Relationship between Non-Small Cell Lung Cancer Fluorodeoxyglucose Uptake at Positron Emission Tomography and Surgical Stage with Relevance to Patient Prognosis

Hubert Vesselle,¹ Eric Turcotte,¹ Linda Wiens,¹ Rodney Schmidt,² Julie E. Takasugi,¹ Tasneem Lalani,³ Eric Vallières,³ and Douglas E. Wood³

Departments of ¹Radiology, ²Pathology, and ³Surgery, Division of Thoracic Surgery, University of Washington, Seattle, Washington

ABSTRACT

Purpose: Because the tumor stage is the most significant prognostic factor for non-small cell lung cancer (NSCLC) and given that NSCLC [¹⁸F]fluorodeoxyglucose (¹⁸F-FDG) uptake appears to have prognostic significance, we examined the relationship between NSCLC ¹⁸F-FDG uptake and surgical stage.

Experimental Design: One hundred seventy-eight patients with a proven diagnosis of NSCLC were enrolled, then imaged with ¹⁸F-FDG positron emission tomography and their disease thoroughly staged. Primary tumor size at computed tomography and ¹⁸F-FDG uptake were compared to overall tumor stage and to T, N, and M stage descriptors. Tumor uptake was quantitated by maximum pixel-standardized uptake value (maxSUV) and then partial volume corrected for lesion size using recovery coefficients.

Results: A significant difference in tumor size was associated with tumors of different TNM stage, T status, N status, or M status. Similarly, the primary tumor maxSUV was significantly associated with TNM stage, T status, and M status. However, we observed no significant difference in the partial-volume-corrected tumor maxSUV for different stages; different T, N, or M descriptors; tumors without evidence of spread (N₀M₀) versus tumors with nodal spread (N₁₂₃M₀); or tumors without spread (N₀M₀) versus all others.

Conclusions: We found an association between tumor stage and ¹⁸F-FDG maxSUV, but this relationship disappeared after correction of tumor uptake for lesion size. Therefore, if partial-volume-corrected ¹⁸F-FDG uptake is prognostic of NSCLC outcome, it is not on the basis of a relationship with tumor stage but through a different mechanism.

INTRODUCTION

Primary lung cancer remains the leading cause of cancer death in the United States, with over 171,900 new patients and 157,200 deaths expected in 2003 (1). Mortality associated with lung cancer continues to increase among women and is expected to account for 25% of all female cancer deaths in 2003, surpassing death from breast cancer (1). Approximately 80% of lung cancers are of non-small cell histology, which includes adenocarcinoma, squamous cell carcinoma, large cell, and mixed histologies. The most critical factor determining prognosis, management, and operability of non-small cell lung cancer (NSCLC) is the tumor stage. The TNM staging system for lung cancer shows a 5-year survival ranging from 1% in stage IV disease to 67% in completely resected stage IA disease (2). Meticulous diagnostic staging of lung cancer is critical to (a) prevent clinical overstaging and the denial of therapy with curative intent; (b) avoid clinical understaging and the subsequent morbidity, time, and cost of ineffective therapies, particularly an unnecessary thoracotomy; and (c) accurately select patients for enrollment in clinical trials. Therefore, every means should be used to establish the correct stage of a newly diagnosed lung cancer before initiating therapy.

