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The Maximum Standardized Uptake Values on Positron Emission Tomography for Nodal Staging in Non-Small Cell Lung Cancer

Katarzyna Szwalbe[1], Szymon Wcisło[1], Artur Terlecki[1], Piotr Misiak[1], Wiesław Tryniszewski[2] and Sławomir Jablonski[1]*

[1]Department of Thoracic, General Surgery and Surgical Oncology, University Clinical Hospital Military Medical Academy - Central Veterans' Hospital, Medical University of Lodz, Poland

[2]Department of Radiological and Isotope Diagnostics and Therapy, University Clinical Hospital Military Medical Academy - Central Veterans' Hospital, Medical University of Lodz, Poland

Keywords

PET; SUVmax; Non-small cell lung cancer; Lymph nodes

Introduction

Lung cancer is the most common diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths) [1]. The initial asymptomatic course of the disease causes the patients are being diagnosed too late when, the cancer is already locally advanced or has disseminated. Around 70% of patients with lung cancer have stage III or IV disease at diagnosis, thus excluding them from surgical resection [2]. Detection of the cancer at an early stage leads to an improved prognosis. Patients diagnosed with stage IA non-small cell lung cancer and undergoing surgical resection having a 5 years survival from 55% to 80% [3,4]. Therefore, it is important to improve diagnostic methods that will result in an accurate assessment of the stage of the lymph nodes advancement to ensure the right decision is made without the need for additional invasive procedures for determining the stage, and thus improve the patient's prognosis.

Lymph node staging is the most important factor in determine treatment in patients with non-small cell lung cancer. PET examination based on increased glucose uptake of cancer cells has been shown to have a sensitivity of 58% to 94% and a specificity of 76% to 96% for the detection of mediastinal lymph node metastasis [5,6]. In addition, the high negative predictive value of PET allows further mediastinal evaluation in peripheral tumors ≤ 3 cm without enlarged lymph nodes (hilus and/or mediastinum) on CT and with PET-negative nodes, can be omitted. However, in the case of tumors >3 cm in diameter, mediastinum should be performed using other staging techniques [7].

The aim of the study was to evaluate the parameters SUVmax of the primary tumor, SUV-LN (SUVmax of lymph nodes) and SUV-R (SUVmax of lymph node/SUVmax of primary tumor) in predicting lymph node metastases.

Materials and Methods

We retrospectively reviewed 98 patients with histologically confirmed Non-small Cell Lung Cancer (NSCLC), who underwent a lung resection (a lobectomy or a pulmonectomy) with systematic hilar and mediastinal lymph node dissection. PET/CT (GE Discovery IQ) was performed as part of the preoperative workup between 2013 and 2016. All patients were fasted for a minimum of 6 h prior to the procedure. FDG PET images were obtained 60 min (range 50 min to 95 min) after injection of approximately 187 MBq of 18F-FDG intravenously, if the patient's blood glucose level was lower than 200 mg/dl. The scan was performed from the skull base to the mid-thigh level. PET/CT images were interpreted by an experienced specialist in nuclear medicine (Voxel Medical Diagnostic Center). For determination of SUVmax, a Region of Interest (ROI) was drawn over the primary tumor. Patients were excluded if they had any chemotherapy or radiotherapy before PET, had distant metastases or relapse was suspected. The average time from PET/CT to surgery was 34 days. The SUV-R was determined in each case, as follows:

$$\text{SUV-R} = \frac{SUV - LN\left(SUV\text{max} \quad of \ \ lymph \ node \ station\right)}{SUV\text{max} \quad of \ \ tumor}$$

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Correspondence:

Katarzyna Szwalbe, Department of Thoracic, General Surgery and Surgical Oncology, University Clinical Hospital Military Medical Academy - Central Veterans' Hospital, Medical University of Lodz, Żeromskiego 113 St, 90-549 Lodz, Poland,

