

Positron Emission Tomography in Staging Early Lung Cancer

A Randomized Trial

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Background: Among patients with early-stage non–small cell lung cancer (NSCLC), preoperative imaging tests are important in defining surgical candidates.

Objective: To assess whether whole-body positron emission tomography and computed tomography (PET-CT) plus cranial imaging correctly upstages cancer in more patients with NSCLC than does conventional staging plus cranial imaging.

Design: Randomized clinical trial with recruitment from June 2004 to August 2007. The centralized, computer-generated, variable block size randomization scheme was stratified by treatment center and cancer stage. Participants, health care providers, and outcome assessors were not blinded to imaging modality assignment.

Setting: 8 hospitals and 5 PET-CT centers in academic institutions.

Patients: Eligible patients were older than 18 years; had histologic or cytologic proof of stage I, II, or IIIA NSCLC on the basis of chest radiography and thoracic CT; and a tumor considered to be resectable.

Intervention: PET-CT or conventional staging (abdominal CT and bone scan). All patients also had cranial imaging using CT or magnetic resonance imaging.

Measurements: The primary outcome was correct upstaging, thereby avoiding stage-inappropriate surgery. Secondary outcomes were incorrect upstaging and incorrect understaging.

Results: 170 patients were assigned to PET-CT and 167 to conventional staging. Eight patients (3 who had PET-CT and 5 who had conventional staging) did not have planned surgery. Disease

was correctly upstaged in 23 of 167 PET-CT recipients and 11 of 162 patients in the conventional staging recipients (13.8% vs. 6.8%; difference, 7.0 percentage points [95% CI, 0.3 to 13.7 percentage points]), thereby sparing these patients surgery. Disease was incorrectly upstaged in 8 PET-CT recipients and 1 conventional staging recipient (4.8% vs. 0.6%; difference, 4.2 percentage points [CI, 0.5 to 8.6 percentage points]), and it was incorrectly understaged in 25 and 48 patients, respectively (14.9% vs. 29.6%; difference, 14.7 percentage points [CI, 5.7 to 23.4 percentage points]). At 3 years, 52 patients who had PET-CT and patients who had 57 conventional staging had died.

Limitation: The relatively small sample and the fact that some patients did not have planned surgery limited the ability to determine precise differences in clinical outcomes that were attributable to testing strategies.

Conclusion: Preoperative staging with PET-CT and cranial imaging identifies more patients with mediastinal and extrathoracic disease than conventional staging, thereby sparing more patients from stage-inappropriate surgery, but the strategy also incorrectly upstaged disease in more patients.

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Lung cancer is the leading cause of death from cancer in North America. The optimal treatment for early-stage non–small cell lung carcinoma (NSCLC) is surgical resection. However, the recurrence rate after intended curative resection is high, and the 5-year survival for stage I disease is only 50% (1). Patients considered for surgery undergo imaging tests, such as radioisotope bone scan; computed tomography (CT) of the chest, liver and adrenals; and CT or magnetic resonance imaging of the brain, to detect metastases and avoid unnecessary surgery. Recently, whole-body positron emission tomography (PET) has emerged as an imaging modality to detect metastases. Whole-body PET is attractive in oncology because many tumors preferentially take up ¹⁸F-fluorodeoxyglucose (FDG). When PET is combined with CT (PET-CT), functional and anatomical information are provided simultaneously.

Three randomized trials have been done in which the addition of PET to conventional staging was compared with conventional staging alone for staging NSCLC (2–4). The outcomes and results differed. The primary outcome

in the van Tinteren and colleagues' trial (2) was futile thoracotomy, defined as procedure done for benign disease, explorative thoracotomy for other reasons, pathologic stage IIIA-N₂ or IIIB disease, or recurrent disease or death within 1 year of randomization. The rate of futile thoracotomy was 41% in the conventional staging group and 21% in the conventional staging plus PET group ($P = 0.003$). In Viney and colleagues' trial (3), the primary outcome was thoracotomy, which was done in 98% of pa-

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Context

Imaging tests may help identify patients with lung cancer who are candidates for curative surgical resection.

Contribution

This randomized trial compared 2 preoperative imaging strategies for patients with early non–small cell lung cancer: whole-body positron emission tomography and computed tomography (PET-CT) plus cranial imaging versus conventional staging plus cranial imaging. The PET-CT strategy identified more patients with mediastinal and extrathoracic disease that precluded surgery but also incorrectly upstaged disease in more patients.

