

Paper

The mediastinal staging accuracy of 18F-Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography in non-small cell lung cancer with variable time intervals to surgery.

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ABSTRACT:

Background: PET/CT scanning can determine suitability for curative therapy and inform decision making when considering radical therapy in patients with non-small cell lung cancer (NSCLC). Metastases to central mediastinal lymph nodes (N2) may alter such management decisions. We report a 2 year retrospective series assessing N2 lymph node staging accuracy with PET/CT compared to pathological analysis at surgery.

Methods: Patients with NSCLC attending our centre (excluding those who had induction chemotherapy) who had staging PET/CT scans and pathological nodal sampling between June 2006 and June 2008 were analysed. For each lymph node assessed pathologically, the corresponding PET/CT status was determined. 64 patients with 200 N2 lymph nodes were analysed.

Results: Sensitivity of PET/CT scans for identifying involved N2 lymph nodes was 39%, specificity 96% and overall accuracy 90%. For individual lymph node analysis, logistic regression demonstrated a significant linear association between PET/CT sensitivity and time from scanning to surgery ($p=0.031$) but not for specificity and accuracy. Those scanned <9 weeks before pathological sampling were significantly more sensitive (64% <9 weeks, 0% \geq 9 weeks, $p=0.013$) and more accurate (94% <9 weeks, 81% \geq 9 weeks, $p=0.007$). Differences in specificity were not seen (97% <9 weeks, 91% \geq 9 weeks, $p=0.228$). No significant difference in specificity was found at any time point.

Conclusions: We recommend that if a PET/CT scan is older than 9 weeks, and management would be altered by the presence of N2 nodes, re-staging of the mediastinum should be undertaken.

INTRODUCTION

Lung Cancer is a leading cause of cancer death and non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers¹. Of the many prognostic factors that determine outcome in NSCLC, tumour stage grouping is the most important². 18-F Fluorodeoxyglucose (FDG) Positron emission tomography (PET) has improved staging in NSCLC as compared to computerised tomography (CT) scanning alone by detecting otherwise occult metastases².

Several meta-analyses have reported a high accuracy rate for FDG-PET staging of regional lymph nodes, with sensitivities of 79-85% and specificities of 89-92% compared to CT with sensitivities and specificities of 57-61% and 77-82% respectively, the results from these studies are summarized in table 1^{4,5,6,7}. Furthermore FDG-PET correlated with CT has been demonstrated to be being superior to its individual components and integrated FDG-PET/CT scanning better

that PET and CT visually correlated⁸⁻¹⁰. Two recent studies randomising patients to conventional staging without PET and conventional staging with PET/CT have shown a beneficial effect of the addition of PET/CT to conventional staging in appropriately selecting patients for curative therapy^{11,12}.

The impact of PET in routine clinical practice

FDG PET is now used routinely as a baseline staging tool in NSCLC. Most international guidelines now endorse the

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TABLE 1:

Mediastinal staging performance of CT as compared to PET in four meta-analytical series

Meta-analysis	CT mediastinal staging performance		PET mediastinal staging performance	
	Sensitivity	Specificity	Sensitivity	Specificity
Dwamena et al (1999) ⁴	60 (58-62)*	77 (75-79)*	79 (76-82)*	91 (89-93)*
Gould et al (2003) ⁵	61 (50-71) [†]	79 (69-98) [†]	85 (67-91) [†]	90 (82-96) [†]
Tolozza et al (2003) ⁶	57 (49-66)*	82 (77-86)*	84 (78-89)*	89 (83-93)*
Birim et al (2005) ⁷	59 (50-67)*	78 (70-84)*	83 (77-87)*	92 (89-95)*

Key to table: * = sensitivity and specificity measurement in means and range in brackets defined by 95% Confidence intervals.
[†] = sensitivity and specificity defined by median values and range in brackets defined by inter-quartile range.

