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ORIGINAL ARTICLE

Using PET-CT to reduce futile thoracotomy rates in non-small-cell lung cancer: a population-based review

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ABSTRACT

Background

Combined positron-emission tomography and computed tomography (PET-CT) reduces futile thoracotomy (FT) rates in patients with non-small-cell lung cancer (NSCLC). We sought to identify preoperative risk factors for FT in patients staged with PET-CT.

Methods

We retrospectively reviewed all patients referred to the BC Cancer Agency during 2009–2010 who underwent PET-CT and thoracotomy for NSCLC. Patients with clinical N2 disease were excluded. An FT was defined as any of a benign lesion; an exploratory thoracotomy; pathologic N2 or N3, stage IIIB or IV, or inoperable T3 or T4 disease; and recurrence or death within 1 year of surgery.

Results

Of the 108 patients who met the inclusion criteria, FT occurred in 27. The main reason for FT was recurrence within 1 year (14 patients) and pathologic N2 disease (10 patients). On multivariate analysis, an Eastern Cooperative Oncology Group performance status greater than 1, a PET-CT positive N1 status, a primary tumour larger than 3 cm, and a period of more than 16 weeks from PET-CT to surgery were associated with FT. N2 disease that had been negative on PET-CT occurred in 21% of patients with a PET-CT positive N1 status and in 20% of patients with tumours larger than 3 cm and non-biopsy mediastinal staging only. The combination of PET-CT positive N1 status and a primary larger than 3 cm had 85% specificity, and the presence of either risk factor had 100% sensitivity, for FT attributable to N2 disease.

Conclusions

To reduce FT attributable to N2 disease, tissue biopsy for mediastinal staging should be considered for patients with PET-CT positive N1 status and with tumours larger than 3 cm even with a PET-CT negative mediastinum.

KEY WORDS

Non-small-cell lung cancer, positron-emission tomography–computed tomography, thoracotomy, lymphatic metastasis or pathology, mediastinal staging, endobronchial ultrasonography, mediastinoscopy, endoscopic ultrasonography

1. INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women[1]. Non-small-cell lung cancer (NSCLC) accounts for most lung cancers (85%), and optimal treatment depends on the stage of the disease. Unfortunately, an estimated 40% of newly diagnosed NSCLC patients present with stage IV disease, and palliative-intent treatment with chemotherapy or radiotherapy is indicated[2]. However, earlier-stage disease is amenable to potentially curative treatment. For stage I and II NSCLC, surgical resection is the treatment of choice[3], but in the presence of mediastinal nodal metastases, definitive chemoradiotherapy or induction therapy followed by surgery are indicated[4–7]. The selection of the most appropriate treatment therefore relies on accurate staging of the mediastinum and assessment for distant metastases. An additional objective of accurate staging is to avoid inappropriate treatments: for example, noncurative lung resection ["futile thoracotomy" (FT)] in the context of a falsely negative mediastinum, or denial of potentially curative surgery because of a false-positive finding[8].

The introduction of positron-emission tomography (PET) has improved the staging of NSCLC through a better assessment of the mediastinum and distant metastases. For identifying mediastinal metastasis, PET has a sensitivity of 80% and a specificity of 88%; in contrast, computed tomography (CT) has 55% sensitivity and 81% specificity[9]. Combined PET-CT identifies unsuspected metastatic disease in 6%–37% of

cases[9,10]. That improvement in staging has translated into improved patient outcomes. Several clinical trials have demonstrated that, in addition to conventional staging (including mediastinoscopy or endobronchial ultrasonography), preoperative PET-CT reduces FTS by about 20%[11–13].

