Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography

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Received 28 June 2007; revised 22 September 2007; accepted 27 September 2007. Available online 30 October 2007.

Abstract

Objective: We sought to assess the incidence, pattern and predictors of occult mediastinal lymph node involvement (N2) in non-small cell lung cancer patients with negative mediastinal uptake of 2-deoxy-2-[^{18}F]-fluoro-d-glucose (^{18}FDG) on integrated positron emission tomography-computerised tomography (PET-CT). **Methods:** All patients who underwent surgical resection in our unit over a 30-month period were reviewed (*n* = 215). All patients had preoperative PET-CT prior to lung resection as an adjunct to a dedicated chest CT. Diabetic patients, patients who received neoadjuvant chemotherapy and those with positive mediastinal nodes on PET-CT (N2/N3) were excluded from this study. The population of interest was 153 non-small cell cancer patients (NSCLC), all of which had no FDG uptake in the mediastinum. No preoperative mediastinoscopy was carried out in this group and all underwent curative intent surgical resection. The pathological results were retrospectively reviewed and correlated with CT and integrated PET-CT findings. **Results:** The incidence of occult N2 disease in NSCLC patients with negative mediastinal uptake of ^{18}FDG on PET-CT was 16% (25 of 153). The highest incidence of occult N2 involvement was in American thoracic society (ATS) 7 (16 of 25 patients, 64%) followed by ATS 4 (seven patients of 25, 28%). In univariate analysis, the following were significant predictors of occult N2 disease: centrally located tumours (*P* = 0.049), right upper lobe tumours (*P* = 0.04), enlarged lymph nodes (>1 cm) on CT (*P* = 0.048) and PET positive uptake in N1 nodes (*P* = 0.006). In multivariate analysis, the following were independent predictors of occult N2 disease: centrally located tumours, right upper lobe tumours and PET positive uptake in N1 nodes (*P* < 0.05). **Conclusions:** In NSCLC patients who are clinically staged as N2/N3 negative in the mediastinum by integrated PET-CT, 16% will have occult N2 disease following resection. Patients with the following: centrally located tumours, right upper lobe tumours and positive N1 nodes on PET should have preoperative cervical mediastinoscopy to rule out N2 nodal involvement, especially in ATS stations 7 and 4 as the incidence of occult nodal metastasis in these nodes is high. This study has potential implications in decision-making and planning best treatment approach.

Keywords: Positron emission tomography; Lymph node staging; Cervical mediastinoscopy

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1. Introduction

Lung cancer remains the leading cause of death among all cancers. In 2006 more than 170,000 new cases were diagnosed in USA alone [1]. Despite adequate advances in surgical management, chemo-radiotherapy and early diagnoses, prognosis is still poor with an overall 5-year survival rate of 14% [2]. The key to successful management relies on multiple factors including an accurate staging. Positron emission tomography (PET) remains the most accurate non-invasive staging tool so far in mediastinal staging. Furthermore, the development of new treatment strategies such as neo-adjuvant chemotherapy, adds to the necessity of detecting mediastinal nodal spread in the hope of downstaging tumours prior to surgical resection to achieve a better prognosis.

PET detects primary non-small cell cancer patients (NSCLC) and mediastinal nodal involvement based on the metabolic uptake of these tumours [3]. PET has been reported throughout recent studies to be highly sensitive and specific in detecting nodal spread especially among N2 positive nodes [4], [5] and [6]. Despite that, cervical mediastinoscopy is still required to verify those positive mediastinal nodes. The consensus that patients with negative mediastinal uptake should undergo resection directly has been the practice in many centres, including our own. Our aim in this study was to evaluate our experience with such a

strategy and to try to refine the indication of cervical mediastinoscopy in patients with negative mediastinal uptake on integrated PET-CT. Accurate prediction of factors associated with occult N2 involvement will allow cervical mediastinoscopy to be used appropriately and sparingly.

