Review Article

Current role of standardized uptake value$_{max}$-derived ratios in N2 fluorine-18 fluorodeoxyglucose positron-emission tomography non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Mediastinal staging is a crucial moment in management of non-small cell lung cancer (NSCLC) patients. In integrated pathways, 18-fluorine fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET/CT) is an indispensable imaging resource with its peculiarities and its limitations. A critical review of work up protocols would certainly help to standardize procedures with important reflections also on the diagnostic value of this examination. In this regard, new semi-quantitative and semi-qualitative indexes have been proposed with the aim of increasing the accuracy of ^{18}F-FDG-PET/CT in mediastinal lymph node staging. These latter, such as $SUV_{n/t}$ and SUV indexes, seem to overcome the problem of spatial resolution and discrimination of malignancy by endorsing a new predictive and prognostic role.

Keywords: Mediastinal staging; lung cancer; ^{18}F-FDG-PET/CT

Submitted Nov 04, 2017. Accepted for publication Nov 21, 2017.
doi: 10.21037/jtd.2017.11.137
View this article at: http://dx.doi.org/10.21037/jtd.2017.11.137

Introduction

Mediastinal lymph node staging is a crucial aspect in the diagnostic and therapeutic work up of non-small cell lung cancer (NSCLC), as it influences both their prognosis and management (1). In 2007, the European Society of Thoracic Surgery (ESTS) first published an integrated algorithm on mediastinal staging based on imaging, endoscopic and surgical techniques with a high negative predictive value (NPV) of 0.94 (2,3), although the best treatment of N2 disease is still controversial due to its high heterogeneity. In this regard, Rusch *et al.* (4) examining 2,876 patients on 4,277 N2-NSCLC patients who underwent R0 surgical resection without any inductive therapy, showed that: (I) the prognosis for single lymph node (N) station (N2a) was the same as N1 patients (5 years survival: 34% *vs.* 35%); (II) the outcome of patients with multiple pathological N2 patterns (N2b) was worse than N2a (5 years survival: 34% *vs.* 20%). In addition, a N2b pathology should be distinguished from N2 bulky disease which, as reported by the American College of Chest Physicians Guidelines (ACCP) (5), is characterized by the radiological finding of mediastinal infiltration that does not allow any morphological distinction or dimensional characterization of lymph nodes. The purpose of the study was to establish the role of 18-fluorine fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET/CT) in the evaluation of NSCLC lymph node mediastinal status.

^{18}F-FDG-PET/CT and mediastinal staging

Staging is performed with different complementary invasive and non-invasive tests. Computed tomography (CT) remains the cornerstone in imaging of lung cancer but, due to its low sensitivity and specificity, it is impossible

to rely only on CT scan (5). Prior to the introduction of PET and its hybrid form (PET/CT), the dimensional criterion at CT appeared to be the only imaging resource available to discern the presence of pathological lymph node involvement and with both low sensitivity (overall sensitivity: range, 57–68%) and specificity (overall specificity: range, 76–82%) (6). PET/CT is a non-invasive staging method of the mediastinum (N2–N3 disease) and, currently, its role is primarily in triaging patients by identifying nodal and metastatic status. However, despite its accuracy for nodal malignancy detection, the cut-off of the maximum standardized uptake value (SUV_{max}) >2.5 is associated with a wide range of sensitivity (40–97%) and specificity (60–96%) (7-9), due to different independent factors: (I) patients' population: habitus, plasma glucose levels, respiratory rate; (II) biological behaviour of tumors: size, location, differentiation, glucose transporter (GLUT) receptor expression, metabolism and glucose clearance; (III) administration and dose of radio-tracer; (IV) imaging acquisition: timing, resolution variability, region of interest (ROI), reconstruction, observational variability (10); (V) the adoption of cut-off criteria for malignancy; (VI) the normalization of SUV_{max} according to mediastinal baseline activity (11). In fact, this latter can elevate the apparent SUV_{max} of a lymph node by hesitating in the "spill-in" and "shine-through" effects, i.e., an intensity summation between SUVs (12,13). This results in a relative instrumental variability of up to 20% (14,15) that has been widely investigated by a recent Cochrane meta-analysis (16). The authors, by including forty-five studies and 6,095 patients, explored both the aspects and limits of mediastinal evaluation with PET/CT. In particular, they reported significant differences both in methods and tracer-dose injections ("protocol bias"). Moreover, they noted some patient-related peculiarities, as studies performed in Western Countries showed greater sensitivity and lower specificity than those performed in Asian ones (AUC: 0.81 *vs.* 0.69, P=0.045 and AUC: 0.84 *vs.* 0.91, P=0.035, respectively), due to a greater proportion of adenocarcinomas in non-smoker patients in the latter. Concerning radiotracers, ^{18}F-FDG dose was associated with overall diagnostic accuracy and its proposed dose was of 300MBq (sensibility: 74% and specificity: 95%). According to these results, the authors concluded that PET/CT alone is insufficient to allow a proper management of NSCLC and should be a part of a clinical pathway supported by other investigations.