E-mail: katarzyna.szwalbe@stud.umed.lodz.pl

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Statistical analyses

Statistical analyses were performed using Statistica 13. The Mann-Whitney-*U* and Fisher's exact test were used to assess differences between benign and metastatic lymph nodes. Receiver Operating Characteristic (ROC) curve analysis was used to compare the diagnostic performance of the two variables SUV-LN and SUV-R and to determine their optimal cut-off values for sensitivity and specificity in detecting metastatic lymph nodes. To define the optimal cut-off thresholds Youden index was used. Comparison between AUC values were performed using Hanley and Hajian-Tilaki KO test. Differences were considered statistically significant when P values were less than 0.05.

Results

This study included 98 patients with non-small cell lung cancer. There were 58 men and 40 women; their average age was 66.9 years (range 51 to 89 years). The mean tumor size was 4.0 ± 1.96 cm (range 1.0 cm to 11.0 cm) and the median SUVmax of the primary tumor was 14.35 (range 1.6 to 35.2). Histological examination revealed: 53 patients with squamous cell carcinoma, 37 patients with adenocarcinoma and 8 patients with other histological types of lung cancer. The clinicopathological characteristics of the patients are presented in Table 1.

Lymph node metastasis were detected in 29 of 98 cases (29.6%), which 15 were N1 stage (hilar or intrapulmonary lymph node metastasis) and 14 were N2 stage (ipsilateral mediastinal lymph node metastasis with or without hilar or intrapulmonary lymph node metastasis). The median SUVmax of primary tumor was higher in the metastatic lymph nodes, but did not reach statistical significance (13.8 *vs.* 15.5; p=0.086).

Table 1: The clinicopathological characteristics of the patients.

Variable	No. of patients (%)
Age	
mean ± SD	66.9
range	51-89
Sex	
male	58 (59.4)
female	40 (40.6)
Tumor size (cm)	
mean ± SD	4.0 ± 1.96
range	1.0-11.0
Histology	
squamous cell	53 (54.1)
adenocarcinoma	37 (37.7)
others	8 (8.2)
Subtypes of adenocarcinoma	
solid	7
lepidic	4
acinar	8
papillary	6
micropapillary	1
Grade of differentiation	
well	4 (4.1)
moderate	57 (58.2)
poor	28 (28.6)

Table 2: Frequency of lymph node in low/high SUVmax group.

Lymph node	Low SUV max N (%)	High SUV max N (%)	Fisher test
Squamous cell carcinoma			
non-metastatic lymph nodes (N0)	21 (58.3)	15 (41.7)	p=0.046
metastatic lymph nodes (N1-N2)	5 (29.4)	12 (70.6)	
Adenocarcinoma			
non-metastatic lymph nodes (N0)	14 (51.8)	13 (48.2)	p=0.39
metastatic lymph nodes (N1-N2)	4 (40.0)	6 (60.0)	

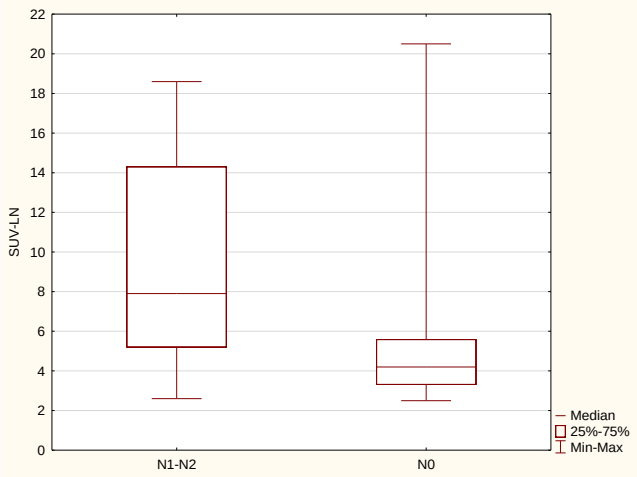

Figure 1: Comparison graph shows the median SUV max of lymph nodes with (N1-N2) and without (N0) metastasis.

