

Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial

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Summary

Background Up to 50% of curative surgery for suspected non-small-cell lung cancer is unsuccessful. Accuracy of positron emission tomography (PET) with 18-fluorodeoxyglucose (¹⁸FDG) is thought to be better than conventional staging for diagnosis of this malignancy. Up to now however, there has been no evidence that PET leads to improved management of patients in routine clinical practice. We did a randomised controlled trial in patients with suspected non-small-cell lung cancer, who were scheduled for surgery after conventional workup, to test whether PET with ¹⁸FDG reduces number of futile thoracotomies.

Methods Before surgery (mediastinoscopy or thoracotomy), 188 patients from nine hospitals were randomly assigned to either conventional workup (CWU) or conventional workup and PET (CWU+PET). Patients were followed up for 1 year. Thoracotomy was regarded as futile if the patient had benign disease, explorative thoracotomy, pathological stage IIIA–N2/IIIB, or postoperative relapse or death within 12 months of randomisation. The primary outcome measure was futile thoracotomy. Analysis was by intention to treat.

Findings 96 patients were randomly assigned CWU and 92 CWU+PET. Two patients in the CWU+PET group did not undergo PET. 18 patients in the CWU group and 32 in the CWU+PET group did not have thoracotomy. In the CWU group, 39 (41%) patients had a futile thoracotomy, compared with 19 (21%) in the CWU+PET group (relative reduction 51%, 95% CI 32–80%; $p=0.003$).

Interpretation Addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer.

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See *Commentary page 1361*

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Introduction

Accurate staging of patients with a pulmonary lesion suspected of being non-small-cell lung cancer is needed to restrict surgical or multimodality treatment to those who will potentially benefit from these treatments. Several imaging techniques and invasive tests are available to the clinician to detect mediastinal lymph-node involvement, distant metastases, or both. International guidelines to make the most of this process^{1–4} have been formulated, but routine clinical practice remains variable.^{5–8} Despite current diagnostic workup, early local and distant relapses are frequent, and surgery is done for preoperatively suspicious lesions that can prove to be benign. Therefore, surgery can be regarded as futile in up to 50% of patients with presumably resectable non-small-cell lung cancer.^{8–10}

Positron emission tomography (PET) with the tracer 18-fluorodeoxyglucose (¹⁸FDG) has emerged in the past decade as a promising oncological imaging tool. Results of several accuracy studies have suggested that ¹⁸FDG-PET is better at assessment of suspicious lung lesions and nodal or extra-thoracic tumour status in non-small-cell lung cancer than conventional workup.^{11–14} Accuracy studies are, however, not designed to show added value of diagnostic tests. Like phase II studies for development of treatments, they are subject to bias, which make generalisation of results to predict an effect in routine practice difficult.¹⁵ In general, these drawbacks lead to overestimation of worth.¹⁶ As a result, whether and to what extent patients will benefit from use of PET in a routine clinical setting cannot be directly inferred from existing published work.^{17,18}

As in assessment of new treatments, new diagnostic technologies need to be compared with current strategies with respect to relevant clinical outcomes.^{19–21} Workers on major health-technology assessment reports^{20,22} concluded that improvement of diagnostic accuracy by PET was difficult to quantify because of variable quality of studies, and that direct evidence on the effect of PET in improvement of patients' outcomes was still lacking.

The PLUS (PET in LUng cancer Staging) study was designed to work with routine clinical workup of patients with suspected non-small-cell lung cancer. We compared the current strategy of conventional diagnostic methods with a strategy in which PET was added to non-invasive diagnostic techniques. The primary outcome measure was number of futile thoracotomies.

Patients and methods

Patients

We invited patients with suspected or proven non-small-cell lung cancer that was judged to be medically operable and potentially resectable by the referring clinician on the basis of clinical staging—but not surgical staging—to participate in the study. Eligible patients had to be older than age 18 years. All patients gave written informed consent in accordance with requirements set by local

medical ethics committees. Eight community and one university hospital recruited patients for the study.

