Prognostic Value of the Quantitative Metabolic Volumetric Measurement on 18F-FDG PET/CT in Stage IV Nonsurgical Small-cell Lung Cancer

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Rationale and Objectives: Stage IV non–small-cell lung cancer (NSCLC) consists of a heterogeneous group of patients with different prognoses. We assessed the prognostic value of baseline whole body tumor burden as measured by metabolic tumor volume (MTV), total lesion glycolysis (TLG), and standardized uptake values (SUV_{max} and SUV_{mean}) of all tumors in nonsurgical patients with Stage IV NSCLC.

Materials and Methods: Ninety-two consecutive patients with newly diagnosed Stage IV NSCLC who had a pretreatment F-18 fludeoxyglucose positron emission tomography/computed tomography scan were retrospectively reviewed. The MTV, TLG, SUV_{mean}, and SUV_{max} of whole-body (WB) tumors were measured with the MIMvista workstation with manual adjustment.

Results: There was a statistically significant association between overall survival (OS) and ln(MTV)/ln(TLG) at the level of WB tumor burden (MTV_{WB}) and of primary tumor (MTV_T). The hazard ratio (HR) for a 1-unit increase of ln(MTV_{WB}) and ln(MTV_T) before and after adjusting for age and gender was 1.48/1.48 (both $P < .001$) and 1.25/1.25 ($P = .006, .007$), respectively. The HR for a 1-unit increase of ln(TLG_{WB}) and ln(TLG_T) before and after adjusting for age and gender was 1.37/1.37 (both $P = .001$) and 1.19/1.19 ($P = .001, .017$), respectively. There was no statistically significant association between OS and ln(SUV_{max}) and ln(SUV_{mean}) at WB tumor burden, primary tumor, nodal metastasis, or distant metastasis ($P > .05$). There was low interobserver variability between two radiologists with concordance correlation coefficients of 0.90 for ln(MTV_{WB}) and greater than 0.90 for SUV_{maxWB}, SUV_{meanWB}, and ln(TLG_{WB}).

Conclusion: Baseline WB metabolic tumor burden, as measured with MTV and TLG, is a prognostic measurement in patients within Stage IV NSCLC with low interobserver variability. This study also suggests pretreatment MTV and TLG measurements may be used to further stratify patients with Stage IV NSCLC and are better prognostic measures than SUV_{max} and SUV_{mean} measurements.

Key Words: F-18 Fludeoxyglucose (FDG); lung cancer; tumor burden.

Lung cancer is the most common cause of cancer death in the world (1) and the second most common cancer in both men and women, and number one cause of cancer-related deaths in the United States. In the United States in 2010, 157,300 people were projected to die from lung cancer, which is more than the number of deaths from colon and rectal, breast, and prostate cancer combined (2). Non–small-cell lung cancer (NSCLC) comprises 80%–85% of all lung cancer cases (3).

Stage IV non–small-cell lung cancer (NSCLC) consists of a heterogeneous group of patients who are often treated with different modalities (4,5). Based on the comprehensive analysis of 67,149 patients with Stage IV NSCLC as defined by the 6th edition of the Union International Contra la Cancrum (UICC)/American Joint Committee on Cancer (AJCC) staging system for NSCLC enrolled in the Surveillance, Epidemiology, and End Results (SEER) program, the patients with distant metastasis have worse prognosis (6). The patients with tumor nodules on both sides of the chest have worse prognosis than those with separate ipsilateral tumor nodules in different lobes. The nodal status is a strong determinant of survival.

Modern positron emission tomography (PET)/computed tomography (CT) scanners provide three-dimensional (3D) metabolic volumetric images. Whole-body metabolic tumor burden (MTB_{WB}) as measured with metabolic tumor volume (MTV) (7,8) and total lesion glycolysis (TLG) of tumors (9) has been developed because it incorporates both metabolic activity and tumor volume. The MTV is the tumor volume on PET measured with a segmentation technique (4,5,7,8,10,11), whereas TLG can be calculated by multiplying the mean standardized uptake value (SUV_{mean}) by the MTV (9). A study with 19 with lung cancer patients (18 with NSCLC and 1

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with small-cell lung cancer) found that the baseline total body MTV measured semiautomatically is a statistically significant prognostic index and better than SUV_{max} and SUV_{mean} in the prediction of patient outcome (7). Additionally, in multiple studies in other types of cancer, the manual or semiautomatic measurement of the baseline MTV has been shown to be better than the SUV in predicting patients' prognosis in small cell carcinoma (12), head and neck cancer (13–15), esophageal cancer (16), and thyroid cancer (17) in locally advanced stages with or without metastasis. It has also been demonstrated that baseline gross tumor volume determined by manual contouring on CT images as part of 3D conformal radiation treatment planning predicts for overall and cause-specific survival as well as local tumor control (18).

