ORIGINAL ARTICLE

The role of Positron Emission Tomography in mediastinal staging of patients with non-small cell lung cancer

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Abstract

Objective: To examine the diagnostic accuracy of positron emission tomography/computed tomography in evaluating the mediastinum of patients with non-small cell lung cancer compared to histopathology results.

Methods: The prospective study was conducted at the Department of Thoracic Surgery of the Pulmonary Hospital in Zakopane, Poland, from September 2008 to August 2012 and comprised patients with radiologically-suspected lung cancer. All patients underwent histological verification by either mediastinoscopy alone or thoracotomy with mediastinal lymphanedectomy. Computed tomography and positron emission tomography/computed tomography data sets were compared with the results of the histopathology examinations.

Results: There were 80 patients in the study. In the diagnosis of mediastinal lymph nodes, computed tomography was able to detect 9(11.25%) true-positive, 17(21.25%) false-positive, 40(50%) true-negative and 14(17.5%) false-negative cases. The sensitivity, specificity and accuracy of the method were found to be 39%, 70% and 61% respectively, while the positive and negative predictive values were 35% and 74%. Positron emission tomography/computed tomography yielded 15(18.75%) true-positive, 12(15%) false-positive, 46(57.5%) true-negative and 7(8.75%) false-negative cases. Sensitivity was 68% while specificity was 79%. The accuracy was 96%, and the positive and negative predictive values were 55% and 87% respectively.

Conclusion: Positron emission tomography/computed tomography had higher diagnostic accuracy than computed tomography in assessing mediastinal lymph nodes of patients with non-small cell lung cancer. However, a positive test requires histopathology confirmation.

Keywords: PET-CT, Lung cancer, Tumour Staging, 18F-FDG. (JPMA 65: 35; 2015)

Introduction

In patients with small cell lung cancer (SCLC), staging of disease in the chest and other areas of the body determines the eligibility of patients for radical surgery. The presence of metastases outside the chest determines eligibility for palliative treatment only. Lymph node metastases on the same side where the primary tumour happened to be is usually not a contraindication to surgical intervention, whereas patients with underlying disease located on the other side (relative to the primary tumour, stage IIIB of the American Joint Committee of Cancer, [AJCC])[1] often do not qualify for surgery because of the associated high operational risk and poor prognosis.

Lymph node size is a criterion to determine metastatic disease. The current consensus considers a lymph node with a short-axis diameter greater than 1cm as a predictor for metastasis.[2] In the preoperative staging of lung cancer, the appearance of the lymph nodes on computed tomography (CT) image has a weak prognostic index since the node may be enlarged due to inflammation or infection and micro-metastatic spread can be found in normal-sized nodes. In this respect, the sub-optimal sensitivity, specificity and diagnostic accuracy of CT and magnetic resonance imaging (MRI) have been established.[3-5]

Positron emission tomography (PET) with 18-F labelled fluorodeoxyglucose (FDG) allows the evaluation of tumour metabolism by showing the tumour as having far greater glucose demand than normal tissues and organs. By integrating functional and anatomic data, PET/CT improved N-staging compared to CT alone. Indeed the benefit of PET/CT compared with PET in nodal staging results mainly in an increase in specificity and positive predictive value (PPV) with additional accurate anatomic information. The sensitivity of PET for detecting distant extra cerebral metastases is very high.[6] The sensitivity and specificity of preoperative PET for mediastinal lymph nodes was proven to be 83% and 85%; specificity was between 89% and 92%[7-9] (Table-1).

It is not clear whether PET/CT scan can reduce mediastinoscopy. The general consensus is that PET/CT can reduce further invasive mediastinal staging because of its high negative predictive value (NPV).

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The current study was planned to examine preoperative diagnostic accuracy of PET-CT in the evaluation of patients with mediastinal lung cancer.

Patients and Methods

The prospective study was conducted at the Department of Thoracic Surgery of the Pulmonary Hospital in Zakopane, Poland, from September 2008 to August 2012 and comprised patients with radiologically-suspected lung cancer.