2. Methods

2.1. Patients and staging

Over a 30-month period, 215 consecutive patients with histologically proven NSCLC underwent staging with integrated PET-CT as an adjunct to CT prior to lung resection. All diabetics, patients who received neo-adjuvant chemotherapy and patients with positive mediastinal uptake on integrated PET-CT (i.e. N2/N3) were excluded (n = 62). The remaining 153 patients were staged as N2/N3-negative by PET-CT and underwent resection with systematic lymph node dissection with no preoperative mediastinoscopy or anterior mediastinotomy. All clinical, operative, radiological and pathological findings were reviewed retrospectively through the review of departmental reports and radiological imaging. Histological classification of NSCLC was based on WHO classification [7]. Preoperative and postoperative staging was based on the tumour-node-metastasis (TNM) staging system [8]. This study was approved by our review board.

2.2. CT imaging

All studies (CT and PET-CT) were interpreted independently. CT examination was performed using Helical scanner (Somatom +4 scanner, Siemens, Germany). All patients had contrast-enhanced CT. Lymph nodes were considered pathological if they were >1 cm in short-axis diameter. All positive nodes were localised according to American thoracic society (ATS) guidelines [9]. A tumour is deemed central if the centre of the tumour is located into the inner 1/3 of the lung parenchyma (adjacent to the mediastinum) on the transverse CT image. Non-centrally located tumour is a tumour in which its centre lies in the outer 2/3 of the lung parenchyma on transverse CT image. All CT images were performed within 4 weeks of surgery.

2.3. Integrated PET-CT imaging

We have previously reported our technique in PET-CT scanning [10]. ^{18}FDG-PET-CT was performed using integrated PET-CT scanner (Discovery ST, GE Medical systems). Patients were fasting for 6 h prior to the procedure and the images were obtained 1 h after intravenous administration of ^{18}FDG. Two-dimensional acquisition method was used. All patients were asked to void just before scanning.

Patients continued to rest for an uptake period of 1 h. Images were obtained from the base of the skull to mid-thigh level. Attenuation-corrected images were obtained and interpreted by an experienced nuclear medicine physician. Primary lesions were considered pathological (i.e. positive) if a definite localised area of higher ^{18}FDG uptake than the surrounding normal tissue existed (excluding physiological uptake). Nodal uptake with a standardised uptake value (SUV_{max}) >2.5 were considered positive. For determination of SUV, a cylindrical region of interest (ROI) was manually placed over the tumour site on the hottest trans-axial slice. The activity concentration within the ROI was determined and expressed as the SUV, where SUV is the ratio of the activity in the tissue to the decay-corrected activity injected into the patient. All SUV measurements were normalised for patient body weight. The maximum SUV within a region of interest (SUV_{max}) was used as our reference measurement [11].

2.4. Surgical resection

All patients underwent resection through a posterolateral thoracotomy. Systematic lymph node dissection was carried out in stations 2, 4, 7, 8, 9, 10 in right-sided tumours, and in 5, 6, 7, 8, 9, 10 for left-sided tumours. The remaining N1 nodes were removed as part of the resection specimen. No preoperative cervical mediastinoscopy was employed in this cohort as the indication for such a procedure in our centre remains a positive uptake in mediastinum (i.e. N2 or N3) with nodal SUV_{max} >2.5. All resected specimens were examined by an experienced pulmonary pathologist using standard techniques with immunohistochemistry performed as per the pathologist's discretion.

Occult N2 involvement refers to a pathologically positive lymph node in a mediastinal lymph node station that was preoperatively staged as N2/N3 negative by integrated PET-CT.

2.5. Statistical analysis

The software package SPSS v11.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analysis. Univariate analysis of data using Fischer's exact test, unpaired *t*-test and ANOVA were conducted where appropriate. Multivariate analysis was carried out using logistic regression (backwards stepwise) method. *P*-values were considered statistically significant if <0.05.

3. Results

Our cohort consisted of 89 men and 64 women with age ranges of 41–82 years and mean (±SD) of 65 (±8.8). All patients' operative and pathological variables together with their distribution are listed in Table 1. Only two patients had open and close thoracotomy due to invasion into unresectable structures (left atrium in the first case and oesophagus in the second case) but had systemic node dissection performed initially. The remaining 151 patients had lung resection and systemic lymph node dissection carried out by two

experienced cardiothoracic surgeons (E.M and V.Y). The breakdown of such procedures is listed in Table 1. A total of 883 lymph node stations were examined averaging six nodal stations per patient.