routine use of PET in selecting patients for radical therapy^{13,14}. In our institution, pre-operative patients with FDG-PET negative mediastinal nodes as assessed by a PET radiologist are not routinely considered for biopsy of the Mediastinal nodes by mediastinoscopy. If considered for radical therapy, such patients proceed directly to surgery or radiotherapy to the primary lesion only. Patients who are considered for radical therapy and who have FDG-PET positive lymph nodes in the mediastinum will have confirmation of the pathological status of the involved lymph nodes with surgical sampling of positive lymph nodes. However, in patients with positive lymph nodes, where the pattern of disease, the activity on PET and the lymph node size are highly suggestive of nodal metastases the PET findings are presumed to be correct and no surgical sampling is undertaken. In addition to the role of FDG-PET for baseline staging in NSCLC, FDG-PET is now used for target definition in the treatment planning process for radical radiation therapy. A large number of radiotherapy planning studies have indicated that there is a significant benefit of using FDG-PET both for selection of patients and as target volume delineation tool^{13,15,16,17}.

Aim of Current Study

This study retrospectively compares the diagnostic accuracy of PET/CT scans in routine clinical practice at our institution in assessing the involvement of N2 disease. In this study we compare varying time frames from PET/CT to surgery with the accuracy of the PET/CT analysis and suggest an optimal timing of the using of PET/CT information or a “best before” time interval.

MATERIALS AND METHODS

Patient identification and data collection

In an institutionally approved retrospective study, we examined the records of all patients at our centre who had a staging FDG PET/CT scan followed by central Mediastinal lymph node (N2) staging, either at the time of radical surgery (lobectomy or pneumonectomy) or at mediastinoscopy, between June 2006 and June 2008. For all patients, at least 4 mediastinal (both N1 and N2) nodes were sampled. Pathological sampling from endoscopic or endobronchial ultrasound was not used. Patients were identified from the Belfast Lung Multidisciplinary Meeting database, which has

TABLE 2:

Study Population Baseline Characteristics

Gender (Male; Female)		35:29
Median Age (range)		65 years (42 to 82)
Median time from Scan to Sampling (Mean, Range)		8 weeks (8.5, 1 to 22)
Median SUVmax of Primary (Range)		11.8 (2.2 to 31.5)
Median SUVmax of Nodes (Range)		4 (2.1 to 11.4)
Surgery Type n (%)	Mediastinal Sampling	4 (6.2%)
	Lobectomy	38 (59.4%)
	Pneumonectomy	22 (34.4%)
Pathological Subtype n (%)	Squamous	36 (56%)
	Adenocarcinoma	25 (39%)
	Adenosquamous	1 (2%)
	Poorly Differentiated	2 (3%)
Pathological Stage (AJCC*) n (%)	I	27 (42%)
	II	23 (36%)
	III	13 (20%)
	IV (2 lobes involved)	1 (2%)
Tumour Stage (T) n (%)	1	8 (13%)
	2	46 (72%)
	3	7 (11%)
	4	3 (5%)
Nodal Stage (N) n (%)	0	36 (56%)
	1	18 (28%)
	2	8 (13%)
	3	2 (3%)

Key to table: SUVmax = Maximum Value of Standardised uptake value within tumour.

* = 6th Edition of American Joint Committee on Cancer staging

TABLE 3:

Sensitivity, specificity and accuracy of PET/CT staging of individual N2 lymph node analysis and timing from scanning to surgical sampling.

Time between PET/CT and Surgery	Patients (n)	TP	FP	TN	FN	Sensitivity* (%)	Specificity* (%)	Accuracy* (%)
≤ 6 Weeks	21	4	1	61	2	67 (22-96)	98 (91-100)	96 (88-99)
6-8 Weeks	17	3	3	65	2	60 (95-15)	96 (88-99)	93 (85-98)
9-12 Weeks	19	0	3	35	6	0 (0-46)	92 (79-88)	80 (65-90)
>12 Weeks	7	0	1	13	1	0 (0-98)	93 (66-99)	87 (60-98)
All Patients	64	7	8	174	11	39 (17-64)	96 (92-98)	91 (86-94)