Implication

A PET-CT–based imaging strategy may help identify advanced disease and prevent futile thoracotomy in patients with non–small cell lung cancer, but it also has false-positive results that incorrectly upstage disease in some patients.

—The Editors

tients in the conventional staging group and 96% in the conventional staging plus PET group ($P = 0.44$). In the most recent trial, patients were randomly assigned to conventional staging or a strategy of PET followed by investigation of any abnormalities (4). Additional conventional staging investigations were also allowed in the latter group. The primary outcome was the number of tests to finalize staging and to define operability. The mean number of tests was 7.9 in each group ($P = 0.90$).

We compared PET-CT with conventional staging in patients with NSCLC being considered for surgery. The primary objective was to compare PET-CT plus cranial imaging with conventional staging plus cranial imaging, to determine the proportion of patients in whom disease was correctly upstaged.

METHODS**Design Overview**

Patients with confirmed clinical stage I, II, or IIIA NSCLC being considered for surgery were randomly assigned to undergo PET-CT plus cranial imaging, or conventional staging (abdominal CT, including the liver and adrenals, and bone scan) plus cranial imaging. Recruitment began in June 2004 and was completed in August 2007. The 12-month follow-up visit after surgery for the last patient entered was in November 2008. Written informed consent was obtained from all eligible patients. The study protocol was approved by the institutional review board of each participating center.

¹⁸F-fluorodeoxyglucose is considered an investigational biologic by Health Canada. Thus, the trial required approval by the federal regulatory agency.

Setting and Participants

Patients were eligible if they were older than 18 years; had histologic or cytologic proof of NSCLC; and had stage I, II, or IIIA disease on the basis of clinical staging that included chest CT and the primary lesion seemed to be technically appropriate for surgical resection according to chest radiography and thoracic CT. Patients were excluded if they had poor pulmonary function, poor Eastern Cooperative Oncology Group performance status (grade 3 or 4), or clinically significant concurrent medical problems making them unfit for surgery; could not lie supine for PET; had cancer (unless they had been disease-free for at least 5 years, had nonmelanotic skin cancer, or carcinoma in situ of the cervix); or had undergone part of the staging strategy under investigation within 8 weeks of randomization. Eligible patients underwent history taking; physical examination; and routine blood analysis, including random glucose, creatinine, liver enzyme, and alkaline phosphatase measurement. The time between the qualifying imaging test (chest radiography and thoracic CT) and randomization needed to be less than 8 weeks.

Patients were recruited from surgical practices in 8 hospitals (4 university and 4 community hospitals) in Ontario, Canada. The PET-CT scanners were located in 5 academic institutions. Of all randomized patients, 90% were recruited from 3 clinical centers, and 93% of the patients in the PET-CT group were examined at 3 of the 5 PET-CT locations.

Randomization and Interventions

An independent statistician created a computer-generated randomization list, stratified by clinical stage (I or II vs. IIIA) and treatment center. A binder, which contained separate allocation sequences for each stratum, was kept in a locked drawer in the trial coordinator's office; access to this binder was limited to the coordinator and the data management assistant who provided the allocation. Within the binder, the allocation sequences were not concealed. After a patient consented, a nurse at a study site telephoned the Ontario Clinical Oncology Group Coordinating and Methods Centre in Hamilton, Ontario, Canada, to obtain the intervention assignment. Patients were allocated in a 1:1 ratio with a variable block size (2, 4, or 6) to undergo PET-CT or conventional staging. Participants, health care providers, and outcome assessors were not blinded to imaging modality assignment.

Imaging Modalities

The 5 PET scanners used for the study had to meet specified performance criteria and undergo quality control evaluation on each day that imaging was performed. Four scanners were PET-CT scanners with full-ring detectors: a Discovery LS4 (General Electric, Waukesha, Wisconsin) in London, a Biograph Duo (CTI/Siemens, Knoxville, Tennessee) at Princess Margaret Hospital in Toronto, and two Philips Gemini Dual machines (Philips Electronics NV, Eindhoven, the Netherlands) in Ottawa and Sunnybrook

Odette Cancer Centre Hospital in Toronto. The numbers of patients scanned on these machines were 64, 55, 39, and 7, respectively. Four patients in Hamilton were imaged with a PET scanner equipped with a partial ring of bismuth germanate detectors, the ECAT ART (CTI/Siemens). Separate non-contrast-enhanced CT of the neck and thorax was done on the same day in these patients for fusion with the PET scan, which was facilitated by the use of fiducial markers.