Computed tomography (CT) of the thorax is a routine part of the clinical staging of NSCLC. CT imaging of the thorax provides valuable information on the location of the primary tumor with respect to anatomical structures, thus aiding in defining the primary tumor (T status) and its resectability. Also provided by CT is an important assessment of hilar and mediastinal lymph nodes (N status) based on their size. However, CT alone has been found to have low sensitivity (64%) and specificity (62%) for identifying malignant N₂ and N₃ lymph nodes (3). The gold standard for establishing nodal status has been surgical staging with mediastinoscopy, mediastinotomy or throracoscopy, and ultimately, thoracotomy. Over the last decade, positron emission tomography with [¹⁸F]fluorodeoxyglucose (¹⁸F-FDG PET) has been shown to provide more accurate noninvasive nodal staging than CT (4). ¹⁸F-FDG PET has also been demonstrated to have a role complementary to that of surgical staging (5), obviating the need for surgical evaluation of patients with PET-detected distant metastatic disease and guiding the selection of the surgical staging approach to confirm stage in patients without distant metastases. In addition, ¹⁸F-FDG PET detects unsuspected extrathoracic metastases in 14–16.9% of patients otherwise deemed potentially resectable (clinical stage IIIA or less; Refs. 5–8).
More recently, 18F-FDG PET has found an additional role beyond identifying unsuspected extrathoracic distant metastases or providing noninvasive mediastinal staging. The 18F-FDG uptake of primary NSCLCs has been reported to have prognostic value in predicting a patient’s survival (9–11). In a retrospective review of 156 patients, Ahuja et al. (9) demonstrated that patients with primary lesions with a standardized uptake ratio <10 had a median survival of 24.6 months, whereas those patients with a ratio >10 had a median survival of 11.4 months. If the primary lesions were >3 cm and had a standardized uptake ratio >10, the median survival was even lower, at 5.7 months; a standardized uptake ratio >10 correlated with poor survival (9). In a series of 125 NSCLC patients, Vansteenkiste et al. (11) demonstrated that tumors with standardized uptake values >7 had a 2-year survival of 43% compared with 82% for those with standardized uptake values <7. A smaller retrospective study of resected NSCLCs also pointed to the tumor standardized uptake value (SUV) as an independent predictor of disease-free survival (10). Considering that the tumor stage is the most significant prognostic factor for NSCLC and that NSCLC 18F-FDG uptake appears to also have prognostic significance, we proposed to examine the relationship between NSCLC 18F-FDG uptake and surgical stage and its descriptors.

**MATERIALS AND METHODS**

**Inclusion and Exclusion Criteria.** This study was conducted under University of Washington Human Subjects Division approval. All patients had a clinical diagnosis of NSCLC and were referred to the thoracic surgery clinics at the University of Washington Medical Center or the Veterans Affairs Puget Sound Health Care System between February 1998 and June 2003. CT imaging of the thorax had been performed on all patients, and those with potentially resectable NSCLC were referred for imaging with 18F-FDG PET. 18F-FDG PET imaging was performed on all patients with the exception of those patients with lesions smaller than 1 cm on the mediastinal windows of the chest CT. This precaution was taken to ensure accurate quantification of 18F-FDG uptake in the primary lesion, in particular, partial volume correction. Patients were excluded if the histology was subsequently found to be different from NSCLC or if the histology could not be confirmed. Patients were also excluded if they had type I diabetes. Patients with a previous history of lung cancer were excluded. If patients had a previous history of other cancers, they had to have been disease free for 5 years. Patients also were excluded if they had received any therapy or surgical staging for their NSCLC before PET. Patients had to be able to tolerate surgical resection if found to be resectable. A total of 178 patients qualified for the study, and those patients were evaluated and managed according to the algorithm depicted in Fig. 1.

**Tumor Size.** Tumor size was determined by averaging all three dimensions of the primary tumor measured on the mediastinal windows of the chest CT.

**PET Imaging.** A dedicated whole-body PET tomograph (PET Advance; General Electric Medical Systems, Milwaukee, WI) was used for all PET imaging. All patients fasted for 12 h before tracer administration. Tracer was administrated through an i.v. catheter placed in the patient’s arm. At the time of i.v. catheter placement, a blood sample was obtained to screen for abnormally high plasma glucose levels. To decrease muscular uptake in the neck and upper thorax that could compromise image interpretation, patients received 1 mg of i.v. lorazepam ~20 min before tracer administration. A Harvard pump (Harvard, Boston, MA) was used to infuse 259–407 MBq (7–11 mCi) of 18F-FDG i.v. over 2 min. Patients were allowed to rest for 45 min, after which time they were placed supine in the scanner with their thorax positioned to fit within two contiguous 15-m wide tomograph fields of view. A 15-min emission scan was first performed over the thoracic field of view encompassing the primary lung cancer to control for the time dependence of the SUV. The SUV of the primary tumor could thus be calculated over a standard time period (45–60 min) after injection for all patients. Imaging was then continued over the other thoracic field of view as well as the abdomen with 10-min emission scans. These were followed by 5-min emissions scans of the neck and pelvis. After all emission studies were com-
pleted, 15-min transmission studies were performed over the three fields of view encompassing the chest and abdomen.

