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Prognostic value of pretreatment volume-based quantitative ^{18}F-FDG PET/CT parameters in patients with malignant pleural mesothelioma

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ABSTRACT

Purpose: To investigate the relationships between pretreatment volume-based quantitative ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) parameters and overall survival (OS) in patients with malignant pleural mesothelioma (MPM).
Materials and methods: We retrospectively reviewed data from 201 MPM patients, of whom 38 underwent surgical resection, and calculated the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), including primary tumors and nodal or distant metastatic lesions, on pretreatment ^{18}F-FDG PET/CT. Relationships between clinicopathological factors (age, sex, performance status, European Organization for Research and Treatment of Cancer [EORTC] score, histological subtype, TNM stage, and treatment strategy), volume-based quantitative PET/CT parameters, and OS were evaluated using a Cox proportional hazards model and log-rank test.
Results: The median follow-up was 15 months (range, 1–96 months; median, 17 months). In a univariate analysis of all patients, older age ($p < 0.05$), high EORTC score ($p < 0.001$), non-epithelioid histological subtype ($p < 0.001$), high T stage ($p < 0.001$), positive N/M status ($p < 0.05$, $p < 0.001$), advanced TNM stage ($p < 0.001$), non-surgical treatment ($p < 0.001$), and high SUVmax ($p < 0.001$), MTV ($p < 0.001$), or TLG ($p < 0.001$) were associated with significantly shorter OS. A multivariate analysis confirmed non-epithelioid subtype (hazard ratio [HR]: 1.69, 95% confidence interval [CI]: 1.14–2.48; $p < 0.05$), non-surgical treatment (HR: 0.58, 95% CI: 0.34–0.95; $p < 0.05$), and high TLG (HR: 1.97, 95% CI: 1.14–3.44; $p < 0.05$) as independent negative predictors.
Conclusions: Pretreatment volume-based quantitative ^{18}F-FDG PET/CT parameters, especially TLG, could serve as potential surrogate markers for MPM prognosis.

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare, aggressive neoplasm originating from mesothelial cells in the pleural cavity's inner lining. MPM tumors are highly chemo- and radioresistant and associated with an especially poor prognosis, with a median survival of <1 year [1]. Multimodality therapy (combined surgery, chemotherapy, and radiotherapy) was first introduced in the 1990s and has improved survival in select patients [2–4]. However, interindividual variability in response to multimodality therapy remains challenging [5]. Most patients present with advanced disease, so radical surgery is rarely indicated. Most patients are candidates for chemotherapy during the disease course. Therefore, prognostic information is important to individual patients and families and to stratify patients in clinical trials. Several potential prognostic factors have been reported, including sex, Eastern Cooperative Oncology Group performance status, white blood cell count,

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and sarcomatoid histological subtype [6]. However, limited data on prognostic factors have been reported using imaging.

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is based on increased glucose uptake by malignant cells and has been advocated for non-invasively assessing the biological aggressiveness of tumors and factors predicting patient outcomes. A high maximum standardized uptake value (SUVmax) in MPM has been identified as an independent poor prognostic factor [7–9]. Recent reports [10–15] identified some volume-based quantitative ^{18}F FDG PET/computed tomography (CT) parameters (metabolic tumor volume [MTV] and total lesion glycolysis [TLG]) as independent predictors. However, these reports had small sample sizes (range, 13–131) and did not previously stratify patients into surgical and non-surgical (chemotherapy) groups [10–15]. Therefore, the true clinical utility of volume-based quantitative ^{18}F FDG PET/CT parameters is unknown.

Here, we aimed to identify whether volume-based quantitative ^{18}F FDG PET/CT parameters predicted overall survival (OS) in a large MPM patient cohort.

2. Materials and methods

2.1. Patients

We retrospectively analyzed 254 newly diagnosed MPM patients who underwent whole-body ^{18}F FDG PET/CT for initial staging before treatment, including pleurodesis, between June 2007 and December 2014. Patients who underwent ^{18}F FDG PET/CT examinations using another PET/CT machine (n = 40) or were lost to follow-up (n = 13) were excluded, for a final study population of 201 patients (165 men and 36 women; median age, 66 years; range, 31–84 years). All patients also underwent routine diagnostic chest and abdominal CT. Contrast-enhanced CT was performed in 78.6% (n = 158/201) of patients. Clinical staging and treatment were decided based on information derived from these examinations at the Thoracic Tumor Board Conference of the Hyogo College of Medicine College Hospital (Hyogo, Japan). The panel consisted of respiratory and internal medicine physicians, thoracic surgeons, radiation oncologists, and radiologists. Disease stage was classified according to the TNM staging system of the International Mesothelioma Interest Group [16]. Patient demographic data and clinicopathological parameters, including histological subtype, treatment strategies, and OS, were collected.

