

PET–CT imaging in non-small-cell lung cancer

→ Mark Levine and Jim Julian

Imaging is performed in patients with early-stage non-small-cell lung cancer (NSCLC) for disease staging and to identify the patients most likely to benefit from surgery. Two recent randomised trials compared conventional staging plus PET with conventional staging alone in patients with NSCLC. Patients who underwent PET were more likely to avoid futile thoracic surgery.

Whole-body PET is an attractive imaging modality for use in oncology as many tumours preferentially take up 18F-fluorodeoxyglucose. The first generation of PET scanners relied on nuclear imaging alone. Subsequently, however, PET was combined with CT to provide functional and anatomical information simultaneously. In patients with early-stage non-small-cell lung cancer (NSCLC), preoperative imaging – radioisotope bone scans, CT of the chest, liver and adrenal glands, and CT or MRI of the brain – is used to identify surgical candidates. Evidence has accumulated over the past 10 years to suggest that PET could be a promising modality for preoperative stag-

ing of patients with NSCLC. However, although cohort studies have shown that (compared with CT) PET improves the accuracy of staging the mediastinum, data are limited on whether PET improves the management of patients.^{1,2}

Disparate results were obtained from three randomised trials, two from the Netherlands and one from Australia,^{3,4,5} which compared the addition of PET to conventional staging versus conventional staging alone for patients with NSCLC. For instance, in one of the Dutch trials,³ the rate of futile thoracotomy was 41% in the conventional-staging group compared with 21% in the conventional-staging plus PET group ($P=0.003$). The primary outcome of the Australian trial⁴

was thoracotomy, which was performed in 98% of patients in the conventional-staging group and in 96% of patients in the conventional-staging plus PET group ($P=0.44$). In the other Dutch trial,⁵ patients were randomly assigned to conventional staging or PET followed by investigation of any detected abnormalities. The study's primary outcome (the mean number of tests required to confirm staging and to define suitability for surgery) was similar in both groups (7.9 tests, $P=0.90$).

Two other recent trials have provided strong evidence that PET–CT has a role in the management of patients with NSCLC. Fischer and colleagues⁶ randomly assigned patients with newly

diagnosed or suspected NSCLC who were being considered for surgery to conventional staging alone (which included blood tests, contrast-enhanced CT of the chest and upper abdomen, and bronchoscopy) or to conventional staging plus PET-CT. All patients underwent additional invasive diagnostic procedures, including endoscopic or endobronchial ultrasonography and mandatory mediastinoscopy. The primary outcome was futile thoracotomy, which was defined as thoracotomy in a patient with pathologic stage IIIA-N2 or IIIB NSCLC, benign disease, explorative thoracotomy conducted for other reasons, or thoracotomy in a patient who developed recurrent disease or died within one year of randomisation. Owing to slow accrual, this trial was terminated after 189 participants were recruited (98 of whom were assigned to the PET-CT group and 91 to the conventional staging only group). In the PET-CT group, 38 patients (39%) were considered to have inoperable disease, 13 of whom were categorised as such on the basis of the PET-CT results (these patients had nine distant and four mediastinal metastases). In the conventional staging only group, 18 patients (20%) were considered to have inoperable disease, none of whom had distant metastases. In total, 60 patients in the PET-CT group underwent thoracotomy, of which 21 procedures (35%) were considered futile, versus 38 of 73 (52%) thoracotomies in the conventional-staging group ($P=0.05$). At the end of the study (mean duration of follow-up 27 months), mortality was 56% in the PET-CT group and 51% in the conventional-staging group.

In North America, conventional staging of NSCLC usually involves brain imaging with CT or MRI, isotope bone scan, and CT of the liver and adrenal glands. Brain imaging was not included in either staging protocol in the

study by Fischer et al.⁶ Although brain metastases cannot be detected by PET, the inclusion of brain imaging in pre-operative staging might have avoided some of the 16 cancer recurrences that occurred within the first year after surgery. Bone metastases commonly occur in patients with NSCLC and are often detected by PET imaging; however, bone scans were not routinely performed in this study. One might speculate that if Fischer and colleagues had included a bone scan in their conventional staging protocol, some of the distant metastases detected by PET-CT could have been identified by conventional staging alone, which would have narrowed the difference between the two groups. Moreover, the sites of distant metastases that were detected by PET-CT were not reported.

Fischer et al.⁶ aggressively pursued the assessment of mediastinal lymph nodes and more than 90% of patients in both groups underwent mediastinoscopy. Such high rates are not always achieved in many surgical settings. In addition, endobronchial ultrasonography and fine-needle aspiration cytology were performed to investigate abnormal imaging results. These tests are not routinely performed in many institutions, a fact that should be borne in mind before one decides whether the study results can be generalised to a given setting. More patients in the PET-CT group than in the conventional-staging group underwent endobronchial ultrasonography (36 vs 24 patients, respectively). Further investigation of abnormal PET scan results in the mediastinum could explain this difference. However, another possible explanation is that endobronchial ultrasonography tended to be preferentially performed in the PET-CT group rather than the conventional-staging group, which could have resulted in increased upstaging of NSCLC in patients who

underwent PET-CT, and thus contributed to a bias in diagnostic suspicion that favoured one group.

Maziak and colleagues⁷ from Canada recently published the results from a randomised trial that compared PET-CT with conventional staging (abdominal CT and bone scan) in patients with NSCLC. All patients had cranial CT or MRI and about 50% of patients in each arm underwent mediastinoscopy. The primary outcome was correct upstaging of cancer, which thereby avoided stage-inappropriate surgery. Disease was correctly upstaged in 23 of 167 (13.8%) patients in the PET-CT group and in 11 of 162 (6.8%) patients in the conventional-staging group ($P=0.046$). The most commonly identified sites of distant metastases in patients from the PET-CT group were bone, adrenal glands and liver. The most common site of metastasis identified in those who underwent conventional staging was bone. Metastases to the mediastinal lymph nodes were also detected by PET-CT. Disease was incorrectly upstaged in eight (4.8%) patients who underwent PET-CT and in one (0.6%) patient in the conventional-staging group ($P=0.037$). At the end of the study (median follow-up 22 months), 52 and 57 patients from the PET-CT and conventional staging group, respectively, had died.

Although there are limited data on whether the use of PET improves patient care, this technology has been widely adopted for many oncologic indications in some jurisdictions. Governments, however, are struggling with the rising costs of health care, which are partly attributed to the implementation of imaging technologies.⁸ The US government recently provided more than \$1 billion for 'comparative effectiveness research' to determine which interventions best improve patients' care, with the hope of obtaining evidence to guide

funding decisions in health care.⁹ The trials by Fischer et al.⁶ and Maziak et al.⁷ are fine examples of this type of research. These studies provide strong evidence that PET-CT identifies more mediastinal and extrathoracic disease than conventional staging alone in patients with NSCLC, and that its use prevents unnecessary surgeries.

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Practice point

PET-CT should be included as part of preoperative staging in patients with NSCLC who are being considered for surgery, as this imaging technique can help identify advanced disease and avoid unnecessary thoracotomy.

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