The two-dimensional imaging mode with scatter septae in place was used to collect all images. After collection, real-time random correction was subsequently applied by use of counts obtained with a delayed coincidence window and deconvolution-based scatter corrections supplied by the manufacturer. The standard filtered back-projection available on the PET Advance system was used to reconstruct the raw PET data with the following reconstruction parameters: 12-mm Hanning filter, 55-cm image diameter, and 128 × 128 array size. Each patient had emission- and attenuation-corrected scans as well as the transmission scan reconstructed. Because the transmission scan is coregistered to the other two scans, it provides anatomical localization details for interpretation. All 18F-FDG PET scans were read prospectively on a dedicated workstation by the same experienced reader and with the benefit of the comparison chest CT scan. From the attenuation-corrected 18F-FDG PET study, regions of interest were drawn over the primary tumor to extract the tumor maximum SUV value (maxSUV) according to a method previously described (12). The SUV is defined as:

\[ \text{SUV} = \frac{C \times \text{FDG}}{W \times \text{ID}} \]

where \( C \) is the radiotracer concentration in a voxel of tissue (μCi/ml), \( W \) is the patient weight (kg), and \( ID \) is the injected tracer dose (mCi). Both the maxSUV and the partial-volume-corrected maxSUV (PVC maxSUV) were evaluated for each primary tumor as follows: The normal lung background (18F-FDG uptake in normal lung) was first evaluated over a large region of interest located at the same axial level but away from the primary lung mass or nodule studied and away from the chest wall and mediastinum. The average SUV over this region of interest was used to calculate the background SUV.

The PVC maxSUV is defined by:

\[ \text{PVC maxSUV} = \frac{\text{maxSUV} - \text{background SUV}}{\text{RC}} \]

where RC represents the recovery coefficient for a lesion of a ground SUV/(background SUV).

The normal lung background (18F-FDG uptake in normal lung) was first evaluated over a large region of interest located at the same axial level but away from the primary lung mass or nodule studied and away from the chest wall and mediastinum. The average SUV over this region of interest was used to calculate the background SUV.

The PVC maxSUV is defined by:

\[ \text{PVC maxSUV} = \frac{\text{maxSUV} - \text{background SUV}}{\text{RC}} \]

where RC represents the recovery coefficient for a lesion of a ground SUV/(background SUV).

RESULTS

A total of 178 patients fit all of the inclusion criteria, and their staging was performed as described in Fig. 1. Table 1 summarizes the descriptive statistics (mean ± SD) for all TNM stages and for each T, N, and M status. The overall stage (IA to IV) was accurately established for 174 of the 178 subjects based on 18F-FDG PET, confirmatory imaging or biopsy, and surgical staging. In four incomplete cases, one of the T, N, or M descriptors could not be defined to establish the overall stage in the follow-up. However, accurate knowledge of the T, N, or M status allowed inclusion of these four cases in this series for analysis of individual descriptors with respect to 18F-FDG uptake. Furthermore, the individual T or N status did not need to be surgically confirmed to establish the overall stage in the following instances: N1M0 disease is always stage IIIB irrespective of the T status, which did not need to be confirmed to establish therapy; T3M0 is also stage IIIB irrespective of the N status. Similarly, M1 disease confers stage IV independent of T and N status, which was not confirmed (2). Eight of the patients with M1 disease had a solitary brain metastasis that had been resected, and those patients had a potentially resectable NSCLC at the time of referral to thoracic surgery clinic. The rationale for including such cases is that if the primary NSCLC is resectable, the overall 5-year survival is 20% (13–18).