Lymph node metastases were present in 32% (17/53) of squamous cell carcinomas and 28% (10/37) of adenocarcinomas. There was no statistically significant difference in the frequency of lymph node metastasis between adenocarcinoma and squamous cell carcinoma (p=0.607).

The median SUVmax was statistical significantly higher for squamous cell carcinoma than adenocarcinoma (15.5 *vs.* 11.0; p<0.001). In squamous cell carcinoma the median SUVmax of primary tumor in patients with malignant lymph nodes was significantly higher than in those without metastases (p=0.031).

As a consequence, we classified histologic types into two groups (high and low SUVmax) according the median SUVmax of primary tumor (15.5 for squamous cell carcinoma and 11.0 for adenocarcinoma). Frequency of metastatic lymph nodes in squamous cell carcinoma was higher in high SUVmax group than in low SUVmax (p=0.046). There was no significant difference in frequency in metastatic lymph nodes between high SUVmax and low SUVmax in adenocarcinoma (p=0.399) Table 2.

The median SUV-LN of malignant lymph nodes was significantly higher than SUV-LN of negative lymph nodes (7.90 *vs.* 4.20; p=0.0042) (Figure 1). There was significant difference in median SUV-R between patients with malignant lymph nodes and those with non-metastatic lymph nodes (0.68 *vs.* 0.22; p=0.0029) (Figure 2). Metastatic and non-metastatic lymph node stations are compared in Table 3.

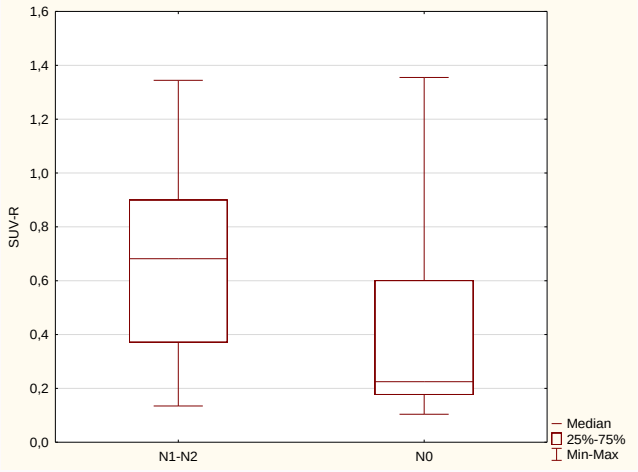

Figure 2: Comparison graph shows the median SUV-R of lymph nodes with (N1-N2) and without (N0) metastasis.

Table 3: The comparison of metastatic and non-metastatic lymph nodes.

	Metastatic (median)	Non-metastatic (median)	p
SUVmax of primary tumor	13.8	15.5	0.086
SUV-LN	7.9	4.2	0.0042
SUV-R	0.68	0.22	0.0029

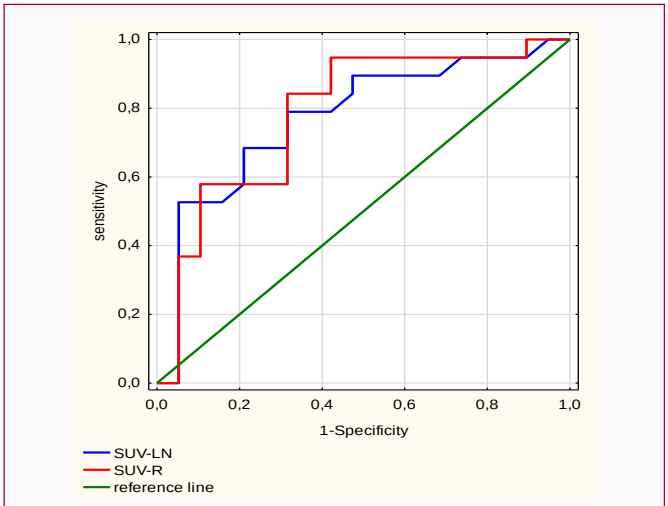

Figure 3: Comparison graph shows ROC curve analysis of SUV-LN (blue line) and SUV-R (red line).

