AUDIT, RESEARCH AND GUIDELINE UPDATE

Test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours

Holly A Pattenden,[1] Maria Leung,[1] Emma Beddow,[1] Michael Dusmet,[1] Andrew G Nicholson,[1,2] Michael Shackcloth,[3] Saifullah Mohamed,[4] Adnan Darr,[4] Babu Naidu,[4] Swetha Iyer,[5] Adrian Marchbank,[5] Amy Greenwood,[6] Doug West,[6] Felice Granato,[7] Alan Kirk,[7] Priyadharshanan Ariyaratnam,[8] Mahmoud Loubani,[8] Eric Lim,[1,2] on behalf of the UK Thoracic Surgery Collaborative

For numbered affiliations see end of article.

Correspondence to
Eric Lim, Academic Division of Thoracic Surgery, The Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; e.lim@rbht.nhs.uk

This paper was presented at the 2013 Annual meeting of the American Society of Clinical Oncology (Chicago, USA) and the15th World Conference of Lung Cancer (Sydney Australia).

Received 13 June 2014
Accepted 30 July 2014
Published Online First 14 August 2014

ABSTRACT

Positron emission tomography-CT (PET-CT) is one of the initial mediastinal staging modality for non-small cell lung cancer; however, the clinical utility in carcinoid tumours is uncertain. We sought to determine the test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours. We collated data from seven institutions, performing a retrospective search on pathological databases for a consecutive series of patients who underwent thoracic surgery (with lymph nodal dissection) for carcinoid tumours with preoperative PET-CT staging. PET-CT results were compared with the reference standard of pathologic results obtained from lymph node dissection and test performance reported using sensitivity and specificity. From November 1999 to January 2013, 247 patients from seven institutions underwent surgery for carcinoid tumours with a corresponding preoperative PET-CT scan. The mean age of the patients was 61 (SD 15, range 73) and 84 were male patients (34%). The pathologic subtype was typical carcinoid in 217 patients (88%) and atypical carcinoid in 30 patients (12%). Results from lymph node dissection were obtained in 207 patients. The calculated sensitivity and specificity of PET-CT to identify mediastinal lymph node disease was 33% (95% CI 4% to 78%) and 94% (95% CI 89% to 97%), respectively. Our results indicate that PET-CT has a poor sensitivity but good specificity to detect the presence of mediastinal lymph node metastases in pulmonary carcinoid tumours. Mediastinal lymph node metastases cannot be ruled out with negative PET-CT uptake, and if the absence of mediastinal lymph node disease is a prerequisite for directing management, tissue sampling should be undertaken.

BACKGROUND

Carcinoid tumours are a rare group of malignancies arising from neuroendocrine cells[1] in the gastrointestinal tract and bronchopulmonary system. Within the lung, they account for 1%–2% of all malignancies[1] and are classified into typical (well differentiated) and atypical (less well differentiated) subtypes.[1] Typical carcinoids form approximately two-thirds of cases and metastasise in approximately 12% with an overall survival rate >90%,[1] but atypical carcinoids are comparatively rarer and more aggressive accounting for one-third of cases with >50% mediastinal lymph node metastases and 5-year survival rate of 40%–75%.[1]

As rare tumour subtypes, it is difficult to conduct large scale studies and hence evidence to inform on diagnosis, staging and management is limited. Many centres include patients with carcinoid tumours in management pathways for non-small cell lung cancer (NSCLC) where ^{18}fluoro-dexoyglucose positron emission tomography-CT (^{18}FDG PET-CT) is widely used to stage the mediastinum.[2] Current British Thoracic Society Guidelines recommends radical treatment without further mediastinal lymph node sampling if there is no significant uptake in normal sized mediastinal lymph nodes on ^{18}FDG PET-CT.[3]

Little is known about the clinical utility of ^{18}FDG PET-CT for mediastinal or distant disease staging in carcinoid tumours as their metabolic activity is often considered low or variable and it is argued whether ^{18}FDG PET-CT serves the same purpose in selecting patients for radical management in carcinoid tumours.

We sought to determine the test performance of ^{18}FDG PET-CT for mediastinal lymph node staging of carcinoid tumours by collating data from member institutions of the UK Thoracic Surgery Research Collaborative.

METHODS

Data from seven institutions (Royal Brompton & Harefield NHS Foundation Trust, Liverpool Heart and Chest Hospital NHS Foundation Trust, Heart of England NHS Foundation Trust, Derriford Hospital, Bristol Royal Infirmary, Golden Jubilee National Hospital and Castle Hill Hospital) were collated on a consecutive series of patients who underwent thoracic surgery for carcinoid tumours from November 1999 to January 2013. Pathologic and radiological reporting was performed by UK accredited pathologists and radiologists. Preoperative ^{18}FDG PET-CT staging reports were obtained from patient records and the site(s) of lymph node uptake documented. Technical conduct, extent of surgery and operative lymph node dissection were performed according to each surgeon's individual practice. The reference standard in this study was postoperative pathologic reporting of lymph node involvement on samples harvested. It was not possible to intentionally blind

To cite: Pattenden HA, Leung M, Beddow E, *et al*. *Thorax* 2015;**70**:379–381.

the pathologists to results of ^{18}FDG PET-CT as this was a retrospective study.

