Prognostic Value of Different Metabolic Measurements with Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography in Resectable Non-Small Cell Lung Cancer: A Two-Center Study

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Introduction: Standard uptake value (SUV) is a quantitative measure for the preferential uptake of a radiopharmaceutical in a tumor compared with the homogeneous distribution in the body. SUV can be based on the maximal value of one pixel (SUVmax) or on the mean value in a region outlined by isodensity contours. The prognostic value of different SUVs in non-small cell lung cancer (NSCLC) is not established. We evaluated this value for SUVmax, SUV70%, and SUV50% among patients with resectable NSCLC.

Methods: All consecutive patients with resectable NSCLC who underwent an attenuation-corrected whole-body fluorine-18 fluorodeoxyglucose positron emission tomography scan from two university hospitals were selected. By adjusting the isocontour in the region of interest on the scan, SUVmax, SUV70%, and SUV50% of the primary tumor were calculated.

Results: Sixty-six patients (50 male, median age 63 years) were included. Of the tumors, 16 were pathological stage IA, 23 were IB, 4 were IIA, 14 were IIB, and 9 were IIIA. Median (range) values for SUVmax, SUV70%, and SUV50% were 6.4 (1.6 –19.1), 5.1 (1.0 –15.7), and 4.0 (0.9 –13.4), respectively. SUVs were associated with survival.

Analysis of residuals of SUVmax as a continuous variable in a Cox’s proportional hazard model for survival suggested no cutoff point and no indication of time-dependency. Patients with a SUV higher than the median value had a worse survival than patients with a SUV lower than median (hazard ratios for SUVmax, SUV70%, and SUV50% all were 2.9; p = 0.02).

Conclusions: SUVmax, SUV70%, and SUV50% measured with fluorine-18 fluorodeoxyglucose positron emission tomography have a similar prognostic value, and no “natural” cutoff point for SUVmax in resectable NSCLC was identified.

Key Words: Non-small cell lung cancer, Fluorine-18 fluorodeoxyglucose positron emission tomography, Standard uptake value, Prognosis.

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associated with a worse prognosis\textsuperscript{6–15} but the prognostic value of the metabolic activity seems stronger in early disease than in advanced disease. Most authors were able to discern different prognostic groups in early-stage NSCLC based on a cutoff level that was often arbitrarily chosen. There is not a good biological reason for a clear cutoff level of SUVs estimated in tumors.

In the present study, we evaluated the prognostic value of different SUVs among patients with early-stage NSCLC in a two-center study. In addition, we explored whether it is possible to define an appropriate cutoff value for SUVs.

**PATIENTS AND METHODS**

**Patients**

All consecutive patients with pathological stage I to IIA NSCLC from two university medical centers who underwent an attenuation-corrected whole-body FDG-PET scan before any treatment were included. Tumor staging was based on preoperative CT and PET scans, mediastinoscopy if indicated, and the resected tumor specimen and mediastinal lymph nodes. Gender, age at diagnosis, performance score, weight loss, histological subtype, tumor size, completeness of resection, and treatment with pre- or postoperative chemotherapy and/or radiotherapy were recorded. Survival analysis was censored on June 1, 2006.

To evaluate whether SUV also has prognostic value in advanced NSCLC, 33 subsequent patients with stage IV disease from University Medical Center Groningen were analyzed in an identical method during the same time period.

The present study was performed using anonymized data that were routinely collected. Therefore, consent was not specifically obtained and institutional review board approval was not necessary.

**PET Imaging**

All PET scans were performed on Siemens ECAT scanners (Siemens/CTI, Knoxville, TN) in two clinical PET Centers (University Medical Centers Groningen and Nijmegen) using the same acquisition protocol. The technical specifications of both Siemens ECAT scanners are similar, and the devices in both institutions were calibrated according to a standardized protocol\textsuperscript{16} Patients fasted for at least 6 hours before scanning. Sixty to ninety minutes after intravenous injection of 220–370 MBq FDG in the forearm, scanning was started using an interleaved protocol (emission-transmission) from mid-thigh to the skull. Measurements were performed consistently for every patient.