The diagnostic performances of SUV-LN and SUV-R were compared by ROC curve analysis. The optimal cutoff value of SUV-LN to predict nodal malignancy was 6.6, which was associated with 78.9% sensitivity and 68.4% specificity (AUC 0.773; 95% CI 0.618-0.928; p=0.0006). The optimal cut-off value of SUV-R to predict nodal malignancy was 0.37, which was associated with 84.2% sensitivity and 68.4% specificity (AUC 0.784; 95% CI 0.631-0.936; p=0.0003). However, according to the ROC curves there was no significant difference in SUV-LN and SUV-R in predicting lymph nodes metastases (AUC 0.773 *vs.* 0.784; p=0.876) (Figure 3).

Discussion

In the present study, despite the higher SUVmax of the primary tumor in the group of patients with nodal metastases compared to the group without metastases, no statistical significance was found. The relationship between tumor SUVmax and lymph nodes metastasis is conflicting in the literature. Özgul et al. and Koksal et al. in their studies showed no correlation between glucose uptake for the primary tumor and lymph node metastases in patients with lung cancer [8,9]. Contrary to the studies by Downey et al. and Zhang et al., in which higher SUVmax values of the primary tumor were observed in the group of patients with metastatic lymph nodes [10,11]. Nambu et al. in their study found that the probability of nodal metastases rose with the increase in SUVmax of the primary tumor in NSCLC patients. In addition, they observed no presence of lymph node metastases in primary tumors with a SUVmax less than 2.5. On the other hand, in the group of primary tumors with SUVmax of 12 or more, the probability of lymph node metastases was high and reached 70%, regardless of the degree of FDG activity in lymph nodes [12].

Our analysis showed no statistically significant difference in the frequency of lymph node metastases between adenocarcinoma and squamous cell carcinoma. At the same time, it was shown that in the group of squamous cell carcinoma higher SUVmax values of the primary tumor are associated with the occurrence of nodal metastases, while in the group of adenocarcinomas; no relationship was found between the SUVmax parameter and the presence of lymph node metastases. Squamous cell carcinomas are characterized by higher SUVmax values of the primary tumor than adenocarcinomas, which is confirmed by our results and previous studies [13-15]. However, adenocarcinomas despite a lower rate of glucose metabolism, are characterized by a higher metastatic potential [16,17]. On the other hand, adenocarcinoma area highly heterogenous group including several subtypes with different degrees of FDG avidity [18,19]. Therefore, metastatic potential may not be true for all subtypes. The difference in glucose uptake is related to the different metabolism of these histopathological types. In the study by Meijer et al. suggested that adenocarcinomas use mainly oxygen glycolysis to produce ATP, while the metabolism of squamous cell carcinoma is based on anaerobic glycolysis under hypoxic conditions [20]. In addition, several publications confirmed the relationship between higher SUVmax in squamous cell carcinomas associated with higher expression of glucose transport proteins, mainly GLUT-1 [21-23].

In presented study we found that both SUVmax of the lymph nodes and SUV-R were higher in the metastatic lymph nodes. Our results were in line with study of Cho et al. [24]. Based on the ROC curve, the cut-off point SUV-LN value was 6.6 with a sensitivity of 78.9% and a specificity of 68.4% and an AUC of 0.773. The ROC curve identified an optimal cut-off SUV-R value of 0.37 indicating the presence of metastases in the lymph nodes (sensitivity 84.2%, specificity 68.4%, AUC 0.784). The SUV-LN to primary tumor SUVmax ratio was first used and defined by Cerfolio and Bryant [25]. The ratio of 0.56 was the optimal cut-off for the occurrence of mediastinal lymph node metastases (sensitivity 94%, specificity 72%; AUC of 0.79). Found that cut-off value was 0.49 (sensitivity 70%, specificity 65%) [26]. However, it should be noted that in both of these studies, group N2 lymph nodes with SUVmax values above 2.5 and 2.75 were taken into account. Based on the obtained results, none of the parameters tested (SUV-LN and SUV-R) was superior in predicting the presence of lymph node metastases (AUC 0.773 *vs.* 0.784). Contrary to these results, Mattes et al. founded the SUV-R was more accurate in predicting nodal metastasis than the SUV-LN (AUC of 0.846 *vs.* 0.653). In their study, they included patients with SUVmax of the primary tumor >2.5 and lymph nodes with SUVmax ranging