Table 1.

Patients, tumours and operative characteristics (*n* = 153)

Variable	Distribution
Gender	
Male	89 (58%)
Female	64 (42%)
Age (years)	
Mean ± SD	65 ± 8.8
Range	41–82
Subtype	
Adenocarcinoma	68 (44%)
Squamous	73 (48%)
Adenosquamous	4 (3%)
Pleomorphic	6 (4%)
Large cell	2 (1%)
Grade	
Well	9 (6%)
Moderate	98 (64%)
Poor	46 (30%)
Site	
Right	89 (58%)
Left	64 (42%)

Variable	Distribution
Primary tumour location	
Central	30 (20%)
Non-central	123 (80%)
Lobar distribution[a]	
RUL	52 (34%)
RML	12 (8%)
RLL	25 (16%)
LUL	45 (29%)
LLL	19 (13%)
Pathological stages (AJCC)	
1A	37 (24%)
1B	49 (32%)
2A	3 (2%)
2B	25 (16%)
3A	29 (19%)
3B/4	10 (7%)
Tumour stage (T)	
T1	45 (29%)
T2	83 (54%)
T3	16 (11%)
T4	9 (6%)
Node stage pathological (N)	
N0	96 (63%)
N1	31 (20%)
N2	26 (17%)
N3	0

Variable	Distribution
Enlarged N2 (>1 cm) on CT	
Yes	27 (18%)
No	126 (82%)
PET positive N1 node	
Yes	20 (13%)
No	133 (87%)
Tumour size (cm)	
Mean ± SD	3.8 ± 1.8
Range	1–12
SUV_{max} of primary tumour	
Range	2.6–39
Mean ± SD	12.0 ± 6.0
Operation type	
Lobectomy	109 (71%)
Pneumonectomy	20 (14%)
Sleeve lobectomy	8 (5%)
Bilobectomy/lobectomy + wedge	14 (9%)
Open and close thoracotomy	2 (1%)

SD: standard deviation; percent of patients in parenthesis.

[a] RUL: right upper lobe; RLL: right lower lobe; RML: right middle lobe; LUL: left upper lobe; LLL: left lower lobe.

Incidence of occult N2 involvement is 16% (25 patients of 153). Univariate analysis for factors associated with occult N2 disease is summarised in Table 2. Factors that are significant in predicting occult N2 disease are: centrally located tumours ($P = 0.049$), right upper lobe tumours ($P = 0.04$), enlarged mediastinal nodes on CT ($P = 0.048$), and PET positive uptake

in N1 nodes (P = 0.006). Multivariate analysis for factors associated with occult N2 disease is summarised in Table 3. These factors are: centrally located tumours (P = 0.007), right upper lobe tumours (P = 0.017) and PET positive uptake in N1 nodes (P = 0.002). As can be seen in Table 4, the most common ATS station for occult N2 involvement was in ATS 7 (16 of 25, 64%) followed by ATS 4 (7 of 25, 28%).

Table 2.

Univariate analysis of factors associated with occult N2 disease in patients with negative mediastinal uptake on integrated PET-CT

Variable	**Pathological N2 (*n* = 25)**	**Pathological non-N2 (*n* = 128)**	***P*-value**
Sex			
Male	16 (64%)	73 (57%)	
Female	9 (36%)	55 (43%)	N/S
Subtype			
Adenocarcinoma	13 (52%)	55 (43%)	
Non-adenocarcinoma	12 (48%)	73 (57%)	N/S
Site			
R	11 (44%)	78 (61%)	
L	14 (56%)	50 (39%)	N/S
Site and nodes (on PET)			
Right			
N0	5 (20%)	70 (55%)	
N1	6 (24%)	8 (6%)	0.001*
Left			
N0	12 (48%)	46 (36%)	N/S
N1	2 (8%)	4 (3%)	
Primary location			