Analysis of the data (Table 2) for the seven TNM stages (IA-IV) showed a significant difference for tumor size (Fig. 3A) and primary tumor maxSUV (Fig. 3B) between stages (KW test, \( P < 0.001 \)). However, we observed no significant difference in the tumor PVC maxSUV between the different stages (KW, \( P = 0.474 \); Fig. 3C). Spearman rank (SR) analysis (Table 2) showed specimens to assess their non-small cell nature and histological subtype as well as the TNM status of each tumor.
a significant correlation coefficient (\( \rho = 0.415; P < 0.001 \)) between primary tumor maxSUV and stage and a significant correlation between tumor size and stage (\( \rho = 0.507; P < 0.001 \)).

When each component of the TNM stage was analyzed separately, we found significant differences (KW) and correlations (SR) between (a) the maxSUV and each T stage (KW, \( P < 0.001 \); SR, \( \rho = 0.420, P < 0.001 \); Fig. 4A); and (b) between tumor size and each T stage (KW, \( P < 0.001 \); SR, \( \rho = 0.621, P < 0.001 \)). We observed no significant difference for the tumor PVC maxSUV among the different T stages (KW, \( P = 0.072 \); Fig. 4B). Dunn’s multiple comparison analysis revealed a significant difference in maxSUV and tumor size between \( T_1 \) and \( T_2 \) tumors (\( P < 0.001 \)), between \( T_1 \) and \( T_3 \) tumors (\( P < 0.001 \)), and between \( T_1 \) and \( T_4 \) tumors (\( P < 0.001 \)) but not between \( T_2 \) and \( T_3 \), \( T_2 \) and \( T_4 \), or \( T_3 \) and \( T_4 \) tumors.

We also evaluated whether tumor \(^{18}\)F-FDG uptake or tumor size was related to the nodal status (N). Nodal stage analysis showed a statistically significant difference and mild correlation between tumor size and nodal status (KW, \( P = 0.035 \); SR, \( \rho = 0.219, P = 0.008 \)). We observed no correlation between primary tumor maxSUV (KW, \( P = 0.056 \); Fig. 4C) or PVC maxSUV (KW, \( P = 0.838 \); Fig. 4D) and N status.

We evaluated the relationship between presence (\( M_1 \)) or absence (\( M_0 \)) of distant metastatic disease and primary tumor size or \(^{18}\)F-FDG uptake. This demonstrated a significant difference and a mild correlation between metastatic disease and tumor size (KW, \( P < 0.001 \); SR, \( \rho = 0.264, P < 0.001 \)) as well as a mild correlation between metastatic stage and maxSUV (KW, \( P = 0.002 \); SR, \( \rho = 0.234, P = 0.002 \); Fig. 4E) but no relationship between metastatic status and PVC maxSUV (KW, \( P = 0.089 \); Fig. 4F).

Finally, we studied the group of patients without observable distant metastatic disease (\( M_0 \)). Those patients without nodal spread (\( N_0 M_0 \)) statistically had lesions that were smaller (KW, \( P = 0.023 \); SR, \( \rho = 0.197, P = 0.023 \)) and of lower maxSUV (KW, \( P = 0.029 \); SR, \( \rho = 0.189, P = 0.029 \)) than those whose disease had already spread to nodes at presentation (\( N_1, N_2, M_0 \); Fig. 5A). However, the PVC maxSUV (Fig. 5B) was not statistically different between the two groups (KW, \( P = 0.859 \)). Similarly, tumors without any observable spread at presentation (\( N_0 M_0 \)) had lower size (KW, \( P < 0.001 \); SR, \( \rho = 0.277, P < 0.001 \)) and maxSUV (KW, \( P < 0.001 \); SR, \( \rho = 0.261, P < 0.001 \)) than those whose disease had already spread either to lymph nodes or hematogenously (\( N_1,2,3, M_0 \); Fig. 5C). However, the two groups do not differ in their PVC maxSUV (KW, \( P = 0.359 \); Fig. 5D).