Patients were imaged after they had fasted for at least 4 hours. Patients were injected with FDG, 5 MBq/kg of body weight ($\pm 10\%$), to a maximum of 500 MBq. Blood glucose was measured before injection of FDG in all patients; if the fasting blood glucose level was greater than 9.7 mmol/L (175 mg/dL), the study was delayed until adequate diabetic control had been established. Patients rested quietly for 60 minutes after tracer injection. For patients who had PET-CT, a low-dose CT scan was initially acquired with the axial field of view extending from the base of the skull to mid-thigh. Immediately thereafter, emission data acquisitions were obtained over the same field of view (Biograph Duo and Gemini Dual, 3 min/bed; Discovery LS4, 5 min/bed; and ECAT ART, 10 minutes/bed). For patients studied with the ECAT ART, transmission data acquisition of 4 min/bed followed the emission acquisition over the same axial field of view.

Images were reconstructed by iterative reconstruction with segmented correction for attenuation with use of either the CT data or transmission data. Data were shown in attenuation-corrected and non-attenuation-corrected formats for interpretation in a 128×128 matrix on a nuclear medicine workstation. Before the trial began, a quality assurance program was established to standardize the scanners and isotopes across the 5 imaging centers and for reading of the PET-CT scans by nuclear medicine physicians.

All PET-CT images were interpreted at the site where the PET study was performed. The interpreter's degree of suspicion for an abnormality was recorded by using a 5-point ordinal scale with the following categories: 0, normal; 1, probably normal; 2, equivocal; 3, probably abnormal; and 4, definitely abnormal (5). The physicians who interpreted the PET scans were free to use information from the standardized uptake value determination to assist in grading of the identified abnormalities according to the 5-point scale. The readers were not provided with cut-off specific uptake values to determine the presence or absence of cancer.

Patients assigned to conventional staging underwent CT of the liver and adrenals (unless the liver and adrenals were adequately visualized to rule out intra-abdominal metastases on the CT before randomization) and a whole-body bone scan. Patient in both groups underwent brain CT with contrast or brain magnetic resonance imaging with gadolinium, according to established and standardized scanning protocols.

Outcomes and Follow-up

Surgery

In patients whose imaging was negative for mediastinal disease, diagnostic confirmation by cervical mediastinoscopy was preferred. All patients, however, required detailed lymph node sampling at thoracotomy. For tumors on the right side, this consisted of removing 1 or 2 lymph nodes from stations 2R (upper paratracheal), 4R (lower paratracheal), 7 (subcarinal), and 10R (tracheobronchial angle), if present. For left-sided tumors, sampling consisted of removing 1 or 2 lymph nodes from stations 2L (upper paratracheal), 4L (lower paratracheal), 5 (aortopulmonary window), 6 (para-aortic anterior mediastinal), 7 (subcarinal), and 10L (tracheobronchial angle), if present. Any other suspicious nodes were also sampled.

Patients with stage I, II, or IIIA disease underwent thoracotomy with resection of the primary lung lesion. Mediastinal node sampling appropriate for the lobe to be resected was performed at thoracotomy regardless of whether cervical mediastinoscopy had been performed. Patients underwent lung resection by open posterolateral thoracotomy or video-assisted thoracotomy. All patients had either lobectomy of the involved lobe or pneumonectomy, where appropriate. Postoperatively, patients could receive stage-appropriate adjuvant therapy (chemotherapy, radiotherapy, or a combination of these methods).