However, several questions remain about the indications for and necessity of using invasive mediastinal staging such as mediastinoscopy and about the role of newer, less-invasive techniques such as endobronchial ultrasonography (EBUS) alone or in combination with endoscopic ultrasonography (EUS) in the context of widespread adoption of PET-CT. Mediastinoscopy, with a sensitivity of 78%, has traditionally been the standard of practice for staging the mediastinum; video mediastinoscopy has a higher sensitivity of 89%[9]. However, in patients with indications for invasive mediastinal staging, a multicentre randomized controlled trial demonstrated that EBUS with EUS (EBUS/EUS) is the best first test and suggested a small, perhaps not worthwhile, incremental benefit of mediastinoscopy in unselected patients with a negative mediastinum[14]. Yasufuku *et al.* suggested that EBUS achieves results similar to those with mediastinoscopy and can effectively replace the latter technique for staging[15]. The recently updated American College of Chest Physicians (ACCP) guidelines recommend EBUS/EUS as the best first test in patients with indications for invasive mediastinal staging. Those indications, unchanged from the previous ACCP guidelines[16], include suspicious mediastinal findings on CT or PET-CT, or a normal mediastinum by PET-CT and an intermediate risk of mediastinal disease (N1 disease or central tumour). The ACCP guidelines also recommend surgical staging (for example, mediastinoscopy, video-assisted thoracoscopic surgery) for patients in whom the clinical suspicion of mediastinal node involvement remains high after a negative EBUS/EUS[9]. In the Canadian context, those recommendations have largely been accepted and incorporated into Cancer Care Ontario's guidelines, although the latter guidelines mention additional factors that can increase the likelihood of N2 disease and warrant invasive or minimally invasive mediastinal staging. The additional factors include adenocarcinoma, tumour histology, degree of differentiation and size, primary tumours that are not avid for fluorodeoxyglucose, and certain well-differentiated low-grade malignancies[8].

Avoiding FT is an important endpoint, but such procedures remain frequent despite the addition of PET-CT to preoperative staging (21% in the Fischer *et al.* trial[11]). Thoracotomies are associated with significant morbidity and mortality[17], and they also delay stage-appropriate combined-modality therapy. The appropriate use of invasive mediastinal staging is an important component of avoiding FTS. The aim of our study was to identify, for FT in patients staged with PET-CT, preoperative clinical risk factors that might help to stratify patients for invasive mediastinal staging.

2. METHODS

2.1 Patients

The BC Cancer Agency (BCCA) provides PET and CT imaging to the entire province of British Columbia (4.5 million people). We conducted a retrospective chart review for all patients referred to the BCCA from January 2009 to December 2010 who underwent staging PET-CT and thoracotomy for NSCLC. During that period, the BCCA in Vancouver housed the only PET-CT scanner in the province.

Eligible patients were identified using diagnosis codes from the BCCA Outcomes and Surveillance Integrated Systems database[18] and were crossmatched with records in the nuclear medicine department. Exclusion criteria were clinical N2 disease, metastatic disease, and any other cancer within 5 years of NSCLC diagnosis. The institutional ethics review board approved the study.

2.2 Data Collection

Data were collected retrospectively. Baseline characteristics were obtained from consultation reports. Performance status was scored according to the Eastern Cooperative Oncology Group (ECOG) criteria[19] and determined from preoperative consultation notes.

Reports from PET-CT imaging were reviewed for tumour characteristics [maximum standardized uptake value (SUV_{max}), size, and N1 status]. The N1 nodal status was recorded as positive if the PET-CT report stated definite or suspicious N1 involvement. A nuclear medicine physician reviewed the PET-CT imaging for missing data such as size measurements and SUV_{max} values. No patients had nodal upstaging on review.

Clinical stage was determined for each patient by incorporating all preoperative imaging and invasive staging procedures, and pathology reports were reviewed for the pathology staging of each patient. Staging accorded with the American Joint Committee on Cancer TNM staging system, 6th edition.

Futile thoracotomy was defined using the established definition published by Fischer *et al.*[11]: benign lung lesion, exploratory thoracotomy, pathologic N2 disease, stage IIIB or IV disease, inoperable T3 or T4 disease, or recurrence or death within 1 year of surgery.

2.3 PET-CT Imaging

All PET-CT imaging was performed at the BCCA's Vancouver Centre on a Biograph 16 eco system with the Hi-Rez option (Siemens, Knoxville, TN, U.S.A.). Images were acquired in 3-dimensional mode from the

base of the skull to mid-thigh, with arms above the head, in fasting patients with blood glucose levels of 11.1 mmol/L or less (<200 mg/dL), approximately 60 minutes after intravenous administration of 8–12 mCi (296–444 MBq) of ^{18}F-fluorodeoxyglucose. The CT images were acquired without intravenous or oral contrast. Images were reconstructed, with and without CT attenuation correction, using iterative protocols with body weight–normalized SUV computation. The PET-CT images were interpreted by any of 4 experienced nuclear medicine physicians who were not blinded to the patient's clinical information or to the results of conventional imaging.

