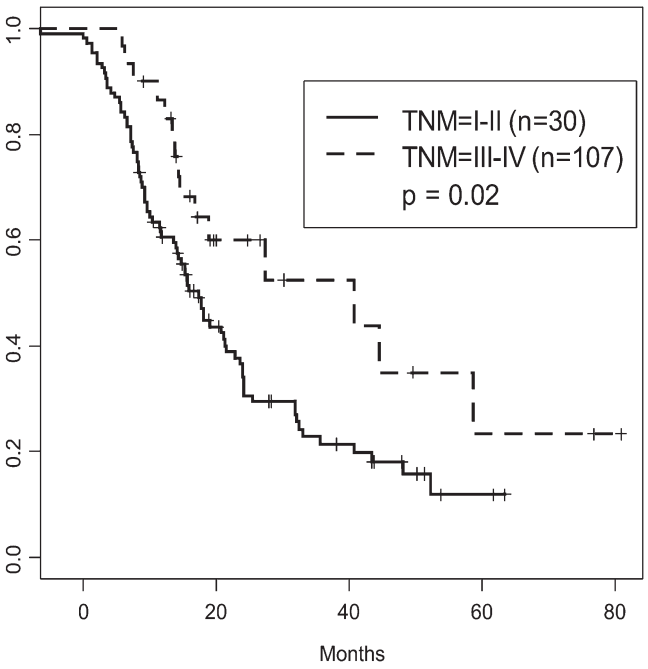

Figure 3. Overall survival by stage. *TNM*, Tumor node metastasis.

The influence of high and low SUV on survival was assessed (Figure 4). The median survival of patients with an SUV of less than 10 was 21 months compared with a median survival of 9.7 months in the group with an SUV of 10 or more. This difference was statistically significant by log rank test ($P = .02$).

An analysis was performed grouping patients with epithelioid and non-epithelioid tumor histology by high and low SUV (Figure 5). Overall survival was assessed across all 4 categories, and a statistically significant difference was observed ($P < .01$). Of note, 20% of the patients who had both a low SUV and epithelioid tumor histology are alive beyond 5 years. In contrast, none of the patients who had both a high SUV and non-epithelioid tumor histology were alive at 2 years.

A multivariable analysis was performed using the Cox proportional hazards method. The most commonly used predictors were included in this model along with SUV. However, type of operation, patient age and sex, and tumor laterality were not statistically significant predictors of survival. Our final model shows that patients whose tumors had an SUV of greater than 10 had a hazard ratio for death of 1.9 when compared with patients with an SUV of less than 10 ($P < .01$). Patients with non-epithelioid tumor histology had

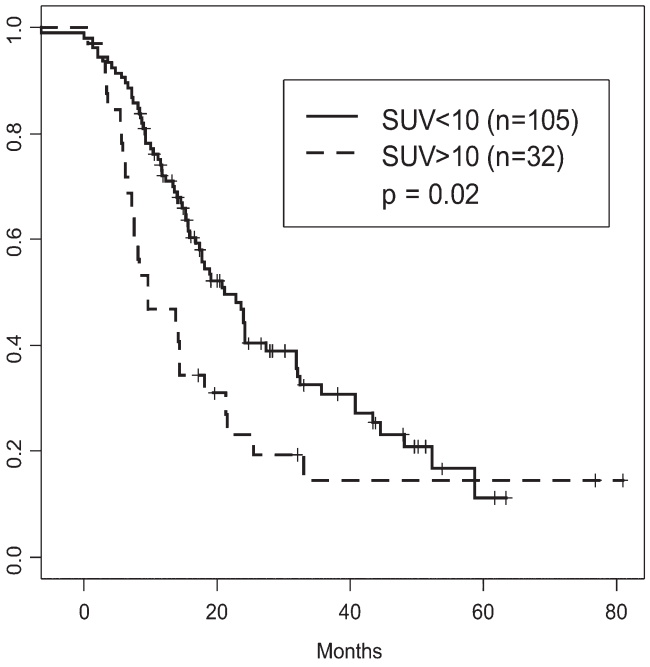

Figure 4. Overall survival by PET SUV. *SUV*, Standard uptake value.