CT scan of the chest was performed prior to PET scanning. On further analysis, those patinets were excluded who were not found fit enough for the procedure.

The remaining patients were treated with mediastinoscopy performed by Transcervical Extended Mediastinal Lymphadenectomy (TEMLA) and/or thoracotomy. Specimens obtained were sent for histological evaluation.

Chest CT scans performed outside our institute were done by specialist radiologists with 15-year experience in oncologic radiology. Mediastinal lymph nodes with a diameter of >1cm were interpreted as suspicious for metastatic lung cancer. The exact localisations were verified.

Foci with pathological FDG uptake on PET/CT scan were identified and quantified using the Standard Uptake Value (SUV). An uptake was considered positive when the following occurred: if the uptake matched with a lymph node, if the uptake showed a maximum SUV (SUVmax) value higher than the physiological mediastinal uptake, and if the uptake was not able to diffuse FDG accumulations suspected of inflammation and/or infection in the surrounding organs and tissues.

After thoracotomy, the specimens were evaluated by a pathologist and the mediastinal metastatic lymph nodes were identified into groups.

All results of diagnostic CT and PET/CT were compared with those of pathological examinations. Since the number of patients was sufficient to perform statistical analysis with the possibility of reaching conclusions applicable in a clinical setting, therefore sensitivity, specificity and accuracy of both methods were calculated, as well as positive and negative predictive values (PPVs and NPVs).

Results

Of the 92 patients initially enrolled, 12(13%) were excluded as 1(1.08%) patient died before mediastinoscopy could be performed, and 11(12%) were found to be unfit for the procedure. The remaining 80(87%) patients represented the study sample. Of them, there were 59(73.75%) were men and 21(26.25%) were women (Table-2).

Accumulation of FDG in the primary tumour of the lungs, as seen on PET/CT, was present in all the 80(100%) patients, with an average SUVmax of 8.66±4.9.

Table-1: Evaluation of N staging with PET/CT compared with PET and CT in meta-analytical series.

	CT mediastinal staging		PET mediastinal staging	
Meta-analysis	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Gould et al (2003)[6]	61 (50-71)†	79 (69-98)†	85 (67-91)†	90 (82-96)†
Toloza et al (2003)[7]	57 (49-66)*	82 (77-86)*	84 (78-89)*	89 (83-93)*
Birim et al (2005)[8]	59 (50-67)*	78 (70-84)*	83 (77-87)*	92 (89-95)*

*= Mean sensitivity and specificity, in brackets 95% confidence intervals.
†= Median sensitivity and specificity, in brackets inter-quartile range.
PET/CT: Positron emission tomography/computed tomography.

Table-2: Baseline characteristics.

Gender (men: women)	59:21:00
Median Age (years)	62.8 (40 to 80)
Average SUV_{max} value of primary tumor	
Range	8.66 ±4.9
Average SUV_{max} value of mediastinal lymph nodes	
Range mediastinic Nodes (Range)	2±1.8
Lymph node sampling (n. %)	
TEMLA	43 (53.5%)
TEMLA+Thoracotomy	37 (46.5%)
Histopathology:	
Squamous cell carcinoma	45 (57%)
Adenocarcinoma	32 (41%)
Large cell carcinoma	2 (2%)
Neuroendocrine cancer	1 (1%)

SUV: Standardised Uptake Value
TEMLA: Transcervical Extended Mediastinal Lymphadenectomy.

Table-3: Results of CT and PET/CT in mediastinal staging. Data on a per-patient basis.

	PET/CT	CT
True positive results	15	9
False positive results	12	17
True negative results	46	40
False negative results	7	14
Sensitivity	68%	39%
Specificity	79%	70%
Accuracy	76%	61%
Positive predictive value	55%	35%
Negative predictive value	87%	74%
Test χ^2	p=0.0004	

PET/CT: Positron emission tomography/computed tomography.