When we considered the subset of 101 cases with primary tumors \( \geq 2.8 \) cm, i.e., those tumors not affected by partial volume effects, we found no association between tumor maxSUV and tumor stage or T, N, and M descriptors (Table 3; Fig. 3D).

**DISCUSSION**

Primary NSCLC \(^{18}\)F-FDG uptake has been reported in three separate series to be of prognostic significance (9–11). However, the basis for this reported prognostic significance of \(^{18}\)F-FDG uptake is not understood and has not been investigated. Because tumor stage is the most significant prognostic factor in NSCLC, we wanted to determine whether a correlation between tumor stage and tumor \(^{18}\)F-FDG uptake could be the basis for the prognostic value of tumor \(^{18}\)F-FDG uptake. Therefore, we evaluated the relationship between primary NSCLC \(^{18}\)F-FDG uptake and tumor stage and its TNM descriptors. In addition, we wished to determine whether tumor \(^{18}\)F-FDG uptake could predict the nodal (N) or metastatic (M) status of a patient. One of the important features of this study is the thoroughness of the surgical and overall staging performed on the patients.

We found an association between tumor size and the T status. This stems from the fact that, by definition, \( T_1 \) tumors are \( \leq 3 \) cm at their greatest dimension (2), whereas most \( T_2 \) tumors have at least one dimension \( > 3 \) cm. However, Dunn’s analysis showed no difference between tumor size and \( T_2, T_3, T_4 \) status. This is likely because these higher T descriptors reflect the involvement of specific anatomical structures, such as the chest wall or the carina, or opacification of the lung in association with the tumor (2), and these are less related to the size of the primary tumor than to the site where the primary tumor originated. In our series, tumor size was also related to nodal status (\( N_0, N_1, N_2, N_3 \)), as had been reported previously by others (19, 20). Finally, the presence of distant metastases is related to tumor size as well, a fact generally accepted in clinical practice but not reported in the literature.

![Table 1: Summary of descriptive statistics (mean ± SD) for all TNM stages and for each T, N, and M descriptors](image-url)
We found that tumor size is associated with tumor stage. This is expected because all stage IA (T1, N0, M0) lesions have a T1 primary tumor, which is by definition <3 cm in diameter. Most, but not all, T2 tumors and, therefore, most stage IB tumors (T2, N0, M0) are >3 cm in size. Thus, for low stages (IA and IB), the direct relationship between tumor size and stage stems from the definition of T1 versus T2. There was no association between tumor size and T2, T3, and T4 status. Hence, for higher-stage lesions the relationship between tumor size and stage implies that the larger the primary tumor, the more likely it has spread to lymph nodes or hematogenously. This result is in keeping with our results showing that the larger the primary tumor at diagnosis, the higher the incidence of associated nodal spread and distant metastases.

We found a definite correlation between primary tumor 18F-FDG uptake quantified by the tumor maxSUV and tumor stage, but this relationship disappeared after the maxSUV was corrected for partial volume effects caused by the small size of some lesions. In addition, when only lesions >2.8 cm were considered, i.e., lesions that do not require partial volume correction of their uptake, we did not find an association between maxSUV and tumor stage. Therefore, if PVC18F-FDG uptake is prognostic of NSCLC outcome, it is not on the basis of a relationship with tumor stage but rather through a different mechanism.

Similarly, we identified a definite relationship between the primary tumor maxSUV and the T and the M descriptors. However, this relationship disappeared when tumor uptake was corrected for partial volume, and it was not observed in lesions >2.8 cm.