Key to Table: TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative
* = 95% Confidence Intervals of result shown in brackets

been prospectively collecting full clinical information on all patients diagnosed with lung cancer in the Belfast area of Northern Ireland since 2006. Patients who had received interval treatment, such as induction chemotherapy, between PET/CT scanning and surgery were excluded from analysis. All patients were scanned using a GE Discovery LS fusion PET/CT scanner using a standardised imaging protocol. Patients were scanned after injection of FDG 375 MBq followed by a 45-min uptake period and CT scan acquisition. A standard diagnostic imaging protocol was used and no special breathing instructions were given during the CT acquisition. Image acquisition was from the vertex of the skull to the mid-thigh region. The PET/CT and pathology data were acquired for each patient. Four patients with nodal-sampling longer than 35 weeks after the staging PET/CT scan were excluded, given the very long time interval for these patients. For each lymph node assessed pathologically and with complete anatomical location descriptors from the surgical procedure, the corresponding radiological status on PET/CT for that given lymph node position was determined. Pathological subtype, size of the primary tumour on PET/CT scan and maximum standardized uptake value (SUV_{MAX}) of the primary and lymph nodes on PET for each patient were recorded. Metastatic involvement of a lymph node on PET/CT was deemed positive or negative by assessment by a consultant PET radiologist, blinded to the pathology report.

Analysis and Statistics

The lymph node status at pathology was considered as the gold standard for comparison purposes. Sensitivity was calculated as true positive / (true positive + false negative) x 100, specificity as true negative / (true negative + false positive) x 100 and accuracy as (true positive + true negative) / total number x 100. The students t-test was used to compare the means of normally distributed data and the Fisher's exact test were used for analysis of the categorical data, given the small numerators in many of the categories analysed. Logistic

regression was undertaken to assess the presence of any correlation between the accuracy of the PET/CT scanning and the time between the PET/CT scan and the surgical procedure. In the logistical regression analysis of the individual lymph node data with time, given that several nodes were taken from the same patient and scan and that these results may not be independent, analysis with robust standard errors was also performed to adjust for any over-estimation of power¹⁸. All calculations were performed using Stata version 9.2 (StataCorp LC, College Station, Texas, USA). Descriptive statistics were used where appropriate.

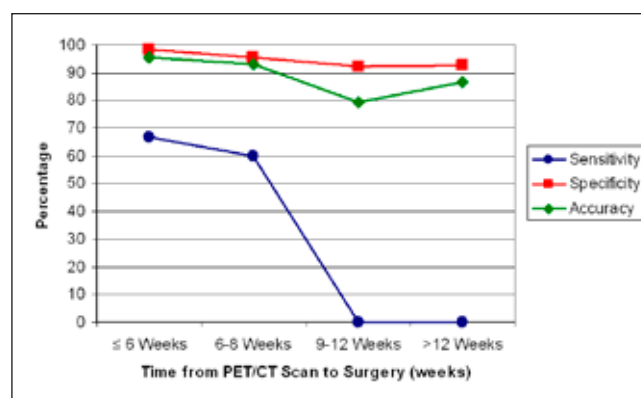


Fig 1. Sensitivity, Specificity and Accuracy of PET/CT staging of individual N2 lymph nodes at various time intervals between scanning and surgery.

RESULTS

Patient and tumour characteristics

From June 2006 to June 2008, sixty-four patients with NSCLC were identified who had been staged with PET/CT scanning and who had undergone subsequent pathological nodal sampling of N2 nodal stations. A total of two-hundred mediastinal (N2) individual lymph nodes were identified. The patient's baseline characteristics are shown in table 2.