Procedures

We randomly assigned eligible patients either PET followed by further invasive diagnostic and therapeutic procedures (CWU+PET) or invasive diagnostic and therapeutic procedures alone (CWU). These procedures are governed by local routine, which is based on current guidelines.¹⁻⁴ Randomisation was done centrally by computer, by a permuted block design, stratified by institute.

All procedures other than PET, including treatment and follow-up, were done in the referring hospitals according to local standards. Follow-up consisted of regular visits (at least every 2–3 months) in the outpatient clinic. Trained data managers obtained all information up to 12 months after randomisation.

We did PET scans with a Siemens ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) at the Vrije Universiteit, Amsterdam. We asked patients to fast for 6 h before the scan. A 1-h whole-body acquisition started 60 min after injection of 370 MBq ¹⁸F-DG. We imaged the mid-femur-skull trajectory with emission scans for 5 min except for the chest, which was imaged with two 10-min scans followed by 5 min of transmission scanning. Images were reconstructed by filtered back-projection (Hanning 0.5; resolution after reconstruction 7 mm full-width at half-maximum) without attenuation correction. Results were communicated to the referring clinician by phone and confirmed in writing, with a hard copy of the PET scan included.

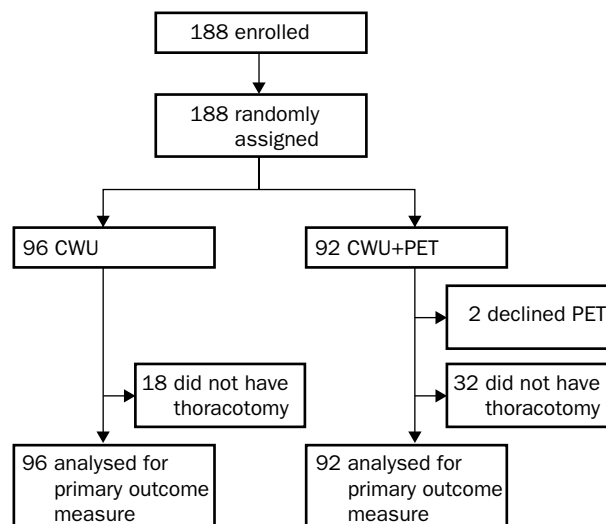
Two readers from a group of three assessed all PET scans; if necessary, consensus was reached with the third reader. Pulmonary and mediastinal lesions were visually associated with mediastinal background activity.²³ Chest computed tomography (CT) scans and transmission-emission overlays defined anatomical correlates for PET abnormalities and localised mediastinal foci.²⁴

The PET report included information on nature of the primary lesion, mediastinal lymph-node involvement, and distant metastases, and concluded with an assessment of tumour-node metastasis (TNM) stage according to CT and PET and a suggestion for further workup. Referring clinicians used this information accordingly. However, potential distant or nodal metastases, which might have a major effect on patients' management, were confirmed by other means. Unconfirmed PET findings were ignored.

The primary outcome measure was number of futile thoracotomies. We classified thoracotomy as futile for the following reasons: benign lung lesion; pathologically proven mediastinal lymph-node involvement (stage IIIA–N2)²⁵ other than minimal N2-disease—ie, intranodal involvement in a single lymph node established at mediastinal dissection;²⁶ stage IIIB disease; explorative thoracotomy for any other reason; or recurrent disease or death from any cause within 1 year after randomisation.

Statistical analysis

Before the trial was designed, we assessed current clinical practice in a retrospective analysis of staging procedures in the two largest participating centres.⁸ On the basis of these results and of published work about PET, we estimated that addition of PET to conventional workup might reduce the number of futile thoracotomies from 45% to 20%. Our sample-size calculation (power of 90%, α of 0.05, two-sided) suggested that a total of 160 patients was required.²⁷ Number of futile thoracotomies with respect to total number of patients randomised in each group was tested by χ^2 test (intention-to-treat analysis). The same test compared



Trial profile

nodal yield between both groups. In addition, we did tests that were based on exact inferences and that were stratified by institute. None of these approaches, however, led to important changes in results. Hence, for reasons of arithmetic simplicity, we report unstratified χ^2 tests and their CIs. Because of the low risk of PET imaging and the short accrual time, no interim statistical analysis was planned.