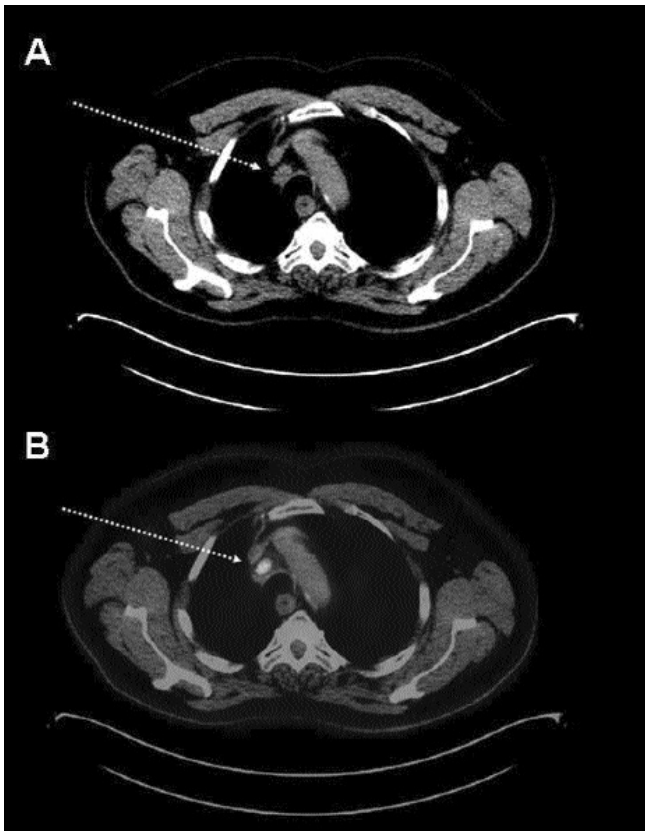

Figure: On the top (A): computed tomograpgy scan of the mediastinum with an oval right paratracheal lymph node having 8mm diameter on short axis (dotted arrow); on the bottom (B) Positron emission tomography/computed tomography fusion scan showing pathological fluorodeoxyglucose uptake at this site (dotted arrow).

Pathologic mediastinal FDG uptake (nodal group 1-8) was found in 23 (28.7%) patients. The uptake was located ipsilaterally in 19(23.7%) cases, while nodal uptake on the opposite side was observed in 4 (5%) cases. A typical pathologic radiopharmaceutical uptake within a central non-enlarged lymph node was noted (Figure).

Pathologically-enlarged lymph nodes were detected through CT in 25(31.25%) cases. There was an ipsilateral uptake in 21(26.2%) cases, and there was uptake on the opposite side in 4(5%). Mediastinal PET/CT and CT scan results were consistent in only 10(12.5%) patients.

PET/CT yielded 15(18.75%) true-positive, 12(15%) false-positive, 46(57.5%) true-negative and 7(8.75%) false-negative cases. Sensitivity was 68% while specificity was 79%. The accuracy was 96%, and the positive and negative predictive values were 55% and 87% respectively (Table-3).

Discussion

The characteristics of the subjects in the study did not differ substantially from those reported by global epidemiological data for lung cancer. In particular, the distribution by gender, age and histology was comparable to data concerning the spread of lung cancer in Pakistani population.[10]

The systematic review (Table-1) clearly defined the better diagnostic performance of PET/CT over CT for N-staging. Indeed, the most important feature of PET-CT in patients with NSCLC is the correct localisation of N1 metastatic lymph nodes over N2/N3. Metabolic imaging can therefore differentiate between AJCC stage IIIA (potentially operable) and IIIB (usually not operable).