The median time between staging PET/CT scan and lymph node sampling was eight weeks, reflecting an often complex assessment and treatment pathway for radical patients. The overall male to female ratio was 1.21 to 1 and the ratio for squamous carcinoma to adenocarcinoma was 1.44 to 1. Of note, adenocarcinomas had a significantly lower primary tumour SUV_{MAX} than tumours with squamous cell carcinoma pathology (mean 10.5 for adenocarcinoma versus 14.5 for squamous carcinoma, student's t-test $p=0.005$), had a non-significantly lower nodal SUV_{MAX} (mean 3.7 for adenocarcinoma versus 5.8 for squamous carcinoma, student's t-test $p=0.052$), and were of smaller size on staging PET/CT (median primary tumour size 3.6cm for adenocarcinoma versus 4.7cm for squamous carcinoma, student's t-test $p=0.042$).

Staging performance and the effect of time on staging accuracy for individual lymph node analysis

Analysis of the staging accuracy for individual lymph nodes revealed relatively poor overall correlation between PET/CT staging and pathological staging of mediastinal lymph nodes with a low sensitivity. The results obtained for all lymph nodes were closer to those expected from CT staging alone with an overall sensitivity 38%, specificity 96% and accuracy 91%. These results are summarised in table 3 and illustrated in figure 1. Using logistic regression, the association between sensitivity, specificity and accuracy with the time interval between PET/CT scanning and surgery was estimated. There was no association between specificity and time ($p=0.249$) and analysis of accuracy and time also failed to reach significance ($p=0.061$). However, logistic regression, demonstrated a significant reduction in sensitivity with time ($p=0.031$) and this remained significant after adjustment for any lack of independence of nodes by using robust standard errors ($p=0.007$). Three different time intervals between PET/CT scanning and surgical sampling (less or equal to

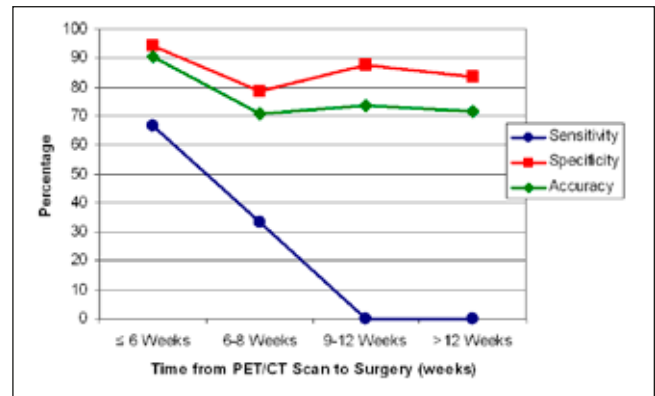


Fig 2. Sensitivity, Specificity and Accuracy of PET/CT staging of N2 lymph node status, for each patient at various time intervals between scanning and surgery.

6 weeks as compared to greater than 6 weeks, less than 9 weeks as compared to 9 weeks or greater and less than 12 weeks compared to greater than 12 weeks) were examined to see if at any given point in time was there a significant reduction in sensitivity, specificity or accuracy. At the cut-point of less than 9 weeks as compared to greater than or equal to 9 weeks from PET/CT scanning to surgery there was a statistically significant difference in the sensitivity and overall accuracy of N2 nodal detection (Fisher's exact test 2-sided significance, $p=0.013$ and $p=0.007$ respectively), with superiority in sensitivity and accuracy for those lymph nodes whose PET/CT scan was within 9 weeks of surgery (sensitivity 64% for less than 9 weeks as compared to 0% for greater than or equal to 9 weeks and accuracy 94% for less than 9 weeks compared to 81% for greater than or equal to 9 weeks). No significant difference for specificity was observed at any of the time intervals.

Staging performance and the effect of time on staging accuracy for individual scan analysis

TABLE 4:

Sensitivity, specificity and accuracy of PET/CT staging of N2 lymph nodes, analysed for individual patient scans with various time intervals from scanning to surgical sampling.