a hazard ratio for death of 2.9 when compared with patients with epithelioid tumor histology ($P < .01$). Patients with stage III and IV tumors had a hazard ratio of 1.8 when compared with patients with stage I and II tumors ($P = .05$)

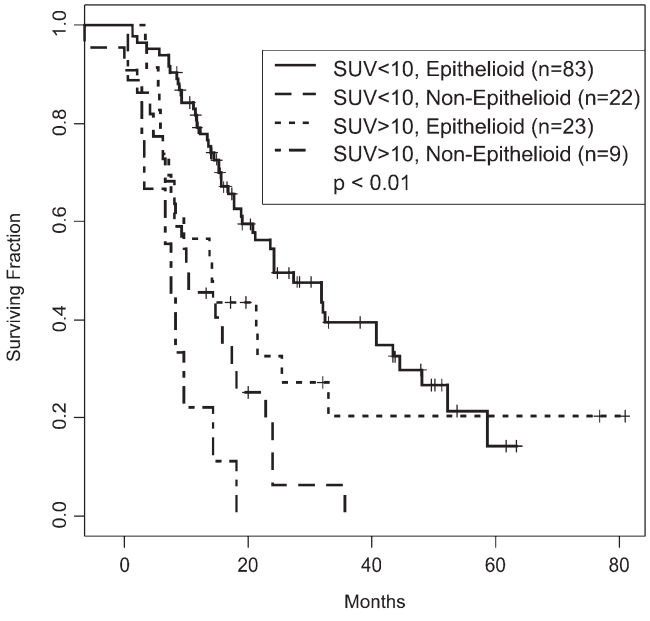

Figure 5. Overall survival by SUV and histology. *SUV*, Standard uptake value.

TABLE 2. Multivariable analysis of prognostic variables

	Hazard ratio	Confidence interval	*P* value
SUV > 10	1.9	1.2-2.9	<0.01
Non-epithelioid	2.9	1.8-4.5	<0.01
Stage III-IV	1.8	1.0-3.1	0.05

SUV, Standard uptake value.

(Table 2). When SUV is used as a continuous variable in the Cox model, the hazard ratio is 1.05 (95% confidence interval 1.02-1.08, $P < .01$). Each unit increase in SUV increases the risk of death by 5%.

Discussion

Current imaging modalities lack the ability to depict the extent of disease accurately in MPM. Previous studies have shown that CT and magnetic resonance imaging provide anatomic information that is imprecise in the preoperative staging of MPM.[1] Approximately 25% of patients undergoing attempt at surgical resection are found to be unresectable at the time of thoracotomy.[2] Several prior small studies (discussed next) investigated the utility of FDG PET scan in mesothelioma.

The first study included 22 patients with pathologically proven MPM.[8] The goal of this study was to evaluate whether PET could help distinguish between benign and malignant pleural disease. PET demonstrated a sensitivity of 92% (22/24) and a specificity of 75% (3/4). SUV data were available in only 18 patients. A survival analysis was not performed. The main point was that differentiating benign from malignant pleural disease still required pathologic confirmation; however, PET did seem to be useful in guiding surgical biopsy.

In 1999 the same group evaluated the prognostic value of FDG PET in 17 patients who had both SUV data and a diagnosis of mesothelioma.[9] A high SUV seemed to correlate with short survival in 6 deceased patients. However, surviving patients and a patient who died postoperatively were excluded from the analysis. Kaplan-Meier analysis using an arbitrary division at an SUV of 4 demonstrated a modest difference in survival; however, interpretation of these results is difficult because more than half (n = 9) of the patients in this series had non-epithelioid histology, which does not reflect the predominance of epithelioid histology among patients with mesothelioma. In addition, the majority of patients with a high SUV also had higher stage tumors and unfavorable histology (mixed or sarcomatoid). A multivariate analysis to control for the influence of treatment (surgical or medical), stage, and histology was not performed. Therefore, meaningful conclusions are difficult to draw from this study.