Results

Baseline characteristics

Between January, 1998, and January, 1999, we enrolled 188 patients from nine hospitals (between five and 50 patients per hospital)—96 in the CWU group and 92 in the CWU+PET group (figure). 70% of patients in each group had clinical stage I/II disease (table 1). Pre-randomisation workup was closely similar for both groups, and included at least a chest CT scan, which usually included the liver and adrenals (89%). All CT scans were done with at least third-generation scanners: spiral modality in 24%, with intravenous contrast in 55%, both equally distributed between each group. In both groups, 58% of patients underwent at least one additional test to identify metastatic disease (table 1). Two patients allocated to the CWU+PET group declined PET (figure). The other 90 patients underwent PET a median of 3 days after randomisation (range 1–13).

Primary outcome

A significantly greater proportion of patients underwent futile thoracotomy in the CWU group than in the CWU+PET group (relative reduction 51%, 95% CI 32–80, $p=0.003$; table 2). The absolute difference of 20% can be interpreted as five patients (95% CI 3–14) who needed PET to avoid one futile thoracotomy. Apparently justified surgery was done in a closely similar proportion of patients in each group (table 2). Futile surgery happened irrespective of clinical stage: 46% (31/68) of patients with clinical stage I/II disease in the CWU group compared with 25% (16/64) of those in the CWU+PET group, and 29% (8/28) of those in the CWU group with clinical stage III disease compared with 11% (3/27) in the CWU+PET group, had futile surgery. Assessment of resectability by CT and PET was discordant in a third of cases, and PET was correct in two-thirds. In 37% of patients undergoing PET, CT was incorrect with respect to the primary outcome

	CWU (n=96)	CWU+PET (n=92)
Characteristic		
Age (years, mean [SD])	65 (10)	66 (10)
Sex		
Men	75 (78%)	69 (75%)
Women	21 (22%)	23 (25%)
Karnofsky index		
70–80	6 (6%)	10 (11%)
90–100	90 (94%)	82 (89%)
Weight loss >5%	15 (16%)	14 (15%)
Clinical stage		
I	63 (66%)	58 (63%)
II	5 (5%)	6 (7%)
IIIA	22 (23%)	23 (25%)
IIIB	6 (6%)	4 (4%)
IV*		1 (1%)
Comorbidity		
Vascular, diabetes mellitus	31 (32%)	30 (33%)
Chronic obstructive pulmonary disease	30 (31%)	23 (25%)
Previous malignancies	13 (14%)	17 (19%)
Definite diagnosis of non-small-cell lung cancer	46 (48%)	48 (52%)
Pre-randomisation imaging tests (CT of the thorax excluded)	56 (58%)	54 (59%)
Bone scan	26 (27%)	25 (27%)
CT/US of the abdomen	46 (48%)	42 (46%)
CT/MRI of the brain	3 (3%)	5 (5%)
CT/MRI of other area	1 (1%)	5 (5%)
Radiograph of other area	7 (7%)	10 (11%)

Data are number of patients (%) unless otherwise stated. CT=computed tomography; US=ultrasound; MRI=magnetic resonance imaging. *Solitary brain metastasis on CT.

Table 1: **Baseline characteristics**

measure. This percentage was closely similar to the proportion of futile thoracotomies in the CWU group.

Our protocol required confirmation of clinically decisive PET results, thus the predictive value of PET alone (ie, without any confirmation) was analysed in 86 assessable patients. Six patients could not be assessed because they either declined PET (n=2), had intercurrent morbidity prohibiting surgery (2), refused surgery (1), or had chemotherapy rather than surgery after revision of tumour histology (1). Six patients who died after apparently curative surgery were allocated to justified thoracotomy (table 3). PET correctly suggested that surgery was justified in 81% (95% CI 68–92) of scans, versus 71% (58–84%) in which PET suggested surgery was futile. Overall accuracy before verification was 76% (67–85%). Better preoperative assessment of patients in the CWU+PET group than in the CWU group was evident in three phases: before surgery with curative intent, at surgery, and during follow-up.