from 2.0 to 6.0 [27]. The limitations of the study were retrospective design and small sample size. Further studies are needed to confirm these results, with more date from a larger number of patients.

Conclusion

Lymph node metastases in squamous cell carcinomas are associated with high SUVmax, while in adenocarcinomas the risk of nodal metastases is similar in both the low and high SUV groups. The results of this study indicate that SUV-LN and SUV-R have a good diagnostic performance for evaluating metastatic lymph nodes. Furthermore, we suggest that PET examination in staging should be interpreted in relation to the histology.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Jones CM, Brunelli A, Callister ME, Kevin NF. Multimodality treatment of advanced non-small cell lung cancer: Where are we with the evidence? Curr Surg Rep. 2018;6(2):5.
3. Liu Y, Shen J, Liu L, Shan L, He J, He Q, et al. Impact of examined lymph node counts on survival of patients with stage IA non-small cell lung cancer undergoing sublobar resection. J Thorac Dis. 2018;10(12):6569-77.
4. Harpole DH Jr, Herndon JE 2nd, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. Cancer. 1995;76(5):787-96.
5. Schimmer C, Neukam K, Elert O. Staging of non-small cell lung cancer: Clinical value of positron emission tomography and mediastinoscopy. Interact Cardiovasc Thorac Surg. 2006;5(4):418-23.
6. Kandathil A, Kay FU, Butt YM, Wachsmann JW, Subramaniam RM. Role of FDG PET/CT in the eighth edition of TNM staging of non-small cell lung cancer. Radiographics. 2018;38(7):2134-49.
7. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45(5):787-98.
8. Ozgül MA, Kirkil G, Seyhan EC, Cetinkaya E, Ozgül G, Yüksel M. The maximum standardized FDG uptake on PET-CT in patients with non-small cell lung cancer. Multidiscip Respir Med. 2013;8(1):69.
9. Koksal D, Demirag F, Bayiz H, Ozmen O, Tatci E, Berktas B, et al. The correlation of SUVmax with pathological characteristics of primary tumor and the value of tumor/lymph node SUVmax ratio for predicting metastasis to lymph nodes in resected NSCLC patients. J Cardiothorac Surg. 2013;8:63.
10. Downey RJ, Akhurst T, Gonen M, Vincent A, Bains MS, Larson S, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. J Clin Oncol. 2004;22(16):3255-60.
11. Zhang S, Li S, Pei Y, Huang M, Lu F, Zheng Q, et al. Impact of maximum standardized uptake value of non-small cell lung cancer on detecting lymph node involvement in potential stereotactic body radiotherapy candidates. J Thorac Dis. 2017;9(4):1023-31.
12. Nambu A, Kato S, Sato Y, Okuwaki H, Nishikawa K, Saito A, et al. Relationship between maximum standardized uptake value (SUVmax) of lung cancer and lymph node metastasis on FDG-PET. Ann Nucl Med. 2009;23(3):269-75.
13. Hanin FX, Lonneux M, Cornet J, Noirhomme P, Coulon C, Distexhe J, et al. Prognostic value of FDG uptake in early-stage non-small cell lung cancer. Eur J Cardiothorac Surg. 2008;33(5):819-23.
14. Um SW, Kim H, Koh WJ, Suh GY, Chung MP, Kwon OJ, et al. Prognostic value of 18F-FDG uptake on positron emission tomography in patients with pathologic stage I non-small cell lung cancer. J Thorac Oncol. 2009;4(11):1331-6.