2.4 Statistical Analyses

The FT and non-FT groups were compared in univariate (Fisher test) and multivariate (logistic regression model) analyses in the R software environment (version 2.15.2: The R Foundation, Vienna, Austria).

3. RESULTS

3.1 Patient Characteristics

Table I shows the characteristics of the 108 patients referred to the BCCA during 2009–2010 who met the inclusion and exclusion criteria. Of those patients, 27 (25%) underwent a FT. Pathologic N2 disease and recurrence within 1 year were the main reasons for FTS, occurring in 10 (37%) and 14 patients (52%) respectively (Table II).

3.2 Clinical Risk Factors for FT

On univariate analysis, PET-CT positive N1 status [odds ratio (OR): 3.77; $p = 0.008$], primary tumour size greater than 3 cm (OR: 3.91; $p = 0.006$), and primary tumour SUV_{max} greater than 15 (OR: 2.98; $p = 0.03$) were associated with FT. A period of more than 16 weeks from PET-CT to surgery trended toward significance (OR: 4.44; $p = 0.06$; Table III).

On multivariate analysis, PET-CT positive N1 status (OR: 4.13; $p = 0.009$) and primary tumour size greater than 3 cm (OR: 4.22; $p = 0.01$) remained associated with FT. Furthermore, ECOG performance status greater than 1 (OR: 4.57; $p = 0.017$) and a period of more than 16 weeks from PET-CT to surgery (OR: 6.98; $p = 0.02$) were also associated with FT (Table III).

The identified risk factors of ECOG performance status greater than 1, primary tumour size greater than 3 cm, and PET-CT positive N1 status were present in 16, 54, and 26 patients respectively. Of patients with those risk factors, 82%, 65%, and 72% respectively did not undergo minimally invasive or invasive mediastinal staging. Of patients who had a risk factor and who did not undergo minimally invasive or invasive mediastinal staging, those with an ECOG performance status greater than 1 had FTS

TABLE I Patient characteristics

Characteristic	*Thoracotomy status*	
	Non-futile	*Futile*
Patients [*n* (%)]	81 (75)	27 (25)
Age (years)		
Mean	65	64
Range	45–82	46–81
Sex [*n* (%) men]	33 (41)	13 (48)
Smoking status [*n* (%)]		
Never-smoker	13 (16)	7 (26)
Current or quit <1 year	34 (42)	8 (30)
Former smoker	34 (42)	12 (44)
Cigarette consumption		
Mean pack years	37	27
ECOG PS at diagnosis [*n* (%)]		
0	29 (36)	5 (18)
1	43 (53)	15 (56)
2	9 (11)	7 (26)
Weight loss 3 months before surgery [*n* (%)]		
<5%	65 (80)	18 (67)
5%–10%	10 (12)	5 (18)
>10%	6 (7)	4 (15)
Invasive mediastinal staging [*n* (%)]		
Mediastinoscopy	13 (16)	6 (22)
Endobronchial ultrasonography (EBUS)	9 (11)	1 (4)
Mediastinoscopy and EBUS	0	2 (7)
None	59 (73)	18 (67)
Tumour histology [*n* (%)]		
Adenocarcinoma	50 (62)	14 (52)
Squamous-cell carcinoma	19 (23)	11 (41)
Large-cell carcinoma	5 (6)	0
Bronchoalveolar carcinoma	3 (4)	0
Other	4 (5)	2 (7)
Mean tumour size (cm)	3.5	4.2
Clinical stage [*n* (%)]		
IA	36 (44)	5 (18)
IB	27 (33)	10 (37)
IIA	4 (5)	1 (4)
IIB	10 (12)	10 (37)
IIIA (because of T3)	1 (1)	0
IIIB (because of T4)	3 (4)	1 (4)
PET-CT positive N1 [*n* (%)]	14 (17)	12 (44)
Mean SUV_{max} of primary tumour	9.5	12.4
Treatment		
Median time between PET and surgery (days)	29	26
Received adjuvant chemotherapy [*n* (%)]	27 (33)	14 (52)

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PET-CT = combined positron-emission tomography–computed tomography; SUV = standardized uptake value.

primarily because of relapse within 1 year of surgery (31%). The FT rate attributable to N2 disease was similar in patients with a tumour size greater than 3 cm and with PET-CT positive N1 status (20% and 21% respectively).