As clinical decisions are made on the presence or absence of mediastinal lymph node metastases only, the unit of measurement in this study was the binary outcome of positive or negative for mediastinal lymph node disease on ^{18}FDG PET-CT and the corresponding operative pathology reports. Lymph nodes were defined as positive as stated on pathology or PET-CT reports, respectively. No uptake or 'negative' annotation on the report was defined as negative. Data compilation was undertaken separately at each institution, anonymised and collated into a central registry.

Patients were excluded from analysis if preoperative ^{18}FDG PET-CT was not performed (or the results unavailable), if the ^{18}FDG PET-CT was performed ≥4 months before surgery, if the postoperative pathological report was not available or if no lymph node dissection was performed.

Continuous data were presented as mean with SD or median with IQR as appropriate to the data distribution. Categorical and count data were presented as frequency and percentage (%). Test performance was assessed as sensitivity and specificity and reported with 95% confidence values. Statistical analyses were undertaken using Stata V.10 (College Station, Texas, USA).

RESULTS

From November 1999 to January 2013, a total of 247 patients from seven institutions underwent surgery for a carcinoid tumour with a corresponding preoperative ^{18}FDG PET-CT scan. We excluded one patient with a 'false' positive ^{18}FDG PET-CT result due to TB. The mean age of the patients was 61 (SD 15, range 73) of which 84 were male patients (34%). The pathologic subtype was typical carcinoid in 217 (88%) and atypical carcinoid in 30 (12%). The mean standardized uptake value in the primary tumour was 4.6 (SD 3.8) for typical carcinoids and 6.1 (SD 4.4) for atypical carcinoids. There was a mean of 38 (SD 21) days between ^{18}FDG PET-CT scan and surgery. Surgery was predominantly via lobectomy and in two cases no resection was performed due to patient choice (table 1).

Results from lymph node dissection were obtained in 207 patients. A median of four stations sampled (IQR 2–7). Positive mediastinal lymph uptake was reported on ^{18}FDG PET-CT in 15 patients of whom two were reported to be involved on subsequent pathology (atypical carcinoid in both cases). Of the 207 patients who underwent lymph node dissection, six patients were reported to have mediastinal lymph node metastases (two typical, four atypical carcinoids).

For our primary outcome, the calculated sensitivity and specificity of ^{18}FDG PET-CT to identify mediastinal (N2) lymph node disease were 33% (95% CI 4% to 78%) and 94% (89% to 97%), respectively.

In our secondary analysis for the test performance of ^{18}FDG PET-CT for hilar (N1) disease, ^{18}FDG PET-CT reported uptake at hilar lymph nodes in 21 patients, of whom five were positive on subsequent pathology (four typical, one atypical carcinoids). Pathologic results from hilar lymph node dissection carried out in 207 patients at the time of surgery found 32 patients with hilar lymph node positive disease (22 typical, 10 atypical carcinoids). The sensitivity and specificity of ^{18}FDG PET-CT at identifying hilar lymph node disease were similar at 16% (95% CI 5% to 33%) and 91% (86% to 95%), respectively.

Table 1 Baseline characteristics

Sample size (n)	247
Mean age, years (SD)	61 (15)
Males, n (%)	84 (34)
Mean tumour max size, mm (SD)	26 (15)
Stage, n (%)	
IA	129 (56)
IB	50 (22)
IIA	24 (10)
IIB	11 (5)
IIIA	16 (7)
IIIB or IV	0
Histology, n (%)	
Typical carcinoid	217 (88)
Atypical carcinoid	30 (12)
Mean FDG PET-CT SUV max (SD)	
Typical carcinoid	4.6 (3.8)
Atypical carcinoid	6.1 (4.4)
Surgical procedure, n (%)	
No resection	2 (1)
Wedge resection	19 (8)
Segmentectomy	5 (2)
Lobectomy	208 (84)
Pneumonectomy	13 (5)
Contingency table results, n	
PET-CT positive/pathology positive	2
PET-CT positive/pathology negative	13
PET-CT negative/pathology positive	4
PET-CT negative/pathology negative	188

FDG PET-CT, ^{18}Fluoro-dexoy-glucose positron emission tomography-CT.