All scans were iteratively reconstructed using ordered subset expectation maximization and were interpreted by experienced nuclear medicine physicians.

**SUV Calculations**

ROIs were semi-automatically drawn around the region of focal FDG uptake in the primary tumor. Semi-automatically means that the tumor is three-dimensionally manually encircled, so that non-spherical tumors are also entirely within the ROI. SUV of the primary tumor was calculated by the following formula: \( \text{SUV} = \frac{\text{activity concentration (MBq/mL)}}{\text{injected dose (MBq)/body weight (g)}} \). SUV\text{max} was defined as the pixel with the highest FDG uptake within the ROI. SUV70\% and SUV50\% were calculated by adjusting the isodensity contour within the ROI by 70\% or 50\%, respectively. SUV70\% is the mean SUV of all pixels with an activity of 70 to 100\% of the pixel with the highest FDG uptake (SUV\text{max}) within the ROI. SUV50\% is similarly calculated by drawing the 50\% isodensity contour in the ROI.

SUVs calculated from different scanners cannot generally be mutually exchanged because of variations in scanning protocols and software settings. However, the difference between two scanners is highly consistent and constant, as was recently demonstrated for our institutions using anthropomorphic phantoms and equal settings and reconstructions\textsuperscript{16} The degree of the variation between our two institutions is approximately 15\%.\textsuperscript{16} To overcome this inter-institutional variation, a correction factor between institutions may be calculated. In this study, we performed the measurements and analyses of SUV using the same protocol and reconstruction method in both hospitals. In our patient group, the median stage-specific SUV was not significantly different between the institutions. Therefore, we combined the retrospective clinical and raw SUV data of both institutions into one study.

**Statistical Methods**

Spearman’s correlation was calculated for the relation between the different SUVs mutually and between SUV and tumor size. SUVs of patients with different histology were compared using the Kruskall-Wallis test. SUVs of patients with different stages were compared using the Jonckheere test for ordered alternatives.

Overall survival was defined as the time between PET scan and date of death or last follow-up. Survival curves were constructed by means of the Kaplan-Meier technique. Survival curves for different groups of patients were compared by means of the log-rank test.

Cox’s proportional hazard regression analysis was used to evaluate the prognostic value of SUV\text{max}, SUV70\%, and SUV50\% and to adjust for other prognostic factors such as disease stage. \( p \) values less than 0.05 were considered statistically significant. The size of the effects was expressed as hazard ratio (HR) with a 95\% confidence interval (CI). A HR greater than 1 indicates increased mortality. The existence of a natural SUV cutoff value and time dependency of SUV was evaluated by means of Martingale and Schoenfeld residuals\textsuperscript{17,18}

**RESULTS**

**Patient Characteristics**

A total of 87 patients were enrolled. Patients who were not treated by resection (\( n = 11 \)), patients with incomplete SUV data (\( n = 6 \)), and patients with insulin-dependent diabetes mellitus (\( n = 4 \)) were excluded. Of the remaining 66 patients (50 male, 16 female) included, median age was 63 years (range, 38–79 years). Performance score was 0 for 20 patients (30\%), 1 for 34 (52\%), 2 for 4 (6\%), and unknown for 8 patients (12\%). Five patients (8\%) had more than 10\% weight loss. Seven patients (10\%) received preoperative che-
motherapy consisting of three cycles of a platinum-based regimen.

Squamous-cell carcinoma was found in 35 patients (53%), adenocarcinoma in 23 patients (35%), large-cell carcinoma in 7 patients (11%), and bronchoalveolar cell carcinoma in 1 patient (1%). Sixteen patients (24%) had pathological disease stage IA, 23 patients (35%) had stage IB, 4 patients (6%) had stage IIA, 14 patients (21%) had stage IIB, and 9 patients (14%) had stage IIIA. Median tumor size was 3.1 cm (range, 0.9–12 cm). At the time of analysis, 25 patients were deceased. The median overall survival of these patients was 1.7 years (range, 0.1–5.7 years). The median follow-up time for living patients was 3.2 years (range, 0.9–5.9 years).