Variable	Pathological N2 (*n* = 25)	Pathological non-N2 (*n* = 128)	*P*-value
Central	9 (36%)	21 (16%)	
Non-central	16 (64%)	107 (84%)	0.049*
Lobar distribution			
RUL	4 (16%)	48 (38%)	0.04*
RML	0	12 (10%)	
RLL	7 (28%)	18 (14%)	N/S
LUL	10 (40%)	35 (28%)	
LLL	4 (16%)	15 (12%)	
Grade differentiation			
Good/moderate	17 (68%)	90 (70%)	
Poor	8 (32%)	38 (30%)	N/S
Primary location and size			
Mean size in central	5.48 ± 1.98	5.30 ± 2.38	N/S
Mean size in non-central	4.08 ± 1.63	3.37 ± 1.47	
Tumour size (cm)			
≤3 cm	8 (32%)	58 (45%)	N/S
>3 cm	17 (68%)	70 (55%)	
Tumour stage (T)			
T1/T2	19 (76%)	110 (85%)	
T3/T4	6 (24%)	18 (15%)	N/S
Enlarged N2 on CT			
No	17 (68%)	109 (85%)	
Yes	8 (32%)	19 (15%)	0.048*

Variable	Pathological N2 (*n* = 25)	Pathological non-N2 (*n* = 128)	*P*-value
Positive N1 on PET			
Yes	8 (32%)	12 (9%)	
No	17 (68%)	116 (91%)	0.006[*]
Tumour size (cm)			
Mean ± SD	4.6 ± 1.9	3.7 ± 1.8	
AC subtype only	4.0 ± 1.8	3.2 ± 1.4	N/S
Other subtype only	5.2 ± 1.8	4.1 ± 1.9	
SUV_{max} primary			
Mean ± SD (overall)	11.6 ± 5.4	11.6 ± 6.2	
AC subtype only	9.4 ± 4.5	8.1 ± 4.2	N/S
Other subtype only	14.0 ± 5.4	14.3 ± 6.1	
SUV_{max} primary[†]			
≤12	16 (64%)	71 (55%)	
>12	9 (36%)	57 (45%)	N/S

SD: standard deviation; RUL: right upper lobe; RLL: right lower lobe; RML: right middle lobe; LUL: left upper lobe; LLL: left lower lobe; N/S: not significant.

[*] Statistically significant (*P* value < 0.05).

[†] Mean SUVmax in study population was 12.

Table 3.

Multivariate analysis of predictors of occult N2 disease in patients with negative mediastinal uptake on integrated PET-CT

Variable	Odds ratio	Confidence interval	*P*-value
Central location	6.11	1.64–22.79	0.007[*]

Variable	Odds ratio	Confidence interval	*P*-value
RUL	0.221	0.06–0.77	0.017*
Positive N1 uptake on PET	0.164	0.05–0.53	0.002*

RUL: right upper lobe.

* Statistically significant (*P*-value < 0.05).

Table 4.

Pattern of N2 involvement in patients with negative mediastinal uptake on PET-CT (*n* = 25)

Patient number	N1 nodes on PET	Pathology positive	N2 station pathologically[a]
1	Negative	Positive	4
2	Negative	Positive	5
3	Negative	Positive	5
4	Negative	Positive	5
5	Negative	Positive	6
6	Negative	Positive	6
7	Negative	Positive	6
8	Negative	Positive	7
9	Negative	Positive	7
10	Negative	Positive	7
11	Negative	Positive	7
12	Negative	Positive	7
13	Negative	Positive	7
14	Negative	Positive	8
15	Negative	Positive	6, 7
16	Negative	Positive	4, 7, 9
17	Negative	Positive	5, 7, 8
18	Positive (ATS 10)	Positive	4
19	Positive (ATS 10)	Positive	7
20	Positive (ATS 10)	Positive	4, 7

Patient number	N1 nodes on PET	Pathology positive	N2 station pathologically[a]
21	Positive (ATS 10)	Positive	5, 7
22	Positive (ATS 10)	Positive	5, 7
23	Positive (ATS 10)	Positive	2, 4, 7
24	Positive (ATS 10)	Positive	2, 4, 7, 8
25	Positive (ATS 10)	Positive	2, 4, 7, 8

ATS: American thoracic society.