Outcomes

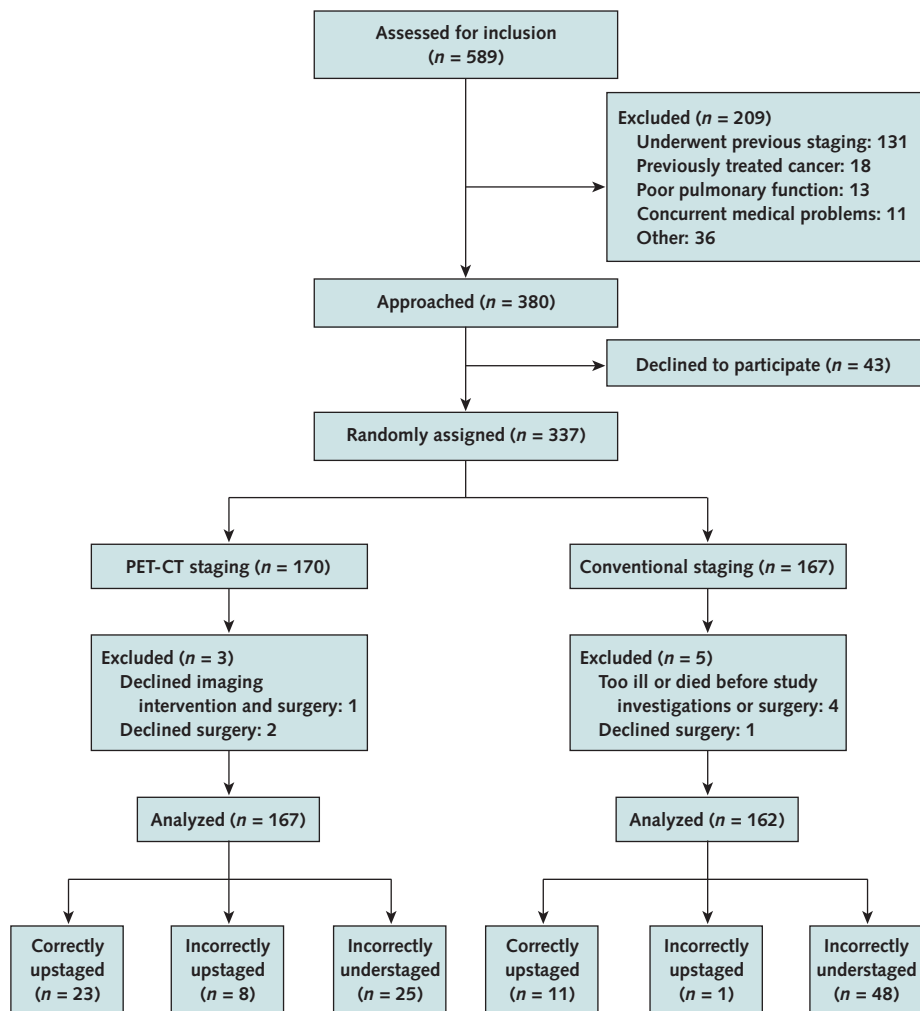
The primary outcome was correct upstaging of cancer (true-positive results) where the imaging strategy identified a patient as having metastatic disease (stage IV) or locally advanced lung cancer (stage IIIB), thereby avoiding stage-inappropriate surgery. Upstaging of cancer was considered correct if the recommended further testing (biopsy or other diagnostic imaging modalities) confirmed it. Histopathologic confirmation during work-up of test abnormalities was not always required to label someone as correctly upstaged.

Other outcomes included incorrect upstaging (false-positive results) and incorrect understaging (false-negative results). The criteria used to define the latter outcome were pathologic stage IIIA or IIIB disease on mediastinoscopy or on lymph node sampling at thoracotomy or local recurrence or development of distant metastases within 1 year of thoracotomy (stage IV disease). Data were collected prospectively on the tests and procedures performed to work up abnormalities detected on the imaging strategies.

Follow-up Procedures and Monitoring

Patients were followed every 3 months for 2 years. Beyond that, they will be followed for survival annually until year 5. At the 3-month follow-up visits, patients underwent history taking and physical examination. Any abnormalities suspicious for recurrence led to further investi-

Figure 1. Study flow diagram.



PET-CT = positron emission tomography and computed tomography.

gations. Low-dose thoracic CT was required at 6-month intervals during the first 2 years of the study.

Quality control measures to ensure that the study data were accurate, consistent, and of high quality were in place throughout the study. A data management plan was developed that outlined the details of case report form completion and review; database validation and verification; and coding conventions, discrepancy management, data editing, and database locking. A standard data query process was used to generate and track queries until resolution. Case report form data were verified with blinded source documentation instead of on-site monitoring.