The study was granted Institutional Review Board approval, and the requirement for informed, written consent was waived.

2.2. Therapeutic regimens

Radical surgery, including extra-pleural pneumonectomy (EPP) and pleurectomy/decortication (P/D), was performed in patients with resectable Stage I–III MPM who could tolerate aggressive surgery *(4)*. Typical trimodality treatment included induction chemotherapy, surgery, and adjuvant radiotherapy [3]. Radical surgery was performed within 42 days following the last dose of induction chemotherapy (3 cycles of pemetrexed [500 mg/m^2] and cisplatin [60–75 mg/m^2] for EPP and 75 mg/m^2 for P/D). P/D was attempted for local diseases from 2013 to present. Adjuvant hemithoracic radiotherapy was performed within 12 weeks after surgery in patients who underwent EPP *(3)*. All patients were treated with three-dimensional conformal radiotherapy (total dose, 54 Gy in 30 fractions). The clinical target volume included the entire ipsilateral hemithorax pleural cavity and chest-wall incisions. The planning target volume included the clinical target volume plus a 5-mm margin in all directions. The dose-volume planning objectives defined for organs at risk were as follows: A V_5 of <50% and a V_{20} of <7% in the contralateral lung (where Vx represents the percentage of the volume receiving X Gy), a liver V_{20} of <50%, a heart V_{45} of <50%, a kidney V_{15} of <20%, and a maximum spinal cord irradiation dose of <48 Gy. Adjuvant chemotherapy (including pemetrexed) was administered post-surgery in patients who underwent P/D.

In patients who were not candidates for surgical resection, chemotherapy was typically administered with pemetrexed and cisplatin. Palliative radiotherapy was administered when indicated.

During follow-up, physical examinations, ^{18}F FDG PET/CT, CT, or brain magnetic resonance imaging was performed to detect disease recurrence and/or metastasis. Patients with suspected recurrence were treated as indicated clinically.

2.3. ^{18}F –FDG PET/CT

The imaging techniques have been described previously [17,18]. Briefly, all ^{18}F FDG PET/CT scans were performed using a PET/CT scanner combined with a 16-multidetector CT (Gemini GXL 16; Philips Medical Systems, Eindhoven, The Netherlands) and gadolinium oxyorthosilicate detectors. Patients fasted for 5 h before the scan and were administered 4.0 MBq/kg body weight of ^{18}F FDG. Static emission images were obtained ~60 min after injection. For attenuation correction and anatomic localization, helical whole-body CT scans were obtained. Immediately after CT scan completion, PET images of the region extending from the head to the mid-thigh and the mid-thigh to the tips of the toes were acquired for 90 s/bed position and 30 s/bed position, respectively, employing a variable sampling method. Subsequent three-dimensional images at 13–14 bed positions for 90 s each and 6 bed positions for 30 s each per patient were taken, thus acquiring 22–24 min of emission scans per patient. Patients breathed normally during PET acquisitions. The transaxial field of view and matrix size of the PET images reconstructed for fusion were 576 mm and 144 × 144 mm, respectively. Attenuation-corrected PET images were reconstructed using a line-of-response row-action maximum likelihood algorithm (n/a subsets, 2 iterations).

2.4. Imaging analysis

All ^{18}F FDG PET/CT images were reviewed in consensus by two experienced observers (A, a double-board-certified nuclear medicine physician and radiologist with 10 years of experience in oncologic ^{18}F FDG PET/CT and CT imaging and B, a board-certified radiation oncologist with 8 years of experience, including 3 in general radiology) with knowledge of consensus in Tumor Board Conference guidelines.

The relevant imaging biomarker measurements obtained from PET were SUVmax, MTV, and TLG. SUVmax was defined as the maximum SUV within the tumor, MTV as the FDG-avid tumor volume, and TLG as MTV × SUVmean, where SUVmean represents the mean SUV.

SUVmax, MTV, and TLG, as well as SUVmean, of whole-body tumors were measured using the PET Edge tool with manual adjustment in MIM Maestro^{TM} version 6.5.2 (MIM Software Inc., Cleveland, OH, USA), which utilizes gradient-based tumor segmentation [19–22]. SUVmax, SUVmean, MTV, and TLG within the bounding region were automatically calculated (Fig. 1).

SUV and volume measurements of whole-body tumors were exported to Microsoft Excel. SUVmax was defined as the maximum activity concentration in the tumor/(injected dose/body weight) and SUVmean as the mean concentration of ^{18}F FDG in the tumor/(injected dose/body weight). Output parameters included SUVmax, SUVmean, MTV, and TLG of individual tumors. Whole-body SUVmax was defined as the maximum SUVmax of all tumors,