15. Lu P, Yu L, Li Y, Sun Y. A correlation study between maximum standardized uptake values and pathology and clinical staging in nonsmall cell lung cancer. Nucl Med Commun. 2010;31(7):646-651.
16. Lee DS, Kim YS, Kay CS, Kim SH, Yeo CD, Kim JW. Distinctive patterns of initially presenting metastases and clinical outcomes according to the histological subtypes in stage IV non-small cell lung cancer. Medicine (Baltimore). 2016;95(6):e2795.
17. Deng HY, Zeng M, Li G, Alai G, Luo J, Liu LX, et al. Lung adenocarcinoma has a higher risk of lymph node metastasis than squamous cell carcinoma: A propensity score-matched analysis. World J Surg. 2019;43(3):955-62.
18. Sun XY, Chen TX, Chang C, Teng HH, Xie C, Ruan MM, et al. SUVmax of 18FDG PET/CT predicts histological grade of lung adenocarcinoma. Acad Radiol. 2021;28(1):49-57.
19. Nakamura H, Saji H, Shinmyo T, Tagaya R, Kurimoto N, Koizumi H, et al. Close association of IASLC/ATS/ERS lung adenocarcinoma subtypes with glucose-uptake in positron emission tomography. Lung Cancer. 2015;87(1):28-33.
20. Meijer TW, Schuurbiers OC, Kaanders JH, Looijen-Salamon MG, de Geus-Oei LF, Verhagen AF, et al. Differences in metabolism between adeno- and squamous cell non-small cell lung carcinomas: Spatial distribution and prognostic value of GLUT1 and MCT4. Lung Cancer. 2012;76(3):316-23.
21. Usuda K, Sagawa M, Aikawa H, Ueno M, Tanaka M, Machida Y, et al. Correlation between glucose transporter-1 expression and 18F-fluoro-2-deoxyglucose uptake on positron emission tomography in lung cancer. Gen Thorac Cardiovasc Surg. 2010;58(8):405-10.
22. Suzawa N, Ito M, Qiao S, Uchida K, Takao M, Yamada T, et al. Assessment of factors influencing FDG uptake in non-small cell lung cancer on PET/CT by investigating histological differences in expression of glucose transporters 1 and 3 and tumour size. Lung Cancer. 2011;72(2):191-8.
23. de Geus-Oei LF, van Krieken JH, Aliredjo RP, Krabbe PF, Frielink C, Verhagen AF, et al. Biological correlates of FDG uptake in non-small cell lung cancer. Lung Cancer. 2007;55(1):79-87.
24. Cho J, Choe JG, Pahk K, Choi S, Kwon HR, Eo JS, et al. Ratio of mediastinal lymph node SUV to primary tumor SUV in 18F-FDG PET/CT for nodal staging in non-small-cell lung cancer. Nucl Med Mol Imaging. 2017;51(2):140-6.
25. Cerfolio RJ, Bryant AS. Ratio of the maximum standardized uptake value on FDG-PET of the mediastinal (N2) lymph nodes to the primary tumor may be a universal predictor of nodal malignancy in patients with nonsmall-cell lung cancer. Ann Thorac Surg. 2007;83(5):1826-30.
26. Iskender I, Kadioglu SZ, Kosar A, Atasalihi A, Kir A. Is there any maximum standardized uptake value variation among positron emission tomography scanners for mediastinal staging in non-small cell lung cancer? Interact Cardiovasc Thorac Surg. 2011;12(6):965-9.
27. Mattes MD, Moshchinsky AB, Ahsanuddin S, Rizk NP, Foster A, Wu AJ, et al. Ratio of lymph node to primary tumor SUV on PET/CT accurately predicts nodal malignancy in non-small-cell lung cancer. Clin Lung Cancer. 2015;16(6):e253-8.