^{18}F-FDG-PET/CT N2 disease: the issue of false negative and false positive results

Although PET/CT is widely used for the study of hilar and mediastinal lymph node malignancies, its results and its benefits are inconsistent (17) due to the occurrence of both false negative and false positive findings. The first ones are found in 7–16% of cases (18), while falsely positive reports are attributable to inflammatory or infectious processes that may increase local glycemic metabolism and thus SUV_{max} (19). Kaseda *et al.* (20), studying 388 NSCLC patients including 76 of whom (19.6%) with PET-avid mediastinal lymph nodes, displayed a NPV and a positive predictive value (PPV) of 56.3% and 87.7 %, respectively. False negative results were reported in 12.3% and the associated risk factors were a central tumor location (P=0.037), adenocarcinomatous histology (P=0.001) and tumor size greater than 3 cm (P=0.002). Gómez-Caro *et al.* (21) reported a 32% prevalence of occult nodal disease. In a study by Park *et al.* (22) involving 144 patients with cN0 NSCLC who underwent preoperative PET/CT, the frequency of nodal upstaging was 14.3%; the actual frequencies of N1 and N2 involvement were 9.5% and 4.8% respectively, while Casiraghi *et al.* (23) highlighted a 13% rate of occult nodal metastases (29 pN+ of 190 NSCLC cN0 patients). However, among the risk factors for false positives results, the history of lung disease (P<0.001) and central tumor location (P=0.021) were recognized (20).

SUV_{MAX} derived ratios for N2 disease assessment

New semi-quantitative and semi-qualitative indexes have been proposed. Among these, the ratio between overall lymph node SUV_{max} to SUV_{max} of primary tumor ($SUV_{n/t}$) and SUV_{index}, as $SUV_{n/t}$ multiplied by primary pulmonary tumor dimension, were studied. Liu *et al.* (9), reported 170 mediastinal lymph node stations from 73 NSCLC patients who underwent ^{18}F-FDG-PET/CT and with a LN SUV_{max} between 2.0 and 7.0. All patients underwent systemic lymphadenectomy for histologic assessment. The authors reported encouraging results in prediction of N2 disease by adopting both SUV_{index} (AUC =0.71, P<0.001) rather than SUV ratio (AUC =0.59, P=0.09) or SUV_{max} alone (AUC =0.67, P<0.001). Moreover, the difference between SUV_{index} and $SUV_{n/t}$ was statistically significant (P=0.0245); for these reasons, the authors proposed firstly the adoption of the index. Mattes *et al.* (10), analyzing 504 intermediate-positive mediastinal lymph nodes in