In 2000, Schneider and colleagues[10] evaluated the utility of PET scan in 18 patients evaluated preoperatively. SUV

data were available in only 9 patients. Two patients were excluded from surgery on the basis of extrathoracic disease. Although PET correctly identified 2 positive lymph nodes that were missed by CT scan, it falsely identified 2 nodes as being positive. This study did not evaluate the role of SUV in predicting survival, and the small number of patients limits the validity of the analyses.

In a previous article we reported scans between 1998 and 2002, 60 preoperatively and 3 to assess disease recurrence after surgery.[3] Increased FDG uptake was seen in all but 1 tumor, which was very early stage disease (IA). PET findings yielded sensitivities of only 19% and 11% for tumor stage and nodal status, respectively. However, a high SUV in the primary tumor correlated with the presence of N2 disease. PET correctly identified supraclavicular N3 or M1 disease in 6 patients. Although PET did not reliably identify the local extent of tumor or mediastinal nodal metastases, extrathoracic metastases were identified in 10%, thereby obviating inappropriate thoracotomy.

Several other small studies exist that investigated the use of PET scanning in mesothelioma but focused primarily on staging rather than survival.[11-13] Accurate patient selection for treatment has become increasingly important because of the development of improved chemotherapy regimens (eg, pemetrexed and cisplatin) and the need to decide which patients might benefit from induction therapy before resection. Our previous analysis in 63 patients showed a survival benefit for those with tumors with an SUV of less than 4. However, there were only 13 patients in this category.[14] Our current study is more than double the size of the prior study, and a similar analysis suggests that an SUV of 10 is a more robust value to dichotomize patients into high and low groups. As greater numbers of patients are studied in the future it is possible that 3 values may be found to separate patients with mesothelioma by prognosis: an SUV less than 4 and greater than 4, and an SUV less than 10 and greater than 10.

The demographic data in this study are consistent with those usually observed in MPM: The majority of patients were male, and most tumors were of epithelioid histology. The differences in survival between epithelioid and non-epithelioid subtypes and among tumor stages are consistent with previously published data.[15,16]

We found no significant difference in the median SUV between epithelioid and non-epithelioid tumors. Although the median SUV of pure sarcomatoid lesions seems lower, there were only 4 such patients in this series (all in advanced stage). Indeed, a previous study of 17 patients with MPM reported 1 sarcomatoid tumor with an SUV of 8.25.[8] Although there are too few patients with sarcomatoid MPM in this study to draw definitive conclusions regarding SUV levels in relationship to this histology, it seems that the SUV may reflect tumor biology independent of tumor histology.

PET SUV was not used to direct treatment; therefore, a selection bias based on SUV results should not exist. It seems that increasing SUV is a predictor of poor prognosis. This finding is not unexpected given the fact that SUV is a reflection of metabolic rate and nodal involvement, which usually correlates with more biologically aggressive tumors and poor survival. To date, histology and TNM stage have been the best predictors of survival. The final Cox model also revealed that patients with an SUV greater than 10 had a 1.9 times greater risk of death than those with an SUV less than 10, that non-epithelioid histology had a 2.8 times greater risk of death than epithelioid histology, and that stage III and IV tumors had a 1.8 times greater risk of death than stage I and II tumors. On the basis of these findings, it seems useful to stratify future clinical trials by SUV, histology, and stage.

Conclusions

PET seems to be a useful tool for staging and predicting the prognosis of MPM. Previous studies have shown the utility of PET in identifying occult metastatic disease,[3] and this study demonstrates the ability to stratify patients for survival when a maximal SUV of 10 is chosen to separate patients into good and poor prognosis groups. When SUV, histology, and stage are taken together, further separation of subgroups may be observed that reflect significant differences in survival, low SUV, epithelioid histology, and low stage predicting the best survival. Although validation of these results in larger studies is needed, it now seems that the combination of SUV, histology, and stage provide a convenient and clinical method of identifying good and poor prognosis patient groups in MPM.

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