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Systematic Review of Studies Reporting on the Accuracy of PET-CT in Detecting Intra Thoracic Lymph Node Metastasis in Patients with NSCLC

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Abstract

Introduction: Therapeutic options and prognosis for patients with Non-Small Cell Lung Cancer (NSCLC) are mainly determined by the metastatic spread of disease the mediastinal lymph nodes. Non-invasive staging using F-Fludeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT). This review aims to assess the accuracy, sensitivity and specificity of FDG-PET/CT imaging for detecting mediastinal lymph node involvement in patients with potentially resectable NSCLC.

Methods: A systematic literature search was conducted to identify eligible full-text articles that were then assessed for quality and data were extracted.

Results: The search identified 45 eligible studies with a total of 5824 patients (median 206, range 23 to 674). The median accuracy of all studies was 83.5% (range 11% to 97%). The median (range) sensitivity, specificity, positive predictive value and negative predictive values of PET-CT at detecting lymph node metastasis in NSCLC were 72% (39% to 97%), 87% (37% to 100%), 64% (13% to 100%) and 91% (81% to 99%) respectively. Sensitivity, specificity and accuracy of PET-CT diagnosis of metastatic lymph nodes were influenced by histologic subtype of NSCLC.

Conclusion: Whilst FDG-PET/CT is helpful in screening for presence of metastatic mediastinal lymph node involvement, its accuracy, sensitivity and specificity is not high enough to justify reliance on FDG-PET/CT scanning alone to make clinical decisions about whether to offer surgery as a single option for patients with potentially resectable NSCLC. The accuracy of FDG-PET/CT should be monitored against the gold-standard of histologic confirmation.

Keywords: PET-CT; Non-small cell lung cancer; Lymph node metastases

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Introduction

Accurate staging is a critical step in the management pathway of patients with Non-Small Cell Lung Cancer (NSCLC) and also informs the prognosis of these patients. Surgical resection is the treatment of choice for patients with early stage (I and II) disease and may form part of multimodality treatment (together with chemotherapy and/ or radiotherapy) for locally advanced disease (stage IIIA) [1]. Tumour location, patient preferences and general fitness are major determinants of diagnostic and treatment decisions and influence the choice of pathway. The presence of lymph nodal involvement with tumour is a significant prognostic factor in NSCLC and is a major determinant of treatment modality [2]. Lung cancer staging can be performed by a variety of tests. The non-invasive imaging tests (CT and combined PET/CT) are generally first line tests. Minimally-invasive Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA), Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) or the more invasive surgical staging or mediastinoscopy are usually performed for patients in whom PET/CT raises the possibility of mediastinal lymph node involvement which needs confirmation as this then determines which treatment modality will be most suitable [3-5]. Surgical staging which involves resection of the primary tumour, systematic lymph node dissection with a prior mediastinoscopy to assess the contralateral nodes is the most definitive staging modality [6]. This approach is highly invasive and only appropriate for patients with early-stage disease in whom surgery is performed with curative intent. Combined PET/CT using (^{18}F)-2-Fluoro-deoxy-D-Glucose (FDG) as a tracer to provide a measure of glucose uptake, with simultaneous low-dose CT to aid localisation is crucial

Table 1: Summary of search strategy on Pubmed (conducted on 1 August 2017).

1	lung cancer
2	non small cell lung cancer
3	surgery
4	lung resection
5	positron emission tomography
6	pet ct
7	lymph node metastases
8	staging

in the assessment of patients with confirmed or suspected lung cancer. It helps identify patients with no mediastinal nodal spread and distinguish those from patients who may have mediastinal nodal disease, distant metastases or both. The results of the PET/CT can then be used to guide biopsies in the latter group of patients. The accuracy of PET/CT is suboptimal in detecting malignancy in normal-sized lymph nodes, in patients with adenocarcinoma and in ruling out malignancy in patients with coexistent inflammatory or infectious disease [7-14]. The main objective of this study is to evaluate the diagnostic accuracy of combined PET-CT for mediastinal lymph node staging in patients with confirmed or suspected NSCLC.