DISCUSSION

Our results represent the largest cohort to date suggesting that ^{18}FDG PET-CT has poor sensitivity (to rule out) but good specificity (to rule in) for the presence of mediastinal lymph node metastases in patients with typical and atypical carcinoid tumours.

The test performance of sensitivity of ^{18}FDG PET-CT for mediastinal lymph node metastases is considerably poorer than for NSCLC (33% vs 84% NSCLC[3]) but the specificity is comparable (94% vs 89% NSCLC[3]). With such a large disparity between the accepted sensitivity of ^{18}FDG PET-CT for mediastinal lymph node staging in NSCLC nodal staging and pulmonary carcinoid tumours, this indicates that further sampling of mediastinal nodes is required in the presence of a negative ^{18}FDG PET-CT result if subsequent management is dependent on the absence of mediastinal lymph node disease.

It is unlikely that a large sample study of the test performance of ^{18}FDG PET-CT is feasible. The results from our study suggested that the test performance for two secondary sites (hilar and mediastinal lymph nodes) was similar and we hypothesise that if the results were to be extrapolated to distant disease, the test performance would be similar.

Due to the multicentre, retrospective nature of our study, it is a limitation that there was no standardised method of mediastinal lymph node management across the participating hospitals. Several of the hospitals practice systematic lymph node dissection, dissecting all stations on ipsilateral side, while others practiced more limited lymph node sampling. Dissections where only one station was removed are obviously of limited benefit when describing the utility of PET-CT to detect the global involvement of lymph nodes. On average, there were a median of four stations sampled (IQR 2–7). We have also not collected any follow-up data in this study and therefore cannot comment on locoregional disease after surgery. This may be an area for

future work, allowing us to define our cases which were microscopically negative as true negatives.

Octreotide (or analogue) scintigraphy is increasingly adopted for gastrointestinal neuroendocrine tumours. A recent study comparing the test performance of octreotide scintigraphy with ^{18}FDG-PET-CT in a cohort of 21 patients with pulmonary carcinoid reported cumulative sensitivities and specificities for the primary tumour, lymph nodes and distant metastases of 76% and 97% (octreotide scintigraphy) versus 85% and 89% for ^{18}FDG PET-CT, respectively,[4] and concluded that octreotide scintigraphy may not significantly improve the identification mediastinal staging above that of ^{18}FDG PET-CT. As there is uncertainty over the empiric use of either technique for lymph node staging we argue against the routine use of either or both techniques without prior decision on the appropriate management of patients with mediastinal and/or distant disease. The European Neuroendocrine Society Guidelines that are currently being prepared are anticipated to recommend radical management for typical carcinoid tumours even in the presence of mediastinal or distant disease as long as each site is treated with a radical intent and if so we would need to reconsider the value or need for preoperative metabolic imaging as a pure staging investigation.

CONCLUSIONS

Our results indicate that ^{18}FDG PET-CT has a poor sensitivity but good specificity to detect the presence of mediastinal lymph node metastases when used for staging pulmonary carcinoid tumours. Mediastinal lymph node metastases cannot be ruled out with negative ^{18}FDG PET-CT uptake and if the absence of mediastinal lymph node disease is a prerequisite for directing management, tissue sampling should be undertaken.

Author affiliations
[1]Department of Thoracic Surgery, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[2]National Heart and Lung Division, Imperial College, London, UK
[3]Department of Thoracic Surgery, Liverpool Heart & Chest Hospital NHS Foundation Trust, Liverpool, UK
[4]Department of Thoracic Surgery, Heart of England NHS Foundation Trust, Birmingham, UK
[5]Department of Cardiothoracic Surgery, Derriford Hospital, Plymouth, UK
[6]Department of Cardiothoracic Surgery, Bristol Royal Infirmary, University Hospitals Bristol NHS Trust, Bristol, UK
[7]West of Scotland Regional Heart & Lung Centre, Golden Jubilee National Hospital, Glasgow, UK
[8]Department of Cardiothoracic Surgery, Castle Hill Hospital, Hull, UK

Contributors EL and HP undertook the study conception and design. All coauthors contributed to collection of data and reporting of the work. EL and HP drafted the article and all authors contributed to the final manuscript.

Funding This project was in part supported by the National Institute of Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1 Pinchot SN, Holen K, Sippel RS, *et al*. Carcinoid tumours. *Oncologist* 2008;13:1255–69.
2 Detterbeck FC. Management of carcinoid tumours. *Ann Thorac Surg* 2010;89:998–1005.
3 Lim E, Baldwin D, Beckles M, *et al*. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010;65(Suppl 3):iii1–27.
4 Kuyumcu S, Adalet I, Sanli Y, *et al*. Somatostatin receptor scintigraphy with ^{111}In-octreotide in pulmonary carcinoid tumours correlated with pathological and ^{18}FDG PET/CT findings. *Ann Nucl Med* 2012;26:689–97.