Time between PET/CT and surgery	Patients (n)	TP	FP	TN	FN	Sensitivity* (%)	Specificity* (%)	Accuracy* (%)
≤ 6 Weeks	21	2	1	17	1	67 (9-99)	94 (73-100)	90 (70-99)
6-8 Weeks	17	1	3	11	2	33 (8-91)	79 (49-95)	71 (44-90)
9-12 Weeks	19	0	2	14	3	0 (0-71)	88 (62-98)	74 (49-91)
>12 Weeks	7	0	1	5	1	0 (0-98)	83 (36-100)	71 (29-96)
All Patients	64	3	7	47	7	30 (7-65)	87 (77-96)	78 (66-88)

Key to Table: TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative

* = 95% Confidence Intervals of result shown in brackets

Analysing the staging accuracy based on the performance of each scan for staging N2 disease, similar results were found (see table 4 and figure 2). For all 64 patients, the sensitivity was 30%, specificity was 87%, and accuracy was 78%. In the comparison of sensitivity, specificity and accuracy with the time interval between PET/CT scanning and surgery, no association was found using logistic regression analysis (sensitivity $p=0.112$, specificity $p=0.448$, accuracy $p=0.205$). When the three various time intervals described above were compared, although early scans had greater staging accuracy, no significance difference in sensitivity, specificity and accuracy was observed between the various time intervals.

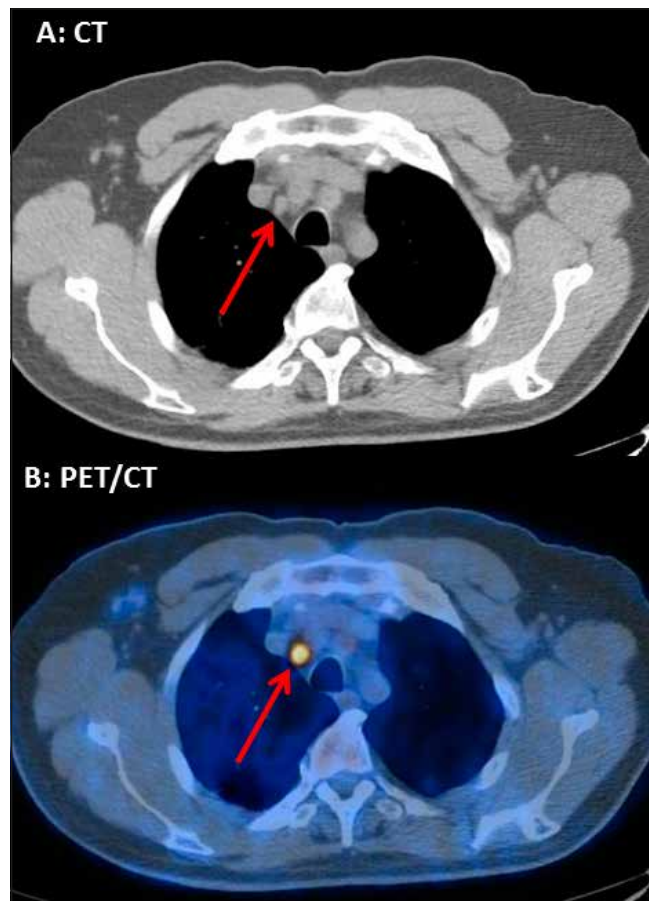


Fig 3. An axial slice on A: CT and on B: fused PET/CT of a patient with true positive upper right paratracheal lymph node at surgery. The red arrows denote the position of the node which is of borderline significance on CT size criteria alone but is clearly FDG avid positive on PET/CT.

Differences in patient and tumour baseline characteristics with time.

To ensure that the time between PET/CT scanning and baseline surgery was not influenced by other patient or tumour characteristics, we compared a number of clinicopathological factors. In comparing stage, SUV_{MAX} and surgery type in those with a time to surgery of less than 9 weeks to those patients who had surgery greater than or equal to 9 weeks from PET/CT, no significant difference in either direction was seen: stage grouping ($p=0.373$); SUV_{MAX} ($p=0.406$); surgery type

(lobectomy, pneumonectomy or sampling) ($p=0.371$). Using logistic regression, no association between these variables and time to surgery was noted (stage grouping $p=0.363$, SUV_{MAX} $p=0.588$ surgery type $p=0.840$).