Relation of SUV and Patient Characteristics

Median SUVmax was 6.4 (range, 1.6–19.1), median SUV70% was 5.1 (range, 1.0–15.7), and median SUV50% was 4.0 (range, 0.9–13.4). The distribution of SUVmax, SUV70%, and SUV50% were skewed to the right. SUVmax, SUV70%, and SUV50% were highly correlated with each other; Spearman’s correlation coefficients for SUVmax and SUV70%, and SUV50%, and for SUV70% and SUV50% were 0.993, 0.990, and 0.997, respectively.

Median SUVs did not differ significantly among histological types of NSCLC: median SUVmax was 7.1 (range, 2–19) for patients with squamous carcinoma, 6.3 (range, 2–15) for patients with adenocarcinoma, and 5.6 (range, 3–19) for large cell carcinoma.

SUVmax, SUV70%, and SUV50% all increased with increasing disease stage (Jonckheere tests all p < 0.001). Median SUVmax for patients with pathological stage IA, IB, IIA, IIB, and IIA was 3.7, 5.6, 5.0, 8.2, and 9.9, respectively (Figure 1). A larger tumor size was correlated with a higher SUVmax (Spearman’s correlation coefficient 0.565).

Exploring a Cutoff Point for SUV

SUVmax, SUV70%, and SUV50% as continuous variables were all significantly associated with survival (p = 0.018, p = 0.012, and p = 0.011, respectively). For the self-chosen cutoff points 7, 8, 9, and 10, SUVmax significantly predicted survival, as shown in Figure 2.

Analysis of Martingale and Schoenfeld residuals of SUVmax as a continuous variable suggests that an increasing value of SUVmax is associated with an increased risk of death without showing a real cutoff value (Figure 3). Because of this, the median values are chosen to dichotomize the data and present survival curves. This has the advantage of dividing the patients into groups of similar size.

SUV and Prognosis

SUVmax, SUV70%, and SUV50% dichotomized at their median value predicted survival (HR 2.93 [95% CI 1.21–7.09] for all three SUVs). Patients with SUVmax higher than median value had a worse overall survival compared with patients with a lower SUVmax (Figure 4). All 66 patients had a tumor resection, and 58 (88%) achieved a complete resection. SUVmax dichotomized at the median value predicted disease-free survival after complete resection (p = 0.03). Seven patients with an incomplete resection received postoperative thoracic radiotherapy.

Pathological disease stage (p = 0.001) and tumor size (p = 0.007) univariately predicted survival, whereas gender, performance score, age older or younger than 65 years, weight loss, preoperative chemotherapy, and histological subtype did not predict survival.

Adjustment by stage in a multivariable analysis showed that SUVmax (and SUV70 or SUV50) provided additional prognostic information beyond pathological disease stage (p = 0.051, p = 0.041, p = 0.041, respectively).

Prognostic Value of SUV in Advanced NSCLC

In contrast to the patients with early, resectable disease, no difference in overall survival was observed (p = 0.949) for the 33 patients with stage IV NSCLC after dichotomizing at their median SUVmax (9.4).

DISCUSSION

To our knowledge, this is the first clinical study to compare different SUVs in NSCLC. One pixel with maximal value within the whole primary tumor, 30% of the pixels with the highest metabolic activity, or even half of the pixels with the highest activity have similar prognostic impact in resectable NSCLC. Nevertheless, pathological TNM disease stage...
estimated with CT or PET remains the strongest independent prognostic factor. Another finding was that no “natural” cutoff point for SUVmax was observed in resectable NSCLC. In addition, the present study is the first two-center study evaluating the prognostic effect of SUV in NSCLC.

Methodological studies show that, provided they are measured with the same equipment and reconstruction methods, SUVmax and average SUV within a ROI are closely correlated,19–21 as they were in the present study. Therefore, it does not seem surprising that they are equally able to predict prognosis. One could, however, argue that an average SUV better represents the true metabolic nature of a tumor and subsequently better reflects the clinical outcome of a patient than the metabolic information coming from a single pixel. However, our data suggest that SUVmax measured in the primary tumor is as effective as SUV70% and SUV50%, and SUVmax is the easiest SUV to calculate.