[a] Only pathologically positive N2 nodal stations are shown.

4. Discussion

Previous studies have shown superiority of PET over CT in mediastinal nodal staging [4], [5] and [6]. The presence of occult N2 disease in patients with negative mediastinal uptake on PET remains a problem. Cervical mediastinoscopy (though superior to both CT and PET) cannot be employed in all cases. The use of cervical mediastinoscopy non-selectively among stage 1 NSCLC is not cost-effective [12] as the incidence of N2 involvement is less than 3% [12] and [13]. On the other hand, as the result of our study reveals, 16% of patients with negative uptake in mediastinum on integrated PET-CT had occult N2 disease following resection. The key to solving this difficult equation relies somewhat on a middle solution based solely on identifying a high-risk population with specific preoperative characteristics that can justify the use of cervical mediastinoscopy. The opposite is also true, if we can identify a low-risk population for occult N2 involvement, then these patients can be spared an additional invasive procedure such as cervical mediastinoscopy. This was the basis of our study, as we attempted to define such a high-risk population where cervical mediastinoscopy can be well justified. The emerging evidence of neo-adjuvant chemotherapy prior to resection adds an extra demand for identifying those patients with occult N2 disease preoperatively in the hope of downstaging prior to resection [14].

Despite superior staging of PET in staging N2 disease, PET remains limited in accurately differentiating N1 from N2 involvement. Previous reports indicated that the use of integrated PET-CT improves anatomic localisation of lymph nodes compared to PET alone [4], regardless if they were N1 or N2. In our series, patients who were staged as N1 (Table 2) by integrated PET-CT had higher incidence of occult N2 disease (32% vs 9%, $P = 0.006$). Previous studies have reported that PET positive uptake in a hilar node is a risk factor for occult N2 disease [13] and [15]. In their work, Verhagen and colleagues [15] have shown that six out of eight patients with positive FDG uptake in N1 nodes had microscopic deposits in N2 nodes following resection and concluded that PET positive uptake in N1 nodes are predictive of microscopic involvement in N2 nodes. Whether this is the case or whether this is merely a

mis-localisation of N1 disease to N2 remains largely speculative. This remains consistent with our work, in which PET positive uptake in N1 node is a significant predictor of occult N2 disease in both univariate and multivariate analysis. Therefore, cases where PET is positive in N1 node could be potentially targeted by employing cervical mediastinoscopy where the risk of occult N2 disease is high. The pattern of N2 disease in this group seems to be involving ATS 7 (16 of 25 patients, 64%) and ATS 4 (seven of 25 patients, 28%) reflecting the close anatomic location of hilar nodes to ATS 7 and ATS 4 (Table 4).

Preoperative planning of the best surgical approach to individualised cases remains heavily dependant on tumour location and proximity to vital structures, which in turn dictate the use of more complex surgical resections than a standard lobectomy (e.g. sleeve resection or pneumonectomy). Centrally located tumours are associated with a higher incidence of occult N2 disease than non-centrally located tumours both in univariate analysis (P = 0.049) and multivariate model (odds ratio 6.11, Table 3).

One might argue the case that centrally located tumours might be larger in size than non-centrally located tumours; however, when both size and location were considered together in our analysis, no significant differences could be elicited (Table 2). This group of patients can be predicted prior to resections based on the preoperative CT images. Cervical mediastinoscopy can thus be a reasonable approach in such cases. This observation remains consistent with previously reported studies showing a higher incidence of N2 disease in NSCLC patients with centrally located tumours. The basis for this seems to be a failure to distinguish involved lymph nodes from the activity of the primary tumour because of a direct obscuring effect by the primary tumour itself [6] and [15].