All cases of suspected upstaging and understaging were reviewed by an independent central adjudication committee of 2 experienced oncologists. If there was a discrepancy between reviewers, a third adjudicator was consulted and a decision was reached by consensus. An external data safety

monitoring committee met every 6 months to review patient safety and protocol adherence.

Statistical Analysis

We postulated that conventional staging would detect occult metastatic disease and prevent stage-inappropriate therapy (noncurative thoracotomy) in 10% of patients and that PET-CT would increase this rate to 25% (5–11). Using a 2-sided α value of 5%, we calculated that 146 patients per group would be required to achieve 90% power to detect this effect. Allowing for 10% loss to follow-up, we planned for a total sample size of 322 patients.

The analysis was based on a modification of the intention-to-treat principle, in which patients who did not proceed to planned surgery were excluded from all further analysis. Stratified exact conditional tests were used to compare the proportion of patients in each group who were correctly upstaged, incorrectly upstaged, and incor-

Table 1. Patient Characteristics at Baseline

Characteristic	PET-CT Group (n = 170)	Conventional Staging Group (n = 167)
Mean age (minimum, maximum), y	67 (41, 87)	66 (38, 88)
Sex, n (%)		
Female	87 (51)	84 (50)
Male	83 (49)	83 (50)
Smoking status, n (%)		
Never	12 (7)	16 (10)
Ex-smoker	110 (65)	106 (63)
Current smoker	48 (28)	45 (27)
ECOG performance status, n (%)		
0	100 (59)	102 (61)
1	63 (37)	58 (35)
2	7 (4)	7 (4)
Mean size of primary tumor (minimum, maximum), cm	3.2 (0.8, 8.7)	3.2 (0.9, 8.5)
Clinical disease stage, n (%)		
IA	83 (49)	75 (45)
IB	50 (29)	54 (32)
IIA	6 (4)	2 (1)
IIB	13 (8)	20 (12)
IIIA*	18 (10)	16 (10)

ECOG = Eastern Cooperative Oncology Group; PET-CT = positron emission tomography and computed tomography.

* Includes 1 patient with stage IIB disease (T₄N₀M₀) at baseline who was allowed into the study because the tumor was considered resectable.

rectly understaged. The strata used in the analyses were stage and location of PET scanner (Toronto, London, Hamilton, or Ottawa). The 95% CI for the difference in proportions was obtained by using the modified Wilson method. The Kaplan–Meier method was used to describe overall survival up to 3 years. Data were analyzed by using SAS, version 9.1 (SAS Institute, Cary, North Carolina) and StatXact, version 8 (Cytel Software, Cambridge, Massachusetts).

Role of the Funding Source

The trial was funded by the Ontario Ministry of Health and Long-Term Care, Canadian Institutes of Health Research, and Cancer Care Ontario. The funding sources had no role in the design or conduct of the study, analysis or interpretation of the data, or the decision to send the manuscript for publication.

RESULTS

Overall, 589 patients were assessed for eligibility and 209 were excluded. Of the remaining 380 patients, 337 (89%) agreed to participate; 170 were randomly assigned to the PET-CT group and 167 to the conventional staging group (Figure 1). No crossovers between groups occurred. Table 1 shows baseline characteristics of the patients.

Five patients who had PET-CT and 3 patients who had conventional staging did not undergo planned surgery

Table 2. Proportion of Patients With Correctly Upstaged Disease

Baseline Disease Stage	PET-CT Group, n/n (%)	Conventional Staging Group, n/n (%)	Difference (95% CI)
IA	5/81 (6)	3/75 (4)	2.2 (−5.8 to 10.1)
IB	8/49 (16)	5/52 (10)	6.7 (−6.8 to 20.5)
IIA	1/6 (17)	0/2 (0)	16.7 (−50.5 to 56.4)
I and IIA	14/136 (10)	8/129 (6)	4.1 (−2.8 to 11.0)
IIB	3/13 (23)	1/19 (5)	17.8 (−6.6 to 45.3)
IIIA*	6/18 (33)	2/14 (14)	19.0 (−11.8 to 44.2)
IIB and IIIA	9/31 (29)	3/33 (9)	19.9 (0.5 to 38.5)
Total	23/167 (14)	11/162 (7)	7.0 (0.3 to 13.7)

PET-CT = positron emission tomography and computed tomography.