Until now, NSCLC staging has been based primarily on surgical resectability of the tumor, no metabolic volumetric information has been used from PET/CT in the UICC/AJCC staging system for NSCLC (4,5). Only a one-dimensional measurement from CT is required for the primary tumor and no dimensional measurement from PET (elevated uptake or not) is required for lymph node or distant metastasis in this staging system. This is partly because the measurement the metabolic tumor burden manually or semiautomatically is time-consuming and therefore it is not clinically practical, especially in Stage IV NSCLC. It is also because the usefulness of this time-consuming measurement has not been fully determined. However, technical and medical progress has led to improvement in neoadjuvant chemoradiation therapy for Stage IV NSCLC and it is now one of the clinically significant therapeutic options (19). Therefore identification of prognostic factors for the patient population having Stage IV NSCLC before therapy is needed.

With development of computer-aided diagnosis (CAD), it is now feasible to create software to semiautomatically detect and quantify all tumors in whole-body PET/CT scans and therefore compute metabolic tumor burden (MTB_{WB}) efficiently (20). However, since the development of such a sophisticated CAD tool is a major undertaking, it is necessary to further determine the prognostic value of metabolic tumor burden in a large patient population with same tumor-node-metastasis (TNM) stage because the stage of disease is already known to provide prognostic information. Here we measured the MTV of whole-body tumor (MTV_{WB}), primary tumor (MTV_T), nodal metastasis (MTV_N), and distant metastasis (MTV_M); and the TLG of whole-body tumor (TLG_{WB}), primary tumor (TLG_T), nodal metastasis (TLG_N), and distant metastasis (TLG_M) semiautomatically with commercially available PET/CT software to further determine the additive prognostic value of metabolic tumor burden in 92 nonsurgical patients with Stage IV NSCLC. This study is to directly test our hypothesis that metabolic volumetric measurement can provide additional prognostic information over the standard UICC/AJCC staging system in patients with Stage IV NSCLC. The prognostic value of the MTV and TLG in this group with Stage IV NSCLC was compared with SUV measurements.

MATERIALS AND METHODS

Patient Recruitment

This study was approved by our hospital's institutional review board and was compliant with the Health Insurance Portability and Accountability Act. We conducted a retrospective review of the medical records of patients with NSCLC. There were 816 cases with NSCLC who were diagnosed and treated in the University of Chicago Medical Center between January 1, 2004, and December 31, 2007. We identified the 92 consecutive nonsurgical patients with Stage IV NSCLC for this study from this retrospective database by inclusion criteria. The inclusion criteria were as follows: 1) all patients had a baseline PET/CT scan, 2) they had no surgery, 3) they had no brain metastasis because our whole-body PET/CT did not cover the whole brain, and 4) they had no history or current diagnosis of other types of cancer. There were 37 male and 55 female patients with median age of 65 years. There were 20 patients with adenocarcinoma, 6 with large cell carcinoma, 21 with squamous cell carcinoma, and 45 with NSCLC not-otherwise specified. Seventy-nine patients had chemotherapy or radiation therapy or both. Seventy-two patients received chemotherapy. Fifty-six received platinum based chemotherapy. Ten received chemotherapy with Tarceva, two were treated with Tarceva and Avastin, one was treated with Taxotere and Cetuximab, one was treated with Avastin and Taxol, one was treated with Gemcitabine, and one was treated with Vinorelbine. Forty-four patients received palliative radiation therapy. Twenty-nine patients received radiation therapy in the chest. Fifteen patients received radiation therapy in other parts of the body. Five of them received radiation in two locations and two of the patients received radiation therapy in three locations. The dose ranged from 3000 cGy to 9000 cGy. However, the radiation dose in four of the patients was not available. In 13 patients, no chemotherapy or radiation therapy was performed. The purpose of the PET/CT scans was to stage the disease or for the diagnosis of lung lesions. The mean of the PET/CT scan-to-therapy time was 4.75 weeks with a standard deviation of 4.75 weeks in the 79 patients who had therapy. They had been followed with CT of the chest and abdomen in the University of Chicago regularly every 1–4 months. These patients were followed by our Cancer Registry semiannually. Their survival status was determined through clinical follow-up and the Social Security Death Index. The clinical follow-up and the Illinois State Death Inquiry System were used to determine the causes of death. The overall survival (OS) defined as the time from initial PET/CT to death was determined based on the described follow-up and records.

Imaging Protocols

PET/CT imaging. The 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) PET/CT scans were performed in accordance with National Cancer Institute guidelines (21) in all 92 patients