The use of CT scan in this era as a stand-alone staging modality in mediastinal lymph node staging is rapidly declining in favour for PET and integrated PET-CT. This is evident as CT depends on the size of lymph nodes as an indicator of malignant lymph node involvement. Previous studies have shown that using CT criteria alone in mediastinal staging leads to a significant proportion of NSCLC patients having a false positive (up to 40%) and false negative (up to 21%) mediastinal nodal staging [16]. However, cases where N2 nodes are enlarged by CT criteria and are FDG-negative by PET criteria (Fig. 1) deserve particular attention as these nodes might be false negatives. These cases are associated with higher incidence of occult N2 involvement than the control group in univariate analysis (32% vs 15%, P = 0.048, Table 2). However in a multivariate model, enlarged lymph nodes on CT (>1 cm) did not achieve a statistical significance in independently predicting occult N2 disease, but showed a trend towards significance (P = 0.06, N/S). This result is compatible with previous results where the sensitivity of PET in mediastinal staging increases in patients with enlarged nodes but its specificity decreases as the lymph nodes size enlarges leading to a higher incidence of false negatives [17]. This in turn can be expected to increase the risk of occult N2 disease.

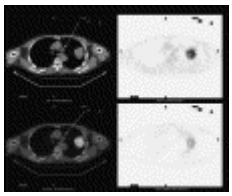

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Fig. 1. Integrated PET-CT image of a patient with evidence of positive N2 node on CT (arrow) but negative FDG uptake on PET. Pathologically, this patient had N2 involvement in that station.

Tumour site in relation to lobar involvement was a significant factor in our study in detecting occult N2 disease. Right upper lobe tumours were associated with a higher incidence of occult N2 disease in both univariate and multivariate analysis. Some earlier observations found that the incidence of occult mediastinal spread tends to be higher among RUL tumours than other sites in patients who are N2 negative by both CT and PET [13]. This may reflect a higher incidence of metastatic spread in one lobe or another due to the anatomical proximity to nodal involvement (especially ATS 7 and ATS 4). The impact of lobar location on nodal spread has been reported where right-sided tumours tend to spread predominantly to ATS 4 and ATS 7 [18]. Our results remain consistent with such observations and the most common ATS positions for detecting occult metastasis in our series were ATS 7 and ATS 4. Furthermore, the combination of right-sided tumours with positive FDG uptake in hilar node on PET was a significant factor in predicting occult N2 disease in univariate analysis (Table 2).

Pathological factors including tumour subtype, grade of differentiation, tumour size, T stage and SUV_{max} of primary tumours were not associated with a significantly increased incidence of occult N2 disease in our study raising the issue of limitation of such factors as predictors (Table 2). Even when attempting to examine some of these factors in combination (Table 2), no significant association was observed. These pathological factors tend to be associated with inherent biological aggressiveness of tumours [19] and are of prognostic significance rather than being predictors of occult metastasis in mediastinal nodes.

In our work, we tried to identify some risk factors for occult N2 disease that can justify the use of cervical mediastinoscopy sparingly and appropriately in NSCLC patients clinically staged as N2/N3 negative by PET-CT. However, whether such a strategy would lead to a lesser incidence of N2 disease in surgically treated patients remains unknown and only prospective randomised trials could properly confirm such findings and further refine the indication of preoperative mediastinoscopy in the era of PET-CT.

5. Limitations of the study

The main limitation of this study is the retrospective nature of our work. To establish the true incidence of occult N2 involvement among patients with negative mediastinal uptake on PET-

CT, prospective or randomised trials are warranted. We elected to exclude patients with neoadjuvant chemotherapy and diabetics as these cases can lead to considerable inaccuracy and this might have caused a selection bias. However, we have examined a relatively large number of patients overall that such a bias may not become significant.

6. Conclusions

Occult N2 involvement remains significant among NSCLC patients with negative mediastinal uptake on integrated PET-CT. These patients deserve particular attention in order to detect them at a reasonable time prior to resection. Cervical mediastinoscopy can be used sparingly in such a subgroup of patients in order to detect these occult nodes. This in turn will lead to a better staging and a better planning of best treatment modality. Larger and prospective trials are warranted.

Acknowledgements

We acknowledge the assistance of Ms Rita Luddy and Ms Mary Devlin in data acquisition.

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European Journal of Cardio-Thoracic Surgery
Volume 33, Issue 1, January 2008, Pages 104-109