* Includes 1 patient with stage IIB disease (T₄N₀M₀) at baseline who was allowed into the study because the tumor was considered resectable.

and therefore did not have an outcome. Thus, the final analysis set included 329 patients (167 in the PET-CT group and 162 in the conventional staging group). Of these, 83 patients in the PET-CT group and 85 in the conventional staging underwent mediastinoscopy. Thoracotomy was performed on 269 patients (138 in the PET-CT group and 131 in the conventional staging group).

Disease was correctly upstaged in 23 PET-CT recipients and 11 conventional staging recipients (13.8% vs. 6.8%; difference, 7.0 percentage points [95% CI, 0.3 to 13.7 percentage points]; *P* = 0.046). Table 2 shows the proportions of patients with correctly upstaged disease, by baseline disease stage and intervention. We found that PET-CT was superior to conventional staging for disease at all stages, but the greatest benefit was seen at higher stages (although the intervention effects seen in stage I or IIA disease versus stage IIB/IIIA disease did not differ statistically). Table 3 shows the sites of metastatic disease that led to upstaging and the corresponding method of confirmation.

Disease was incorrectly upstaged in 8 PET-CT recipients and 1 conventional staging recipient (4.8% vs. 0.6%; difference, 4.2 percentage points [CI, 0.5 to 8.6 percentage points]; *P* = 0.037). In 4 PET-CT recipients, the abnormal sites were adrenals, pituitary, tonsils, and contralateral lung, which upon investigation were negative for cancer. The other 4 PET-CT recipients had abnormal mediastinal nodes which were negative on mediastinoscopy. In the conventional staging recipient with stage IIIA disease, the nodes were normal on mediastinoscopy.

Disease was incorrectly understaged in 25 PET-CT recipients and 48 conventional staging recipients (14.9% vs. 29.6%; difference, 14.7 percentage points [CI, 5.7 to 23.4 percentage points]; *P* = 0.002). In the PET-CT group, 11 patients had pathologic stage IIIA or IIB disease (9 on mediastinoscopy and 2 on lymph node sampling at thoracotomy), and 14 patients developed recurrence (3 local and 11 distant) within 1 year of thoracotomy. In the

Table 3. Diagnostic Confirmation for Patients With Correct Upstaging and Metastatic Disease

Site of Metastatic Disease	PET-CT Group (n = 19)*		Conventional Staging Group (n = 11)	
	Patients, n	Method Used or Reason Not Confirmed	Patients, n	Method Used or Reason Not Confirmed
Bone only	1	Biopsy	1	Biopsy
	2	Imaging	5	Imaging
	1	Multiple sites of radionuclide uptake†	2	Multiple sites of radionuclide uptake†
Left adrenals only	1	Not confirmed; developed Pancoast tumor		
Contralateral lung only	1	Biopsy		
	2	Imaging		
Kidney only			1	Biopsy
Ipsilateral lung, different lobe	2	Biopsy		
Liver and bone	1	Multiple sites of radionuclide uptake†	1	Multiple sites of radionuclide uptake†
Bone and shoulder soft tissue	1	Multiple sites of radionuclide uptake†	–	–
Bone and thyroid	1	Imaging	–	–
Right adrenals, bone, and brain	1	Adrenals only confirmed by imaging†	–	–
Left adrenals and brain	1	Brain only confirmed by imaging	–	–
Right adrenals and bone	1	Imaging	–	–
Brain only	3	Imaging	1	Imaging

PET-CT = positron emission tomography and computed tomography.

* 4 additional patients in the PET-CT group with correctly upstaged disease did not have metastatic disease (1 patient had another cancer, and disease was upstaged to IIIA and deemed unresectable in 3 patients).

† 7 patients had positive bone scans without subsequent confirmation.

conventional staging group, 41 patients had stage III disease (12 at mediastinoscopy and 29 at thoracotomy), and 7 had recurrence (1 local and 6 distant). Eight of 11 patients with IIIA or IIIB disease in the PET-CT group developed recurrence in 1 year compared with 9 in the conventional staging group. Overall, at 1 year, 22 PET-CT recipients with incorrectly understaged disease and 16 conventional staging recipients developed recurrence (13.2% vs. 9.9%; difference, 3.3 percentage points [CI, -3.7 to 10.3 percentage points]; *P* = 0.40).