Methods

Criteria for consideration of studies for review

We considered all prospective or retrospective studies that assessed the diagnostic accuracy on combined PET/CT in assessing lymph node involvement (N1-3) in suspected or confirmed NSCLC. All studies must have used histology as the reference standard for confirming lymph node involvement with metastatic NSCLC. Histological confirmation of PET-CT results was from samples obtained following surgical resection and mediastinal lymph node sampling, mediastinoscopy, Video-Assisted Thoracoscopic Surgery (VATS), EBUS-TBNA, EUS-FNA or a combination of any of these methods. Patients having combined PET-CT with FDG as the radiotracer were included. Studies in which PET-CT was performed with other tracers were excluded. We excluded patients who were being restaged following induction treatment. Review articles were excluded to minimise selection bias. We did not predetermine a cut-off value for definition of a positive result of mediastinal lymph node involvement by PET-CT Maximal Standardised Uptake Values (SUV_{max}).

Electronic searches

An electronic search was performed on Pub med for studies published up to 1 August 2017. We included all studies published in English language with full-text available. The search strategy is summarised in Table 1. All identified articles were systematically reviewed to assess for suitability according to the criteria for consideration for this review.

Data collection and analysis

The first stage of screening involved review of all studies identified by the literature search for potential inclusion in the review by title an abstracts. This stage excluded all studies that were not of PET-CT in NSCLC. The next stage involved review of full articles of those studies that met the inclusion criteria outlined above. For studies where only subgroup of patients met the inclusion criteria, data was extracted only for this subgroup.

Results

Results of the search

There were a total of 396 studies identified by our search strategy. Following review of the titles and abstracts of these studies, we excluded 241 studies. We obtained the full publications for the remaining 155 studies. Of these full publication articles, a total of 45 studies met the inclusion criteria and were included in the analysis. The included studies had a total of 5824 patients (median 206, range 23 to 674). The prevalence of nodes positive for metastatic disease ranged from 8.4% to 47%. All studies were conducted after 1994.

Patient selection

A substantial number of studies only included patients who were having resection of their NSCLC with systematic lymph node dissection of sampling. Some studies only included patients with T1 tumours. These restrictive selection criteria exclude a significant number of other patients who have PET-CT as part of work up for their lung cancer.

Positivity of lymph nodes on PET-CT was reported as above a cut-off SUV_{max} of 2.5 in some studies while others reported positivity as SUV_{max} greater than background (Table 2). The studies used a variety of PET-CT scanners. The majority utilised a Discovery scanner of Biograph scanner. The remainder were other or did not report the scanner used. The studies analysed used different criteria for test positivity of lymph nodes. These included activity > background (19 studies), $SUV_{max} \geq 2.5$ (15 studies) and other/ mixed (11 studies).

Accuracy, sensitivity, specificity, positive and negative predictive values of PET-CT

The accuracy of PET-CT at detecting lymph node metastasis is detailed in Table 2. The median accuracy of all studies was 83.5% (range 11% to 97%). The median (range) sensitivity, specificity, positive predictive value and negative predictive values of PET-CT at detecting lymph node metastasis in NSCLC were 72% (39% to 97%), 87% (37% to 100%), 64% (13% to 100%) and 91% (81% to 99%) respectively. Sensitivity, specificity and accuracy of PET-CT diagnosis of metastatic lymph nodes was influenced by histologic subtype of NSCLC [7,18].

Discussion

This extensive review of a large number of studies containing nearly 600 patients shows that PET-CT has a specificity and negative predictive value for detecting lymph node metastases in patients with NSCLC which is close to 90%. The positive predictive value, sensitivity, and to a less extent, accuracy of PET-CT is less reliable. We found a great degree of heterogeneity in the studies with regards to type of scanner used, cut off values for positivity of PET-CT, SUV_{max} values as well as type of lymph nodes detected as positive (mediastinal i.e. N2/N3; as well as hilar/ intrapulmonary i.e. N1). Despite the large number of studies that were examined in this review, there is a wide variation in the results of sensitivity and specificity analyses, as well as the accuracy and both negative and positive predictive values. There are various reasons, we believe, that account for this. Firstly, the studies cover a period of over 20 years during which the PET-CT scanning with FDG has evolved. Secondly, there are a variety of PET-CT scanners that were used for the various studies and as reported by Schmidt-Hansen et al. [6], in their review this has a bearing on the accuracy of the comparability of the various studies. Thirdly, the proportion of patients with adenocarcinoma was varied in the

Table 2: Summary of studies reporting on role of PET-CT in detecting lymph node metastases in NSCLC.