We studied the group of patients with N0M0 status, i.e., those cases without any evidence of tumor spread through the lymphatic system (N0) or hematogenously (M0) at presentation. We then compared those patients with the group of patients with tumors that had spread to the lymph nodes (N1, N2, or N3) or to distant sites (M1). We found no significant difference in the
Fig. 4 Scatter graphs showing maximum pixel-standardized uptake value (maxSUV), and partial-volume corrected standardized uptake value (PVCmaxSUV) versus each T, N, and M descriptor. Data are the mean ± SD (bars).

Fig. 5 Scatter graphs showing maximum pixel-standardized uptake value (maxSUV), and partial-volume corrected standardized uptake value (PVCmaxSUV) versus TNM subgroups. A and B, N0M0 patients (no evidence of tumor spread) versus N1,2,3M0; C and D, N0M0 patients versus all other cases. Data are the mean ± SD (bars).
PVC tumor uptake of the two groups. Therefore, PVC tumor 18F-FDG uptake does not differentiate tumors without any spread from those that had already spread at the time of presentation. Similarly, PVC maxSUV did not differentiate tumors without nodal spread (N0M0) from those with nodal involvement (N123M0) at presentation. PVC 18F-FDG uptake also does not differentiate between presence (M1) or absence (M0) of metastatic disease.

We have previously described the importance of partial volume correction in 18F-FDG PET when relating NSCLC uptake to tumor proliferation rate (12). Its use in relating tumor uptake to tumor stage has not been reported in the literature, and studies of the prognostic significance of 18F-FDG uptake in NSCLC have not used partial volume correction despite their inclusion of many small lesions (9–11). In particular, in the study by Vansteenkiste et al. (11), lesions >3 cm in size all had a SUV >7, conferring a worse outcome to these tumors, whereas lesions <3 cm varied in uptake above and below SUV 7. Hence, it is likely that in that study (11), the SUV of small lesions was significantly affected by their size. We identified a significant relationship between tumor 18F-FDG uptake and tumor size when we analyzed the data reported in the study by Higashi et al. (10). It is critical to correct for physical partial volume effects in PET imaging because as tumors get smaller, those effects lead to a gradual lowering of the measured maxSUV based on a physical measurement artifact and not on a biological difference. Not correcting for such effects would lead to interpretation of a lower maxSUV as lower metabolic activity of the tumor. Consequently, meaningful comparisons among primary tumors of different sizes would not be possible. We therefore believe that prognostic studies of NSCLC 18F-FDG uptake need to correct for partial volume effects if they are to identify true biological differences, beyond size differences, that are responsible for differing outcomes. The previously published studies (9–11) showing the prognostic significance of FDG uptake in NSCLC did not perform partial volume correction of uptake values. We predict that when such correction is performed, the FDG uptake of the primary tumor will no longer be prognostic. Longer follow-up of our patient series should clear up this issue in the future.

In conclusion, we have found an association between tumor stage and tumor uptake, but this relationship disappears after correction of tumor uptake for lesion size. Therefore, if PVC 18F-FDG uptake is prognostic of NSCLC outcome, it is not on the basis of a relationship with tumor stage but rather through a different mechanism. This study also underscores the importance of correcting for partial volume effects to evaluate the biological significance of differences in tumor uptake. At present, we are monitoring the patients of this study for evidence of tumor recurrence and will determine whether for this series of patients the PVC tumor 18F-FDG uptake is predictive of their overall outcome or whether the reported prognostic significance of noncorrected 18F-FDG uptake depends on the size of the primary tumor.

REFERENCES

Relationship between Non-Small Cell Lung Cancer Fluorodeoxyglucose Uptake at Positron Emission Tomography and Surgical Stage with Relevance to Patient Prognosis

Hubert Vesselle, Eric Turcotte, Linda Wiens, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/14/4709

Cited articles
This article cites 18 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/14/4709.full.html#ref-list-1

Citing articles
This article has been cited by 6 HighWire-hosted articles. Access the articles at:
/content/10/14/4709.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.