Before surgery with curative intent

After randomisation, 18 patients in the CWU group did not proceed to thoracotomy for the following reasons

	CWU (n=96)	CWU+PET (n=92)
No thoracotomy	18 (19%)	32 (35%)
Confirmed N2/3	10	18
Confirmed distant metastases	1	7
Benign primary lesions	2	3
Other tumour	2	1
Intercurrent morbidity, refusal	3	3
Thoracotomy	78 (81%)	60 (65%)
Non-futile thoracotomy	39 (41%)	41 (44%)
Futile thoracotomy	39 (41%)	19 (21%)
Benign	7	2
Explorative thoracotomy	1	1
IIIA–N2	6	4
IIIB	6	2
Recurrence or death within 1 year	19	10

Table 2: **Specification of primary outcome**

	Thoracotomy		No thoracotomy		Total
	Justified	Futile	Justified	Futile	
Thoracotomy indicated by PET					
Yes	33	6*	2†	0	41
No	13‡	6§	26¶	0	45

*Benign disease in two patients, advanced disease in four. †PET suggested hilar lymph-node involvement, but mediastinoscopy was positive. ‡PET suggested benign disease in one, advanced disease in 12 (including patients in whom PET could not exclude mediastinal lymph-node involvement adjacent to the primary tumour. §Thoracotomy and follow-up showed advanced disease. ¶PET suggested benign disease in three, advanced disease in 23.

Table 3: **Accuracy of PET in prediction of need for thoracotomy**

(table 2): tumour-positive mediastinal lymph-node biopsy sample (n=10); shrinking lesion at preoperative chest radiograph (2); adrenal metastasis diagnosed by revision of CT confirmed by fine-needle aspiration (1); small-cell lung cancer (2); cardiac disease prohibiting surgery (1); death due to local progression before surgery (1); and surgery declined (1). Thus, 78 patients underwent thoracotomy with curative intent.

63 patients (66%) underwent 67 mediastinal lymph-node staging attempts: mediastinoscopy, 62; mediastinotomy, four; video-assisted thoracoscopy, one. Of the ten patients with biopsy-proven mediastinal lymph-node involvement precluding surgery, in five, the final N-stage was diagnosed at CT-indicated mediastinal lymph-node stations; in two, CT suggested absent and hilar adenopathy; and in three, confirmation was obtained at stations not enlarged at CT, one of which proved to have a contralateral-positive biopsy, rather than only ipsilateral involvement, as suggested by CT. 25 patients underwent thoracotomy without additional staging procedures after randomisation: 22 had cT1/2N0M0, two had cT2N2 (nodes not accessible by mediastinoscopy, and mediastinoscopy impossible after previous neck surgery, respectively), and one had cT3N0.

In the CWU+PET group, 32 patients did not proceed to thoracotomy for the following reasons (table 2): tumour-positive lymph nodes (n=18; two after PET-guided lower cervical node biopsies); confirmed stage IV disease after PET (7; skeletal, liver, and adrenal metastasis confirmed by biopsy; cerebral metastasis by CT and magnetic resonance imaging); PET and clinical course suggesting benign disease (3; two had a normal PET scan); intercurrent morbidity prohibiting surgical treatment (2); biopsy-confirmed neuroendocrine tumour treated with chemotherapy (1); and surgery declined (1). Thus, 60 patients in the CWU+PET group underwent thoracotomy with curative intent.

67 patients (73%) had 68 mediastinal lymph-node staging attempts: mediastinoscopy, 59; mediastinotomy, five; and rigid bronchoscopy, four. Of the 18 patients with biopsy-proven mediastinal lymph-node involvement precluding surgery, pathological N-classification was established at a CT-enlarged nodal station in eight versus a PET-positive mediastinal lymph node in 16. In six patients, the final N-stage was diagnosed at sites shown by CT and PET (2N3, 4N2). In ten patients, only PET suggested the positive biopsy site (4N3, 6N2), five of which had a normal CT scan. In two patients, PET had suggested hilar adenopathy (N1) with positive biopsies of ipsilateral lower tracheobronchial nodes (with CT read as N0 and N1, respectively). In three patients, the mediastinal lymph-node procedure had been done while awaiting confirmation of coexistent PET-suspected distant sites. Number of nodal stations sampled at mediastinoscopy was closely similar in each group.