172 patients undergoing ^{18}F-FDG-PET/CT (tracer dose: 400 MBq) before or after endoscopic biopsy, reported that $SUV_{n/t}$ was significantly more accurate in predicting lymph node malignancy (AUC =0.846) than SUV_{max} (AUC =0.653) and indicated that the optimal cut-off was 0.28 with 90% sensitivity and 68% specificity. Moreover, the authors revised LN SUV_{max} threshold to 2.85 with 93% sensitivity and 82% specificity. Cerfolio *et al.* (24), in a series of 239 patients with 335 FDG-avid mediastinal lymph nodes, reported that a $SUV_{n/t}$ of 0.56 was the optimal cut-off with a sensitivity of 94% and specificity of 72%, respectively. Iskender *et al.* (25), analyzing 223 PET-positive lymph nodes, identified 0.49 as the optimal cut-off of $SUV_{n/t}$ (70% sensitivity and 65% specificity). On the contrary, Lee *et al.* (26), evaluating 104 lung cancer patients with 372 mediastinal LNs, did not detect any significant differences in $SUV_{n/t}$ cut-off between: (I) pathological and benign lymph nodes (0.4 *vs.* 0.4; P=0.18); (II) maximum Hounsfield units (mHUs) (137 *vs.* 81 HU; P=0.10) and average Hounsfield units (aHUs) (44 *vs.* 33 HU; P=0.38). However, this study showed an important limit since the majority of the enrolled population presented with a primary pulmonary adenocarcinoma and therefore both data collection and results, influenced by the peculiar biological characteristics of this tumor. Even in this case, there was a high degree of variability due to different study designs. In fact, while Mattes *et al.* (10) conducted their analysis only on a cohort of intermediate FDG-avidity LNs (SUV_{max} from 2.0 to 6.0), the other studies (24,26) included in the analysis all patients with SUV_{max} greater than 2.5. Although semi-quantitative indexes have a discrete diagnostic performance, the problem of false positives and negatives still remains. These are related to technical factors that can interfere with the glucose uptake and therefore with SUV_{max}. First of all the partial volume effect (PVE), which is the PET/CT resolution limit that hesitates in a SUV_{max} underestimation for smaller lesions and could generate false negative findings for lymph nodes smaller than the primary lung cancer. The issue is even more important in the case of mediastinal lymph nodes, since their involvement is usually characterized by microscopic invasion (8). In this regard, Gould *et al.* (27) reported that smaller lymph nodes are more likely to be malignant than larger ones if their SUV_{max} is comparable to the primary neoplasm, suggesting a profound revision of the role of SUV for small lesions. Another PET-related false negative result comes from both the doubling time and tumor differentiation, as in the case of ground glass nodules (19). Finally, false negatives can be found after performing mediastinoscopy. In particular, the presence of suspected PET LNs could be denied by the bioptic procedure, due to its rate of false negative results of 4.4–8.2 (28). Concerning "spilling-in" effects, other quantitative comparative ratios have been suggested. Kuo *et al.* (29), in a retrospective study of 102 patients with NSCLC, proposed the node to the aorta and the node to liver SUV ratio. The authors demonstrated that a node/aorta SUV ratio >1.37 and a node/liver SUV ratio >1.02 exhibited a sensitivity of 85.7% and 71.4% and specificity of 50.5% and 61.9% for staging N2-disease, validating their diagnostic value. In addition, these proposed reports also allow a prognostic stratification of cN2 NSCLC patients. Indeed, as reported by Stiles *et al.* (30) analysing 503 patients with NSCLC in a quartile cohort study, $SUV_{n/t}$ correlates with prognosis in a scalar manner (3 years disease-free survival Q1 =73% *vs.* 3 years disease-free survival Q4 =58%; P=0.01).

Conclusions

The evaluation of N2-disease in NSCLC patients represents a milestone for the therapeutic process and ^{18}F-FDG-PET/CT plays an indispensable and complementary role in the diagnostic pathway, as this examination highlights peculiar characteristics of the disease itself. The adoption of standardized indexes would allow both technical and protocol bias to be overcome in order to have a valid comparison between patients and different centers. From literature, it seems now clear that SUV_{max} as the only predictive and prognostic parameter of the disease has been overcome. In fact, SUV_{max} have to be correlated with dimensional and tomographic attenuation characteristics which are fundamental for a correct preoperative evaluation of patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of Interest to declare.

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Cite this article as: Divisi D, Barone M, Crisci R. Current role of standardized uptake valuemax-derived ratios in N2 fluorine-18 fluorodeoxyglucose positron-emission tomography non-small cell lung cancer. J Thorac Dis 2018;10(1):503-507. doi: 10.21037/jtd.2017.11.137