Among patients with a delay of more than 16 weeks from PET-CT to surgery (7 patients; mean delay: 30 weeks), the FT rate was 57%; among patients operated within 16 weeks of PET-CT, the rate was 23% ($p = 0.02$).

Table IV shows the sensitivity and specificity of the identified risk factors alone or in combination for FT. The presence of PET-CT positive N1 status or a primary tumour size greater than 3 cm had a sensitivity of 100% for N2-related FT, and the combination of both factors had a specificity of 85% for N2-related FT.

4. DISCUSSION

This retrospective study of patients staged with PET-CT for NSCLC found a FT rate of 25%, of which 37% was attributable to N2 disease and 52% to recurrence within 1 year. We identified 4 preoperative clinical risk factors for FT—namely, PET-CT positive N1 status, preoperative ECOG performance status greater than 1, primary tumour size greater than 3 cm, and a period from PET-CT to surgery of more than 16 weeks.

The definition of FT in this study, which was taken from the landmark randomized controlled trial by Fischer *et al.*[11], is controversial. The outcome of patients with incidentally discovered pathologic N2 disease is variable, and 5-year survival rates of 15%–40% have been observed, depending on the thoroughness of the preoperative staging[20]. Furthermore, adjuvant chemotherapy has been shown to improve survival in the N2 setting[21], with a less clear role for adjuvant radiotherapy[22]. Nonetheless, preoperative identification of N2 disease remains an important endpoint, to the extent that it identifies patients eligible for neoadjuvant chemotherapy[23] or concurrent chemoradiation. In the latter context, the role of surgery remains controversial[6,24].

The low rate of minimally invasive or invasive mediastinal staging (28%) in patients with N1 disease in our study is likely multifactorial, including limited access to EUS/EBUS and a practice shift from traditional mediastinoscopy to reliance on imaging studies. In 2005, the blinded prospective study by Pozo–Rodriguez[25] of the efficacy of combined parallel CT-PET compared with surgical staging for the mediastinum indicated a sensitivity of 97% and a negative predictive value of 98% for mediastinal disease. Those data, in combination with the availability and ease of PET-CT imaging, resulted in increased reliance on single-modality staging. However, sensitivity varies from one study to another, and a recent review of integrated PET-CT

TABLE II Reasons for futility of thoracotomy

Reason	*Distribution [*n *(%)]*
Pathologic N2	10 (37)
Recurrence within 1 year	14 (52)
Pleural involvement	1 (4)
Death within 1 year	1 (4)
Incomplete resection	1 (4)
TOTAL	27 (100)

TABLE III Risk factors analysis in futile thoracotomy

Variable	*Category*	*Analysis*			
		Univariate		*Multivariate*	
		Odds ratio	p *Value*	*Odds ratio*	p *Value*
Age	>70 Years	1	1		
Sex	Male	1.34	0.51		
Smoking status	Ever-smoker	0.54	0.263		
ECOG PS	>1	2.76	0.113	4.26	0.02
Weight loss	>5%	2.01	0.188		
Histology	Squamous	2.22	0.089		
Primary tumour size	>3 cm	3.91	0.006	4.22	0.01
PET-CT result	Positive N1	3.77	0.008	4.13	0.009
SUV_{max} of primary	>15	2.98	0.03		
Adjuvant chemotherapy	Yes	2.13	0.109		
Time from PET-CT to surgery	>16 Weeks	4.44	0.06	6.98	0.02

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PET-CT = combined positron-emission tomography–computed tomography; SUV = standardized uptake value.