In 13 patients without evidence of mediastinal lymph-node involvement on chest CT, PET suggested otherwise, which was confirmed in six. Four patients could not be assessed for various reasons (patient refusal, exploratory surgery), and at thoracotomy, no mediastinal lymph-node involvement was noted in the remaining three patients. False-positive PET-suspected rib metastases were recorded in two patients (fibrodysplasia, trauma). 18 patients underwent thoracotomy without additional staging procedures after randomisation and PET: 17 had clinical stage cT1/2N0/1 and one cT1N2 (nodes inaccessible by mediastinoscopy).

At surgery

Patients in the CWU and CWU+PET groups underwent thoracotomy at a median of 22 days (range 8–118) and 28 days (4–106), respectively. Number of patients proceeding to thoracotomy was significantly higher in the CWU group than in the CWU+PET group (table 2; $p=0.013$). In the CWU group, 20 thoracotomies were futile versus nine in the CWU+PET group. 12 patients who had CWU were upstaged and seven had benign disease (table 2). In the CWU+PET group, six patients were upstaged and two had benign disease (table 2). In three of the patients with IIIA–N2 disease, PET suggested mediastinal lymph-node involvement, which was not confirmed by mediastinoscopy. In both groups, one open-and-close procedure was done, since residual lung capacity precluded the pneumonectomy that was necessary to achieve radical surgery.

In total, a closely similar number of different nodal stations were sampled in CWU and CWU+PET groups (mean 4.3 [SD 1.9] *vs* 4.6 [1.8], respectively). The yield of preoperative mediastinal lymph-node staging was 63% in the CWU group compared with 83% in the CWU+PET group ($p=0.16$).

During follow-up

In the CWU group, 14 patients developed clinically noticeable recurrences within 12 months of randomisation after apparently curative surgery. Patients relapsed with metastases in the brain ($n=3$), lymph nodes (2), bone (2), kidney (2), soft tissue (3), adrenal gland (1), and liver (1), with multiple sites in four patients. Most relapses arose beyond 180 days of randomisation. Nine of the 14 patients who relapsed died during follow-up. Another four died of surgery-related causes, without clinical evidence of relapse. One patient died of reasons not definitely due to cancer or surgery. Of all patients who underwent surgery in the CWU group, 17 had distant metastases within the year of follow-up. In all but two patients, these sites had been screened before randomisation, or there had been no indication for such screening according to 1997 guidelines ($n=5$).⁴

In the CWU+PET group, four patients relapsed after apparently curative surgery, two with bone metastases, and one with metastases in the brain and skeleton after refusal of a PET scan and undergoing curative surgery (pT1N0M0). In the other patient, a pulmonary metastasis of melanoma (primary site unknown) had been resected, but disseminated involvement (skin, breast, adrenal) became apparent during follow-up. All patients with recurrent disease were alive 12 months after randomisation. Five patients died of surgery-related causes and one patient died of an unknown cause.

Discussion

Our study showed that addition of PET to conventional workup can strikingly reduce the number of futile

thoracotomies in patients with suspected potentially resectable non-small-cell lung cancer. The main effect of PET was to upstage patients (12% in the CWU group compared with 27% in the combined group). Obviating surgery in such patients improves patients' management.

Our findings are directly applicable to clinical practice. Data from the Netherlands Cancer Registry²⁸ suggest that our study probably included about 65% of all eligible patients diagnosed in these nine hospitals.