In the Hamilton center (which used a PET scanner equipped with a partial ring of bismuth germanate detectors), disease was incorrectly staged in 2 of the 4 PET-CT recipients (overstaged in 1 patient and understaged in 1 patient) and correctly upstaged in 1 recipient. Of the remaining 163 PET-CT recipients, disease was incorrectly staged in 31 (overstaged in 7 patients and understaged in 24 patients) and correctly upstaged in 22.

On the basis of the staging strategy interventions, further work-up procedures were sometimes performed before treatment. In the PET-CT group, 51 such procedures were performed, compared with 81 in the conventional staging group (Table 4). Thirty-eight (22.8%) PET-CT recipients and 64 (39.5%) conventional staging patients had at least 1 procedure (*P* = 0.001). No serious adverse events were associated with these procedures.

The median duration of follow-up was 21.8 months (minimum, 0.1 months; maximum, 46.0 months) in the PET-CT group and 22.5 months (minimum, 0.2 months; maximum, 38.3 months) in the conventional staging group. Overall, 109 patients died over the 3 years of the study, 52 in the PET-CT group and 57 in the conven-

tional staging group (Figure 2); of these, 83.5% died of lung cancer.

DISCUSSION

We found that compared with conventional staging, staging with PET-CT doubled the proportion of patients whose tumor was correctly upstaged, thereby avoiding unnecessary surgery. This effect occurred at all stages of tumor presentation but was greater in patients who presented with more advanced tumor stage. Conventional staging most often detected bone metastases, whereas PET-CT de-

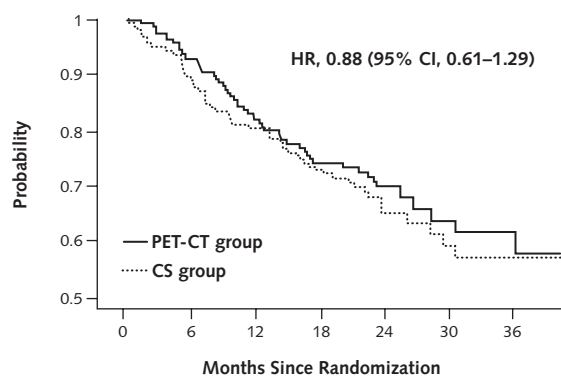
Table 4. Work-up Procedures

Work-up Procedure*	Procedures, n	
	PET-CT Group (n = 167)	Conventional Staging Group (n = 162)
CT (thorax, liver, adrenal, brain, bone, neck)	23	38
MRI (liver, adrenal, brain, bone)	10	12
Biopsy (liver, adrenal, bone FNA, and core)	4	8
Ultrasonography (liver, kidney, pelvis)	2	6
Radiography (bone, chest)	5	13
Bronchoscopy	0	1
Bone scan	3	1
Surgeries, scopes, mammography	4	2
Total	51	81

CT = computed tomography; FNA = fine needle aspiration; MRI = magnetic resonance imaging; PET-CT = positron emission tomography and computed tomography.

* 38 (22.8%) PET-CT recipients and 64 (39.5%) conventional staging recipients had at least 1 procedure (*P* = 0.001).

Figure 2. Probability of survival.



Patients at risk, <i>n</i>								
PET-CT group	170	156	133	105	56	30	21	
CS group	167	144	130	106	61	29	17	

CS = conventional staging; PET-CT = positron emission tomography and computed tomography; HR = hazard ratio.

tected a broader range of metastases, including bone, adrenal, and lung.

Disease was incorrectly upstaged in almost 5% percent of PET-CT recipients, and in half of these patients, PET-CT results were falsely positive in the mediastinum. Categorizing such patients as having inoperable disease could preclude them from potentially curative treatment (6). Thus, in patients with NSCLC, PET-CT positive mediastinal nodes should be confirmed with pathologic examination.

Disease was incorrectly understaged in almost twice as many conventional staging recipients as PET-CT recipients, mainly because PET-CT is more sensitive to disease in mediastinal nodes. Therefore, patients with advanced disease would avoid futile thoracotomy and be offered stage-appropriate treatment (such as chemotherapy plus radiation).