DISCUSSION

As stated earlier, PET and PET/CT data are becoming increasingly integrated into both surgical and radiation oncology management strategies for NSCLC^{3-7,15-17,19,20}. The four systematic reviews listed in table 1 clearly define a benefit of PET over CT in terms of accuracy for staging of the mediastinum⁴⁻⁷. Further to this, a number of studies demonstrate higher accuracy rates and clinical utility for fused in-line PET/CT scans compared to PET alone or PET co-registered with CT⁸⁻¹². This retrospective study highlights that, despite the superior staging accuracy PET/CT over CT there remains potential uncertainty of PET/CT for detecting metastatic mediastinal lymphadenopathy. In assessment of the PET/CT scan central mediastinal lymph nodes (N2) were deemed negative by assessment by a PET radiologist. Whilst the radiologist will consider both the lymph node size ($<1.0\text{cm}$ in the short axis) and the SUV_{MAX} ($\text{SUV}_{\text{MAX}} <2.0$), the final determination of N2 positivity on PET/CT is made by a clinical assessment by the radiologist. Figure 3 illustrates an example of N2 lymph node which is $<1.0\text{cm}$ in its short axis but is highly FDG avid on PET and was positive at surgery.

The false negative rate was 10.9% with 7 out of 64 patients being incorrectly identified as having no N2 disease on the PET/CT. This may represent micrometastatic disease present in small lymph nodes, whose small size are unlikely to be detected by PET/CT which has in our study are a resolution of 5mm slices. Central tumours with occult nodes on PET or could be related to lymph node size. In this study Pathological sampling commented on the presence of metastatic disease only and did not measure the size of the positive node to enable comparison to size on the pre-op PET scan. Furthermore, the reporting radiologist did not report the SUV_{MAX} for those N2 nodes deemed negative on PET/CT. Hence it is not possible to assess the impact of nodal size and SUV_{MAX} thresholds on the staging accuracy of PET/CT for N2 nodal stations. Positive N1 nodes on the basis of size or SUV_{MAX} criteria did not affect the decision to proceed with radical surgery for these patients and therefore had no bearing on the staging accuracy or the likelihood to surgically sample N2 lymph nodes. Clearly a false negative rate is to be expected with the known potential of micro metastatic disease, particularly in adenocarcinoma. Figure 4 illustrates an example a false negative pre-tracheal lymph node which was positive at surgery.

PET scanning accuracy and Radiotherapy Planning Implications

Elective nodal irradiation is no longer routinely used in the treatment of NSCLC with radiotherapy²¹. Delivering radiotherapy to involved nodal volumes based on CT data alone does not result in a high rate of nodal failure²². PET

based elective nodal irradiation has also been shown to have a low rate of isolated nodal failure^{19,20}. In our study, those patients with scans less than 9 weeks old had a negative predictive value of 90% (95% Confidence Intervals 74-98%). This would suggest that, if the PET scans were used within 6 weeks, only 10% of scans would fail to delineate involved tissue for the purposes of radiotherapy planning. This is comparable to the results obtained by De Ruyscher et al and Klopp et al^{19,20}.

“Best before date” of PET/CT scanning and optimal timing of scan acquisition

A short time interval between PET/CT scanning and radical therapy with either surgery or radiotherapy is clearly desirable. Even with the most efficient organisation, patients with lung cancer, because of comorbidity, may experience non-elective delays owing to inter-current illness. In our study, the median time interval between staging scan and surgery was 8 weeks with a percentage increase in patients operated on in 6 weeks from 26% in 2007 to 44% in 2008. This suggests an improvement in the local patient pathway. At what time point should the findings of baseline staging be questioned? In our study we found that, if mediastinal sampling was undertaken within 9 weeks of the PET/CT scan, mediastinal staging was of high accuracy and was comparable to the literature standards⁴⁻⁷. However, scans older than 9 weeks had a reduced sensitivity and increased false negative rate. This is likely to reflect the progression of the cancer over time and the detection of previously occult metastases. This raises the question, should pre-operative staging with PET/CT occur after determination of fitness for radical treatment? For centres with complex referral patterns and in patients with high prevalence of co-morbid illness, it may be desirable to time the PET/CT in close proximity to a planned intervention. This would ensure a higher accuracy of PET/CT. In our centre, dedicated tracking clerical staff who are attached to our multi-disciplinary team follow the clinical course of each patient suspected or newly diagnosed lung cancer in an attempt to reduce unnecessary delays to definitive treatment.