The accuracy of SUV can be influenced by several factors, of which ROI defining, image reconstruction, tracer administration, scanning time, and patient factors such as glucose metabolism and body weight are most well known.20,22,23 We diminished this variability of SUV by using the same scanning and reconstruction protocol in both institutions, because a previously performed study and results from this study showed that the differences between our institutions were highly consistent and constant.16 In addition, the interobserver and intraobserver agreement in SUVs was found to be excellent.24 These findings show that SUVmax is an easily reproducible and reliable prognostic parameter, permitted that the same scanning and reconstruction settings are used or a correction factor is applied between different institutions.

In contrast with several other reports,6,8,10–13 none of the SUVs could be identified as an independent prognostic factor in multivariate analysis. In their series of 100 patients with resected NSCLC, Downey et al. found that SUVmax greater than 9 (their observed median value) and primary tumor size larger than 3 cm and their interaction significantly predicted survival.12 In our study, the SUVmax was associated with survival even when adjusting for stage of disease. In a large study with 315 patients planned for resection, SUVmax higher or lower than the median value was the strongest prognostic factor, stronger than disease stage I/II versus III/IV and even complete resection.13 Similarly, in Sasaki et al.’s study of patients with early-stage NSCLC, SUVmax dichotomized at 5 and tumor size were independent predictors for survival, whereas nodal status and treatment were not.6 Noteworthy, most of these studies use tumor size (T) without NM status. TNM disease stage is more powerful in predicting survival of resectable tumors than T status alone.4 Therefore, the difference between these previous studies and our findings could be explained by the fact that we tested all separate TNM disease stages (IA to IIIA) instead of only T status in multivariate analysis. Interestingly, Veselle et al. recently reported that the correlation of SUVmax with tumor stage disappeared after correcting tumors smaller than 3 cm for partial volume effects.25 It is indisputable that SUVmax has prognostic value, although the strength of its effect varies among the reported studies.26
It is not clear which factor is most important in the prognosis of NSCLC. Two suitable candidates are the total tumor load in the body as expressed by TNM status and the biological behavior of the primary tumor as expressed by SUV, or perhaps a combination of these two factors. For example, if tumor load is high, as in advanced NSCLC, SUV may not have additional prognostic power, in contrast to cases with a low tumor load, such as early-stage NSCLC, in which metabolic activity of a tumor may play an important role. Based on these assumptions, one would expect that SUVmax would not be associated with survival in stage IV NSCLC. This is supported by our finding that SUVmax did not predict survival in 33 consecutive patients with stage IV NSCLC, in line with the observations of Lee et al. in advanced disease. In addition, although median SUV generally increases with increasing disease stage, this increase is more pronounced for the lower disease stages, in contrast to the findings of Kusaka et al. and Kuchar et al. 13 This is in agreement with the loss of prognostic value of SUV in the more advanced disease stages. Therefore, SUV seems to be most useful in early-stage NSCLC.

Some groups have proposed data-driven cutoff values of SUV by calculating post hoc the discriminative value (expressed as p value) for several self-chosen cutoff points. The cutoff point with the lowest p value was then considered the most suitable, regardless of the number of patients in the groups above and below the cutoff value. By applying the same method, we observed that SUV is a predictor for survival for several different cutoff values, but we question whether this methodology is appropriate. First, this methodology may lead to overestimation because it is data-driven and because of the effects of multiple testing. Second, there is no biological reason for a cutoff level phenomenon in tumors. SUV represents FDG uptake in a tumor caused by the up-regulation of trans-membrane glucose receptors GLUT 1 and GLUT 2 and consequently is an indirect measurement for proliferation. The extent of this up-regulation represents a continuous variable. In addition, SUVmax is highly correlated with Ki-67 expression, a marker of cell proliferation. It is therefore plausible that no natural cutoff point for SUV was observed.

In conclusion, our two-center study showed that SUVmax, SUV70%, and SUV50% have similar prognostic impact in resectable NSCLC. In the absence of a biological cutoff point, the median SUVmax of the primary tumor, which divides the patients into groups of similar size, may be used. An interesting application of such a strong prognostic indicator as SUV is its use as a stratification parameter in trials involving adjuvant chemotherapy.

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