On the other hand, the results of a recent prospective study involving a large group of patients questioned the sensitivity and accuracy of PET,[11] and the clinical significance of false positive and negative results with it.[12,13] Another meta-analysis[14] of 14 studies showed that lymph node size has a significant impact on the results of PET. The probability of mediastinal spread in a patient with negative PET having lymph nodes <15mm in diameter is only 5%, but the probability increases to 21% if the diameter of the lymph nodes is above 16mm. It is important to stress that NSCLC patients with higher preoperative risk can benefit more from PET-CT, as demonstrated by studies.[15] In fact, in these patients a negative mediastinal PET avoids the need for invasive procedures such as mediastinoscopy. In patients in advanced AJCC stages IIIB or IV, the presence of positive lymph nodes on the opposite side of the primary tumour avoids the need for surgery.

In our group, a positive result in the metabolic assessment of mediastinal lymph nodes was associated with a three-fold higher risk of metastasis which was more statistically significant than the negative results obtained from PET/CT. This translates directly into higher predictive values compared to CT examination. The comparative analysis of positive and negative results of chest CT and PET/CT scans suggests that the latter is more accurate in the evaluation of mediastinal lymph nodes. The true results accounted for only 61% of the CT scans, and 76% of the PET/CT scans.

The current study did not take into account the PET evaluation criteria adopted by some studies (visual or SUV-based).

Conclusion

The study confirmed high specificity level and average sensitivity level of PET/CT. The NPV was satisfactory and suitable for clinical decision-making. Suboptimal sensitivity of PET/CT is with a small occurrence of

metastasis at its early stage of development. On the other hand, the risk of a false positive value is significant and, therefore, positive results obtained from mediastinal PET/CT always require histopathological confirmation.

References

1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. 7th ed. New York, NY: Springer; 2010.
2. Verschakelen JA, Bogaert J, De Wever W. Computed tomography in staging for lung cancer. Eur Respir J 2002; 35: 40s-48s.
3. Sommer G, Wiese M, Winter L, Lenz C, Klarhöfer M, Forrer F, et al. Preoperative staging of non-small-cell lung cancer: comparison of whole-body diffusion-weighted magnetic resonance imaging and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography. Eur Radiol 2012; 22: 2859-67.
4. Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003; 348: 2500-7.
5. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. Chest 2002; 122: 1037-57.
6. Li J, Xu W, Kong F, Sun X, Zuo X. Meta-analysis: accuracy of 18FDG PET-CT for distant metastasis staging in lung cancer patients. Surg Oncol 2013; 22: 151-5.
7. Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med 2003; 139: 879-92.
8. Toloza E, Harpole L, McCrory D. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003; 123: 137S - 46S.
9. Birim O, Kappetein AP, Stijnen T, Bogers AJ. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. Ann Thorac Surg 2005; 79: 375-82.
10. Moore MA, Ariyaratne Y, Badar F, Bhurgri Y, Datta K, Mathew A, et al. Cancer epidemiology in South Asia - past, present and future. Asian Pac J Cancer Prev 2010;11: 49-66.
11. Billé A, Pelosi E, Skanjeti A, Arena V, Errico L, Borasio P, et al. Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: accuracy of integrated positron emission tomography and computed tomography. Eur J Cardiothorac Surg 2009; 36: 440-5.
12. Tandberg DJ, Gee NG, Chino JP, D'Amico TA, Ready NE, Coleman RE, et al. Are discordant positron emission tomography and pathological assessments of the mediastinum in non-small cell lung cancer significant? J Thorac Cardiovasc Surg 2013; 146: 796-801.
13. Al-Sarraf N, Aziz R, Gately K, Lucey J, Wilson L, McGovern E, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008; 33: 104-9.
14. de Langen AJ, Raijmakers P, Riphagen I, The size of mediastinal lymph nodes and its relation with metastatic involvement:a meta-analysis. Eur J Cardiothorac Surg 2006; 29: 26-9.
15. Baum RP, Hellwig D, Mezzetti M. Position of nuclear medicine modalities in the diagnostic workup of cancer patients: lung cancer. Q J Nucl Med Mol Imaging 2004; 48: 119-42.