High SUVmax on FDG-PET Indicates Pleomorphic Subtype in Epithelioid Malignant Pleural Mesothelioma

Supportive Evidence to Reclassify Pleomorphic as Nonepithelioid Histology

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Background: We have recently proposed to reclassify the pleomorphic subtype of epithelioid malignant pleural mesothelioma (MPM) as nonepithelioid (biphasic/sarcomatoid) histology because of its similarly poor prognosis. We sought to investigate whether preoperative maximum standardized uptake value (SUVmax) on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) correlates with histologic subtype in MPM.

Methods: Clinical data were collected for 78 patients with MPM who underwent preoperative FDG-PET. We retrospectively classified the epithelioid tumors into five subtypes: trabecular, tubulopapillary, micropapillary, solid, and pleomorphic. Tumors were categorized by SUVmax into two groups: low (<10.0) and high (≥10.0).

Results: The median overall survival of epithelioid tumors with high SUVmax (n = 12) was significantly shorter (7.1 months) than that of epithelioid tumors with low SUVmax (n = 54, 18.9 months, $p < 0.001$) and comparable to nonepithelioid tumors (n = 12, 7.2 months). Epithelioid tumors with pleomorphic subtype (n = 9) had marginally higher SUVmax (mean ± SD: 10.6 ± 5.9) than epithelioid nonpleomorphic subtype (n = 57, 6.5 ± 3.2, p = 0.050), and were comparable to that of nonepithelioid tumors (n = 12, 9.1 ± 4.8). Among the epithelioid tumors with high SUVmax (n = 12), 50% (n = 6) showed pleomorphic subtype. In contrast, among epithelioid tumors with low SUVmax (n = 54), 6% (n = 3) showed epithelioid pleomorphic subtypes (p = 0.001). A positive correlation between mitotic count and SUVmax was observed (r = 0.30, p = 0.010).

Conclusions: Pleomorphic subtype of epithelioid MPM showed higher SUVmax than the epithelioid nonpleomorphic subtype and was similar to nonepithelioid histology. Preoperative SUVmax on FDG-PET in epithelioid MPM can indicate patients with pleomorphic subtype with poor prognosis, supporting their reclassification as nonepithelioid.

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Diffuse malignant pleural mesothelioma (MPM) is an uncommon but aggressive tumor with median survival of 9 to 12 months despite multimodal therapy (surgery, chemotherapy, and radiation therapy).[1] Histology and tumor, node, metastases (TNM) stage are the only standard predictors of survival.[2–4] Although epithelioid MPM has a better prognosis than nonepithelioid (biphasic and sarcomatoid) tumors, prognosis within epithelioid histology is variable. We have recently reported the prognostic utility of histologic subtyping in epithelioid MPM, and proposed that the pleomorphic subtype should be reclassified as nonepithelioid histology because of similar clinical outcomes.[5] However, to the best of our knowledge, the biological reasons for this similarity in prognosis remain unexplored.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a standard radiographic tool in clinical practice, which assesses the metabolic activity of tumor cells.[6–8] In addition to facilitating prognosis, maximum standardized uptake value (SUVmax) on FDG-PET reflects histology in lung cancer. SUVmax is significantly lower in lung adenocarcinoma than in squamous cell carcinoma.[9–11] To investigate the biology of the pleomorphic subtype in epithelioid MPM, our aim in this study was to determine the correlation between preoperative SUVmax and histologic subtypes of epithelioid MPM. In addition, we investigated the correlation between SUVmax and tumor proliferation on the basis of mitotic count.

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PATIENTS AND METHODS

Patients

Tumor slides were available for 148 patients who received a diagnosis of MPM between 1998 and 2009 at Memorial Sloan-Kettering Cancer Center (MSKCC). Of these, 78 patients underwent FDG-PET before surgical resection. Fifty of 78 patients (64%) underwent PET scans at MSKCC. Seventy-one patients (91%) were not treated with any chemotherapy before the PET scans. Clinical information was collected through a database maintained by the Thoracic Service, Department of Surgery at MSKCC. Institutional review board approval was obtained at MSKCC before the study began. There were 66 patients with epithelioid tumors and 12 with nonepithelioid tumors (six biphasic and six sarcomatoid). Clinical variables recorded in the prospectively maintained database included age, sex, laterality, TNM stage, and surgical procedure. TNM staging was based on the reported imaging findings, the surgeon's intraoperative findings, and the pathologic evaluation of the resected specimens using the 6th edition of the *American Joint Commission on Cancer Staging Manual*.[12] All patients were followed until date of death or last follow-up.

