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Effect of adipose tissue volume on prognosis in patients with non-small cell lung cancer

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ABSTRACT

Objective: This study evaluated the relationship between adipose tissue volume and survival in patients with non-small cell lung cancer (NSCLC).

Methods: We retrospectively included 171 NSCLC patients who underwent staging ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and subsequent curative surgical resection or definite chemoradiotherapy. Maximum standardized uptake value (SUV) of lung cancer normalized by lean body mass (SULmax) and volume and mean SUV of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were derived from PET/CT images. The relationships of volume and mean SUV of SAT and VAT with survival were assessed.

Results: Of the 171 patients, 79 (46.2%) experienced disease progression and 61 patients (35.7%) died during follow-up. SULmax had significant negative correlation with SAT volume ($p = 0.003$), but not with VAT volume and mean SUV of SAT and VAT ($p > 0.05$). On multivariate analysis, advanced TNM stage and high SULmax were significantly related with worse progression-free survival (PFS) and high SAT volume was significantly associated with better PFS ($p < 0.05$). Patient subgroups of high SULmax (> 4.6) and low SAT volume ($< 75\ cm^3$) had the highest disease progression rate of 61.7%, while other patient subgroups showed rates between 21.1 and 33.3%. SAT volume was significantly related with overall survival on univariate analysis, but failed to show significance on multivariate analysis. Only TNM stage was an independent prognostic factor for overall survival.

Conclusion: SAT volume had significant favorable effect on PFS in patients with NSCLC.

1. Introduction

The prevalence of obesity has increased globally over the past several decades and has become a significant public health problem. There is growing evidence that obesity elevates the risk of cancer and progression via metabolic and inflammatory mediators and adipose inflammation [1]. In various kinds of cancers including colon, breast, ovary, and pancreatic cancers, obese patients have a worse prognosis than normal weight individuals [2–4]. In contrast to most kinds of malignancies, recent studies with non-small cell lung cancer (NSCLC) and renal cell carcinoma have documented favorable prognosis in obese patients compared to normal weight/underweight patients, which is referred to as obesity paradox [2,5–8]. The exact mechanisms of the obesity paradox in NSCLC remain debatable. Differences in the biological characteristics of tumors and nutritional status between obese and normal weight patients have been speculated as causes of the phenomenon [5,9]. In renal cell carcinoma, tumors in obese patients are reported to display less aggressive features on gene expression analysis [8].

Currently, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a widely used non-invasive imaging modality for staging, assessing treatment response, and predicting prognosis in patients with NSCLC [10–13]. High FDG uptake in NSCLC is related with worse prognosis; however, consistent with the obesity paradox, the prognostic value of tumor FDG uptake is also affected by the body mass index (BMI) [9]. Furthermore, in recent

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studies, FDG uptake of adipose tissue, which reflects glucose metabolism in adipose tissue, showed significant relationship with tumor stage, FDG uptake of primary tumor, and clinical outcome [14–16]. Considering the significant association between BMI and NSCLC prognosis, the amount and FDG uptake of adipose tissue might influence prognosis in patients with NSCLC. However, no published study has evaluated the clinical implication of the volume and FDG uptake of adipose tissue in NSCLC.

In the present retrospective study, we measured volume and FDG uptake of subcutaneous (SAT) and visceral adipose tissue (VAT) separately and investigated their relationship with clinical outcomes in patients with NSCLC.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of our university and followed the principles of the Declaration of Helsinki. Because of the retrospective nature of the study, the requirement to obtained informed consent was waived.

The electronic medical records of all patients with NSCLC who underwent a pre-treatment PET/CT scan as a part of their routine staging procedure from March 2012 to May 2015 were retrospectively reviewed. Among these patients, we recruited those with a primary tumor size > 1 cm on staging contrast-enhanced chest CT and who underwent curative surgical resection or definite chemoradiotherapy. Patients who had a distant metastasis on pre-treatment imaging studies or a history of another malignancy were excluded. A total of 171 patients met all inclusion criteria and were enrolled in the present study. They all underwent a pre-treatment work-up including a physical examination, blood tests including serum cholesterol and triglyceride levels, contrast-enhanced chest CT, brain magnetic resonance imaging, and FDG PET/CT. BMI was defined as weight divided by the square of height, and was calculated for each patient using weight and height measured at the time of PET/CT scan. According to the recommendation of the World Health Organization Expert Consultation for Asian populations, normal weight, overweight, and obesity were defined as BMI < 23.0 kg/m^2, 23.0–24.9 kg/m^2, and ≥25.0 kg/m^2, respectively [17].