When comparing the 2 staging strategies, it is important to consider subsequent procedures and tests which are performed as a result of the interventions. It is reassuring that in our trial, PET-CT did not increase the number of subsequent procedures.

An English-language MEDLINE search to March 2009 identified 3 randomized trials of PET in patients with potentially surgically resectable NSCLC (2–4). The design of our trial differed from these 3 trials, which compared conventional staging alone with conventional staging plus PET. In planning our trial, we asked, “How does PET-CT compare with conventional staging in the work-up of NSCLC?” and, “Could PET-CT replace conventional staging?” Although cohort studies suggested that PET improved the accuracy of staging the mediastinum in NSCLC compared with CT, data were limited on whether PET improved clinical management (7–13). Unlike the other randomized trials, which used PET alone, we used PET-CT in all but 4 patients.

Our trial has limitations. Although it is larger than 2 of the 3 previous randomized trials of PET in early-stage NSCLC, the sample size was still relatively small, and the lower confidence limit for the difference in the proportion of patients with correctly upstaged disease was only 1.4%. In addition, because there were relatively few PET-CT scan locations, adherence to strict quality control guidelines was easier to achieve; our results may not be fully generalizable to a larger setting in which many different imaging machines are used. In most cases, the sites of metastases for the primary outcome were confirmed with biopsy or imaging tests. Four PET-CT recipients and 3 conventional staging recipients, all of whom had correct upstaging of disease, had positive bone scans without subsequent confirmation. However, the clinicians treating these patients considered them to be positive for disease because their scans had multiple abnormal sites of radio-nuclide uptake. The adjudication committee concurred with the local decisions.

In conclusion, preoperative staging with PET-CT identified more patients with mediastinal and extrathoracic disease than conventional staging did. However, falsely positive mediastinal nodes on PET-CT imaging can inadvertently exclude patients from potential curative surgery. Staging with PET-CT spared more patients from stage-inappropriate surgery.

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References

- Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest*. 1997;111:1718-23. [PMID: 9187199]
- van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preop-

- erative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet*. 2002;359:1388-93. [PMID: 11978336]
3. Viney RC, Boyer MJ, King MT, Kenny PM, Pollicino CA, McLean JM, et al. Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *J Clin Oncol*. 2004;22:2357-62. [PMID: 15197196]
 4. Herder GJ, Karmer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, et al. POORT Study Group. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. *J Clin Oncol*. 2006;24:1800-6. [PMID: 16567772]
 5. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer*. 1999;35:1773-82. [PMID: 10673991]
 6. Rusch VW. Mediastinoscopy: an endangered species? [Editorial]. *J Clin Oncol*. 2005;23:8283-5. [PMID: 16219928]
 7. Investigating extrathoracic metastatic disease in patients with apparently operable lung cancer. The Canadian Lung Oncology Group. *Ann Thorac Surg*. 2001;71:425-33; discussion 433-4. [PMID: 11235682]
 8. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koëter GH, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med*. 2000;343:254-61. [PMID: 10911007]
 9. Saunders CA, Dussek JE, O'Doherty MJ, Maisey MN. Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. *Ann Thorac Surg*. 1999;67:790-7. [PMID: 10215230]
 10. Weder W, Schmid RA, Bruchhaus H, Hillinger S, von Schulthess GK, Steinert HC. Detection of extrathoracic metastases by positron emission tomography in lung cancer. *Ann Thorac Surg*. 1998;66:886-92; discussion 892-3. [PMID: 9768946]
 11. MacManus MP, Hicks RJ, Ball DL, Kalff V, Matthews JP, Salminen E, et al. F-18 fluorodeoxyglucose positron emission tomography staging in radical radiotherapy candidates with nonsmall cell lung carcinoma: powerful correlation with survival and high impact on treatment. *Cancer*. 2001;92:886-95. [PMID: 11550162]
 12. Ung YC, Maziak DE, Vanderveen JA, Smith CA, Gulenchyn K, et al; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. *J Natl Cancer Inst*. 2007;99:1753-67. [PMID: 18042932]
 13. Hicks RJ, Kalff V, MacManus MP, Ware RE, Hogg A, McKenzie AF, et al. (18)F-FDG PET provides high-impact and powerful prognostic stratification in staging newly diagnosed non-small cell lung cancer. *J Nucl Med*. 2001;42:1596-604. [PMID: 11696627]

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