Pathologic diagnosis was based on standard histologic, histochemical, and immunohistochemical criteria.[13–15] As a positive marker of immunohistochemistry for MPM, we used standard immunohistochemical markers including calretinin, WT-1, cytokeratin 5/6, and D2-40. As negative markers for MPM, we used carcinoembryonic antigens, CD15, B72.3, BerEP4, and thyroid transcription factor-1. In addition, pathologic diagnosis was correlated with gross distribution of the tumor and absence of an intrapulmonary lesion on radiologic imaging.

Technique of FDG-PET

The following technique was used for PET scans performed at MSKCC. Patients received 10 to 15 mCi (370–555 MBq) of FDG intravenously. Patients were instructed to fast for 6 hours or more before injection; plasma-glucose levels were measured before imaging. Approximately 60 minutes after injection, torso images were acquired with either GE Advance (GE Medical Systems, Waukesha, WI) or HR plus (Siemens/CTI, Knoxville, TN) PET scanners. Beginning in November 2001, studies were also acquired on hybrid PET/computed tomography (CT) imaging systems, including the Biograph (Siemens/CTI, Nashville, TN) and Discovery LS (GE Medical Systems, Waukesha, WI). The Biograph data was acquired in three-dimensional (3D) mode. All the other scanners used two-dimensional (2D) PET image acquisition. Discovery LS incorporates a PET Advance tomograph, and Biograph incorporates an HR plus PET tomograph. For PET/CT, a low-dose CT scan was acquired first to allow for PET attenuation, correction, and anatomic localization of PET abnormalities. Each PET dataset was reconstructed for image display using iterative algorithms, with and without attenuation correction. Experienced radiologists with specific expertise in nuclear medicine interpreted PET imagery at the time of diagnosis. Uptake of FDG by tumor was quantified by PET region-of-interest analysis with the SUVmax. SUV was calculated as:

$$\text{SUV} = \frac{(\text{Decay-corrected activity[kBq]/tissue volume [ml]})}{(\text{Injected-FDG activity [kBq]/body weight [g]})}$$

Histologic Evaluation

All available hematoxylin and eosin–stained slides (median 7, range, 1–43 slides/case) of epithelioid MPM lesions were reviewed by a single pathologist (K.K.) for the purpose of this study, using an Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard eyepiece of 22 mm diameter; problem cases were reviewed by two pathologists (W.D.T. and K.K.). Histologic classification for epithelioid MPM was done according to the 2004 World Health Organization criteria (<10% sarcomatoid component).[15] Epithelioid MPM comprised one or more of five histologic patterns,[5] which were recorded in 5% increments: (1) trabecular, (2) tubulopapillary, (3) micropapillary, (4) solid, and (5) pleomorphic. Tumors were classified as pleomorphic subtype when cytologic pleomorphism comprised at least 10% of the tumor.[5] The remaining tumors were classified according to the predominant histologic patterns.

Mitoses were evaluated using high-power-field (HPF) at ×400 magnification (0.237 mm^2 field of view) in the 50 HPF areas with the highest mitotic activities,[16–19] and counted as an average of mitotic figures per 10 HPF. In the cases in which only small areas of viable tumor were available for review, the best attempt was made to assess the equivalent of 10 full HPFs of viable tumor for mitosis counting.[17]

We also recorded the following histological factors: presence of lymphatic or vascular invasion, necrosis (%), fibrosis (%), and myxoid change (%).

Statistical Analysis

Associations between clinicopathologic variables and histologic findings were analyzed using a Fisher's exact test for categorical variables and Wilcoxon test for continuous variables. Overall survival (OS) after surgery was estimated using the Kaplan-Meier method, with patients censored if they were alive at the time of last follow-up. An analysis of time to recurrence (TTR) was restricted to patients who underwent surgery that was deemed to be a complete resection. Nonparametric group comparisons were performed using log-rank test. All p values were based on two-tailed statistical analysis and a p value < 0.05 was considered to indicate statistical significance. All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC).

RESULTS

Clinicopathologic Demographics and Their Associations With OS

The clinicopathologic profile of 66 patients with epithelioid MPM is outlined in Table 1. Median age was 63 (range, 29–81); and 65% (n = 43) were men. The tumor involved the left pleura in 50% (n = 33) of the cases. Three patients (5%) were stage I, 16 (24%) were stage II, 33 (50%) were

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