Our definition of futile thoracotomy as operationalisation of health outcome of PET in potentially resectable non-small-cell lung cancer is based on consensus of current surgical management of non-small-cell lung cancer in the Netherlands, and is supported by international guidelines.^{1,3} Non-curative surgery unnecessarily increases burden of disease and risk. The life expectancy of patients with locally advanced non-small-cell lung cancer might improve if they receive preoperative or neoadjuvant treatments, including chemotherapy or chemoradiation.²⁹ If resection in any cancer patient who survived clinically disease-free for 1 year had been deemed to be justified (rather than futile, classified in this trial by perioperative IIIA–N2/IIIB stage), the overall conclusion would be much the same (39% *vs* 16% futile surgery in the CWU and CWU+PET groups, respectively; $p=0.001$). Likewise, if surgery for benign disease and non-cancer-related death were excluded, there would still be a difference (29% *vs* 13% respectively; $p=0.007$). Only one patient (in the CWU+PET group) was reported with minimal N2 disease at thoracotomy.

Unexpected distant metastases during follow-up were noted in tissues that had been screened or in patients who were not at risk in accordance with the guidelines.⁴ Our finding of 8% confirmed distant metastases in the CWU+PET group is slightly below figures from other studies,^{12,13,30,31} in which 11–14% unexpected distant metastases have been reported.

In retrospect, mediastinal lymph-node staging procedures were fully compliant with 1997 international guidelines⁴ and were done in about two-thirds of patients. In the CWU group, the sensitivity of these efforts was about 60%, which is closely similar to results from other multicentre trials.¹⁰ Although our trial was not designed to address the issue, our data suggest a high yield of invasive preoperative mediastinal lymph-node staging if guided by PET of suspected nodes. At the time when our trial was designed (in 1997),³² the interaction between PET and mediastinoscopy was unclear. Rigorous accuracy studies^{13,33} have since shown that the negative predictive value of PET for mediastinal lymph-node involvement could be sufficiently high to refrain from mediastinoscopy in non-central tumours.

Some aspects typically associated with management of patients, as opposed to diagnostic accuracy, became apparent during our trial. First, because ¹⁸F¹⁸FDG uptake does not always suggest malignancy, and surgery is the only chance of cure for most patients with non-small-cell lung cancer, PET findings that would preclude surgical treatment need to be verified. This requirement is supported by the estimated diagnostic accuracy of PET alone in this study (table 3). The claimed superior accuracy—eg, mediastinal lymph-node involvement versus CT^{11,13}—needs to be translated into relevant outcome measures, ie, into cases upstaged by preoperative biopsy rather than at surgery with curative intent. Even if false-positive PET findings might not adversely affect the ultimate result of workup, they are likely to invoke additional tests, generating an unnecessary burden on the patient, delay, and costs.

Second, clinical decision-making takes into account the complete diagnostic profile of the patient, and not merely the result of a single test. Therefore, a patient with a clinical and radiological profile strongly suggesting malignancy underwent thoracotomy despite a PET-negative primary lesion. This decision was justified in retrospect (diagnosis of bronchioloalveolar cell cancer). Finally, in some cases, preoperative radiological follow-up already suggested benign disease and obviated surgery. PET would not have affected this decision. Such data cannot be derived from accuracy studies because of masking for the new procedure, and are difficult to model in decision analysis.³⁴

In conclusion, addition of PET to standard workup in routine clinical practice improved selection of surgically curable patients with non-small-cell lung cancer.

Contributors

H van Tinteren was responsible for study design and statistical analysis, and developed the study protocol. O S Hoekstra was the study coordinator, was responsible for PET, and developed the study protocol. E F Smit was the pulmonologist and principal investigator, and developed the study protocol. J H A M van den Bergh, A J M Schreurs, R A L M Stallaert, and J C van Mourik were coprincipal investigators. P C M van Velthoven was senior advisor as a former surgeon. E F I Comans and G J J Teule were nuclear medicine physicians and coresponsible for PET. F W Diepenhorst was responsible for management of clinical data. P Verboom was responsible for economic assessment of design of the study. P E Postmus was head of the pulmonology department and coinvestigator. M Boers was methodological advisor and was involved in the writing of the report. G J J Teule was head of the department of nuclear medicine and was responsible for the ideas that led to this trial and for the running of the study.

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Conflict of interest statement

None declared.

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