Study	No of participants	Prevalence of mediastinal nodes %	Accuracy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value	Negative predictive value
Kaseda [15]	388		83	47	91	56	88
Lin [16]***			43	96	38	13	99
Shigemoto [17]	265	25	91		93	70	
Wang [18]	122	§	33	54	92	79	
		§§	29	84	86	82	
D'Amico [19]	80		96	68	79	55	87
Xu [20]	101	43	87	52	96	74	89
Li [21]	219		74	74	73	54	87
Booth [22]	64		90	39	96		
Billé [7]	244§	33	54	92	79		
	109§§	29	84	86	82		
Carillo [23]***	33			49	80	49	83
Lee [24]	160		11	86	81		
Ose [25]	112		84	50	95	58	93
Li [26]	200		78	44	83	29	91
Sivrikoz [27]	68		93	73	98	89	93
Hu [28]	53		76	94	67	56	96
Saydam [29]	42		74	84	65	66	83
Fischer [30]	79			69	81	64	84
Sit [31]	107		80	52	86	46	89
Ventura [32]	19			94	73	66	96
Lee [33]	43		81	42	97	83	81
Tasci [34]	172		93	72	94	49	98
Liu [35]	39		92	65	95	79	90
Sanli [36]	78			82	90	56	97
Perigaud [37]	51	20		40	85	40	85
Fischer [38]	98		79	64			
Billé [39]	159	30	81	54	92	74	82
Shinya [40]‡	34			92	93		
Hwangbo [41]	117	26	63	70	60	38	85
Yi [42]	150	47		70			
Lee [43]**	110	19	97	81	98	64	99
Al-Sarraf [44]†	206		93	42	98	66	95
Yang [45]	122		85	86	85	64	95
Tournoy [12]	52	36		84	85		
Lee [46]	126		82	86	81	56	95
Kim [47]	674	27	86	61	96		
Yi [13]	143	24	90	56	100		
Kim [48]	150	23	88	47	100	100	94
Bryant [49]	397	36		91	88		
Pozo-Rodríguez [50]	132	28		97	44		98
Shim [51]	50	8.4	84	84	84		
Halpern [52]	36	28	78	-	-	-	-
Cerfolio [53]	129	-	96	69	94	49	99
Aquino [54]		-		71-76*	89-96	70-86	90-91
Vansteenkiste [55]	68	-	95	93	94	-	-

Wahl [56]	23	41	81	82	81	-	-
Total	5824						

*Reported as range
†Patient aged > 65 years
**Cut off SUV_{max} of 5.3
‡Cut off SUV_{max} of 4
***Cut off SUV_{max} of 2.5
§Values for adenocarcinoma in this row
§Values for squamous cell carcinoma in this row

studies we looked at. It has been noted that lung adenocarcinoma a less likely to be FDG-avid, have a higher incidence of occult lymph node metastatic disease and accuracy of PET-CT may be influenced by dose of FDG [6,7,13]. Fourthly, the cut-off values for positivity of PET-CT for detecting lymph node metastases was varied with some studies reporting on values of $SUV_{max} \geq 2.5$, others on activity > background and others still had no specified cut off values reported. Indeed, some of the studies reported on different cut-off values within then same study. Fifthly, a number of studies reported on the accuracy of PET-CT at detecting NSCLC metastatic to intra thoracic lymph nodes in patients accrued from populations with high incidence of tuberculosis [31,47]. The reference standard for comparing PET-CT was histological confirmation of tumour involvement of lymph nodes. However, the method of obtaining lymph node samples varied and included samples obtained by cervical mediastinoscopy, EBUS-FNA, and samples obtained at lung resection (either by thoracotomy or VATS resection). Whilst these tests have all been shown to have robust and reliable accuracies, there are limitations to this and it is possible that variables such as the level of experience of the endoscopists performing EBUS or surgeons would influence accuracy of staging. Whilst our methodology of review in this study is different from some previously published reviews, the results are consistent with these studies [6,57,58]. We believe these results are important in informing clinical practice as they highlight the fact that whilst the sensitivity and specificity of PET-CT is reasonable, it should be used as part of a clinical decision pathway to direct the next step in patient management which may be biopsies, if PET-CT is positive for lymph node involvement, or radical local treatment of the lung cancer if negative.

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