TABLE IV Sensitivity and specificity of risk factors for futility of thoracotomy because of N2 disease

Risk factor	*Sensitivity*	*Specificity*
Tumour size >3 cm	90	54
PET-CT positive N1	60	79
ECOG PS > 1	10	86
PET-CT positive N1 AND tumour size > 3 cm	50	85
PET-CT positive N1 OR tumour size > 3 cm	100	48
PET-CT positive N1 OR tumour size > 3 cm OR ECOG PS > 1	100	38

PET-CT = positron-emission tomography–computed tomography; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

suggests a median sensitivity of 62% and a negative predictive value of 90%[9]. Cerfolio *et al.*[26] similarly demonstrated a 26% rate of unsuspected N2 disease in patients with PET-CT positive N1 status, most of which was located in the posterior mediastinum, being accessible only by EUS, which was not widely used. Our results support the ACCP recommendation in its guidelines for invasive mediastinal staging in patients with clinical N1 disease and a radiographically normal mediastinum by PET-CT, given that 21% of patients with PET-CT positive N1 status who did not undergo invasive mediastinal staging underwent FT attributable to N2 disease.

Primary tumour size is not an indication for invasive mediastinal staging in the ACCP guidelines[9], but the Cancer Care Ontario guidelines do make that recommendation for T2 tumours, based on the worse prognosis for larger tumours seen in the International Association for the Study of Lung Cancer staging project[8]. Indeed, we found a FT rate of 20% attributable to N2 disease in patients with a tumour size greater than 3 cm who did not undergo invasive mediastinal staging. In fact, a tumour size greater than 3 cm had higher sensitivity for N2 disease (80%) than did PET-CT positive N1 status (60%). Furthermore, the presence of either clinical risk factor had a sensitivity of 100% for N2 disease, and the presence of both had a specificity of 85%. Those observations are hypothesis-generating and suggest that studies investigating larger tumours and invasive mediastinal staging could be helpful.

A preoperative ECOG performance status greater than 1 was associated with FT in the present study. Interestingly, FT was mainly attributable to relapse within 1 year of surgery in such patients and not to N2 disease at surgery. Such patients might have early microscopic hematogenous spread that could explain their worse systemic symptoms and pattern of FT. Blood or other biomarkers might be useful in identifying such patients. However, the small number of patients with ECOG performance status greater than 1 ($n = 16$) and the retrospective nature of our study limit the validity of that finding.

The median time from PET-CT to surgery in the FT group was 26 days in this population-based study. Some of the studies that established very high sensitivities and negative predictive values of PET-CT in the mediastinum involved patients whose PET imaging was performed within 72 hours of surgery[25]. Mohammed *et al.*[27] showed that clinical progression occurred in 21% of patients after 16 weeks' delay in surgery, and initially higher T and N stages were associated with more rapid progression. We also observed that delay in surgery beyond 16 weeks is associated with a higher FT rate, although the time to surgery was more than 16 weeks in only 6% of patients. The small sample size means that we cannot exclude the possibility that a time of less than 16 weeks from imaging to surgery is also detrimental. Our results might therefore not necessarily question the negative predictive value of PET-CT found in the study by Rodriguez *et al.,* but rather might identify the same risk factors that Mohammed *et al.* reported for rapid disease progression and FT attributable to delays in treatment. Our results support the suggestion of Mohammed *et al.* to create rapid access clinics to streamline investigations. A primary tumour size larger than 3 cm or PET-CT positive N1 status could be used to prioritize patients for surgery.

The strength of our study is that it offers a glimpse of real-world practice because of its use of a population-based database. The study nevertheless has a number of limitations, including its retrospective nature, potential for referral bias, and small sample size. The number of events was low, but our results accord with the known literature and suggest other areas of potential importance to evaluate.

5. CONCLUSIONS

Our findings support the ACCP guidelines recommending invasive mediastinal staging of patients with a PET-CT positive N1 status. Additionally, the size of the primary tumour and the patient's ECOG performance status are important considerations in preoperative assessment. Proper staging is needed to ensure that patients receive stage-appropriate therapy for their NSCLC.

To reduce FT attributable to N2 disease, tissue biopsy for mediastinal staging should be considered for patients with a PET-CT positive N1 status and with tumours larger than 3 cm even in the presence of a PET-CT negative mediastinum.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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