Study Limitations

This investigation has a number of limitations, of which the greatest is the small sample size. The numbers in the categories of true positive, false positive and false negative are particularly small. Hence a significant effect on specificity may have been missed or conversely, the association between sensitivity and accuracy with time may have been overestimated. Although, with the small numbers in this study, the sensitivity falls to 0 after 9 weeks owing to the lack of true negative N2 nodes. If a larger cohort was available for analysis, then sensitivity is likely to be higher. This uncertainty is illustrated by the wide 95% confidence intervals seen for the sensitivity results seen in tables 3 and 4. Furthermore, analysing several nodes from the same patient's PET/CT scan, may lead to an inherent bias dependent on the characteristics of that patient or their scan. Patient or tumour based ‘factors’ that cannot be standardized with

use of our scanning protocol, that may lead to a repeated measurement effect and thus bias in a given direction include: the pathological subtype; the SUV_{MAX} of the tumour; patient blood glucose level; body mass composition; tumour stage; extent of surgery. We have examined the relationship of stage, SUV_{MAX} and type of surgery with time and have found no significant relationship. However, there remains the potential for such bias. Finally, the retrospective nature of this study is a potential limitation of this study. However, performing a prospective study with elective delays to surgery would not be ethical to undertake, hence any further information suggesting an optimal time-frame to surgery will be retrospective in nature.

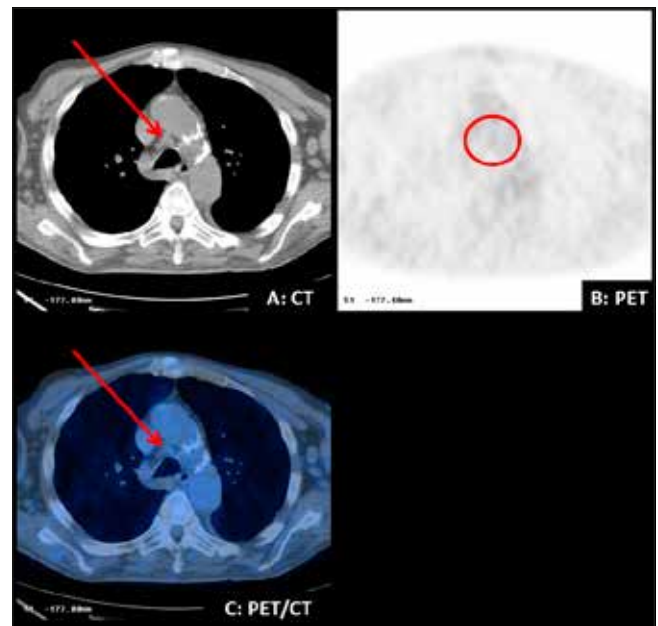


Fig 4. An axial slice on A: CT, on B: attenuated corrected PET and on C: Fused PET/CT on a patient with a false negative pre-tracheal lymph node on PET. Although the CT image suggests nodal positivity by size criteria, the PET (region of interest denoted by red circle) does not demonstrate any significant uptake in this region. The enlarged node was positive at surgery.

CONCLUSION

This study provides some suggestive evidence, but with significant limitations, of an association between time from PET/CT scanning to surgery and the specificity and accuracy of PET/CT scanning in assessing central mediastinal (N2) nodal status. We suggest that in order to improve the outcomes of patients with NSCLC, PET/CT scan data older than 9 weeks, should be regarded as potentially inaccurate for the purposes of central mediastinal (N2) nodal staging.

The authors have no conflict of interest

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