Based on the results of pre-treatment examinations, T and N stages of the patients were assessed according to the seventh edition of the American Joint Committee on Cancer Staging guidelines. Curative resection or chemoradiotherapy was performed according to the clinical stage and condition of the patient. The median interval between FDG PET/CT and initial treatment was 6 days (range, 1–30 days). In patients who received curative surgical resection, lobectomy, bilobectomy, or pneumonectomy with systematic lymph node dissection was performed and histopathological stage was assessed. In patients treated with chemoradiotherapy, stereotactic body radiotherapy with a total cumulative dose of 45–65 Gy was performed, and chemotherapy was performed concurrently with or sequentially after radiotherapy. The chemotherapy consisted of cisplatin or carboplatin with paclitaxel- or pemetrexed-based doublet therapy. After the initial treatment, follow-up examinations including blood tests, chest radiography, and contrast-enhanced chest CT were performed every 3 months for the first 3 years and every 6 months thereafter. In cases with abnormal findings on follow-up studies, further diagnostic studies and/or histopathological confirmation were performed to confirm disease progression.

2.2. FDG PET/CT scan

FDG PET/CT scans were performed using a dedicated PET/CT scanner (Biograph mCT 128 scanner, Siemens Healthcare, Knoxville, TN, USA). All patients were instructed to fast at least 6 h and had a blood glucose level of < 150 mg/dL before FDG injection. PET/CT scans were performed from the skull base to the proximal femur approximately 60 min after the intravenous injection of 4.07 MBq/kg of FDG. Initially, low-dose CT scan without contrast-enhancement was performed at 100 mA and 120 kVp. Subsequently, PET data were acquired at a 1.5 min for each bed position. PET images were reconstructed with an iterative algorithm using TrueX and time-of-flight reconstruction with attenuation correction (two iterations and 21 subsets).

2.3. FDG PET/CT image analysis

FDG PET/CT images of all patients were retrospectively analyzed using a United States Food and Drug Administration-approved DICOM viewer (OsiriX MD for Mac OS; Pixmeo, Geneva, Switzerland) without knowledge of clinical outcomes. Initially, a spheroid-shaped volume of interest (VOI) was drawn over the primary tumor lesion and the maximum standardized uptake value (SUV) of primary cancer lesion was calculated. SUV normalized by body weight is strongly affected by body weight. Accordingly, we used SUV normalized by lean body mass (SUL), which is more consistent across a population, to representing the FDG uptake of primary cancer lesion [18,19]. Lean body mass for each patient was calculated with using formulas of James [20]. For men, lean body mass was calculated as $1.1 \times (\text{body weight}) - 128 \times ((\text{body weight}) / (\text{height}))^2$, and for women, lean body mass was calculated as $1.07 \times (\text{body weight}) - 148 \times ((\text{body weight}) / (\text{height}))^2$. Maximum SUL of the primary cancer lesion (SULmax) was calculated by multiplying maximum SUV by the lean body mass divided by body weight.

Afterwards, the volume and mean SUV of SAT and VAT were measured (Fig. 1). On three consecutive slices of CT images at the level of the L4 spine, the adipose tissue area was automatically computed using an attenuation range of −50 to −200 Hounsfield units (HU) [21–23]. SAT and VAT volumes were separately measured in cm^3. SAT was defined as extra-peritoneal fat tissue between skin and muscle, and VAT was defined as intra-abdominal fat tissue [21]. The areas of SAT and VAT on CT images were exported to corresponding PET images, and the mean SUV of SAT and VAT were measured. For measuring FDG uptake of VAT, areas with FDG uptake of vessels, bowel and urine were manually removed.

2.4. Statistical analyses

For continuous variables, the Kolmogorov-Smirnov test was performed to assess the normalcy of the data distribution. Pearson's correlation coefficients were calculated to evaluate the relationship between variables. The prognostic values of the variables for progression-free survival (PFS) and overall survival (OS) were assessed using a Cox proportional hazards regression test in univariate and multivariate analyses. Only variables that showed significance ($p < 0.05$) on univariate analysis were included in the multivariate analysis. All continuous variables in the survival analysis were grouped into two categories according to the optimal cut-off values determined by maximally selected chi-square statistics. Survival time was calculated from the time of initial treatment until disease progression (for PFS) or death (for OS) occurred. Disease progression was defined as the detection of newly developed metastatic lesion on follow-up imaging examinations, or a ≥20% increase in the size of a known malignant lesion. For estimation of survival curves of variables, the Kaplan-Meier method was used to calculated cumulative PFS and OS. Disease progression rates between groups were compared using chi-square test. Analyses were performed using R 2.13.0 software (The R Foundation for Statistical Computing, Vienna, Austria) and MedCalc Statistical Software version 17.4.4 (MedCalc Software, Ostend, Belgium). A *P*-value < 0.05 was considered significant.