

## Staging Lung Cancer Using Positron Emission Tomography and the Impact on Care

Viney RC, Boyer MJ, King MT, 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.

### Study Overview

**Objective.** To measure the impact of positron emission tomography (PET) on clinical management and surgical outcomes for patients with stage I-II non-small cell lung cancer (NSCLC).

**Design.** Randomized controlled trial with intention-to-treat analysis.

**Setting and participants.** Patients were recruited from 6 participating surgeons at 4 tertiary hospitals in Sydney, Australia. Patients were randomized to surgical resection or to PET with <sup>18</sup>fluorodeoxyglucose (FDG-PET) before surgery. Eligible patients had a diagnosis of NSCLC and were able to tolerate thoracotomy. All patients were staged with a chest radiograph and computerized tomography (CT) scanning of the thorax and brain. Mediastinoscopy was not mandated. Radiographic studies were reviewed by a radiologist and the patient's surgeon and must have demonstrated stage I or II disease.

**Intervention.** FDG-PET scans were performed at 1 center. Scans were interpreted by a single physician and reported using the tumor-node-metastasis staging system of the American Joint Committee on Cancer. CT images were available to the PET physician but were not used in interpretation of the PET scans. Patients randomly assigned to PET were assigned a "PET stage" based on the results of the PET scan. Local or distant metastatic disease detected by PET was confirmed by biopsy. If abnormalities detected by PET were unable to be confirmed, patients proceeded to thoracotomy. Further management, including mediastinoscopy, surgery, and postsurgical therapy, was at the discretion of the surgeon. For patients randomly assigned to no PET, thoracotomy was arranged.

**Main outcome measure.** The proportion of patients undergoing thoracotomy.

**Main results.** Of 183 patients, 92% had stage I disease. 91 were

randomized to PET and 92 to no PET. Compared with conventional staging, PET upstaged 22 patients (stage IIIA disease suggested in 13 patients, stage IIIB in 6, and stage IV in 3), confirmed staging in 61, and staged 2 patients as benign. Of the 13 patients in whom PET suggested stage IIIA disease, 12 patients were confirmed to have stage III disease and 1 had stage I disease. Among the 6 patients with stage IIIB disease by PET staging, 4 were found to be false-positive for NSCLC. Two of the 3 patients identified as PET stage IV subsequently had metastatic disease confirmed. All patients who were PET stage I-II ( $n = 61$ ) proceeded to thoracotomy—2 were found to have benign disease and 6 were stage IIIA on pathologic staging. The sensitivity and specificity of PET for identification of mediastinal disease was 73% (95% confidence interval [CI], 54%–92%) and 90% (95% CI, 82%–98%), respectively. In patients who had a single lymph node involved, PET correctly identified 55% of cases. When multiple lymph nodes were involved, PET correctly identified 71% of cases. PET led to further investigation or a change in clinical management in 13% of patients and provided information that could have affected management in a further 13% of patients. There was no significant difference between the trial arms in the number of thoracotomies avoided ( $P = 0.2$ ).

**Conclusion.** For patients who are carefully and appropriately staged as having stage I-II disease, PET provides potential for more appropriate stage-specific therapy but may not lead to a significant reduction in the number of thoracotomies avoided.

### Commentary

Lung cancer remains the leading cause of cancer-related death in the United States for both men and women. Although systemic chemotherapies and novel agents have contributed to incremental improvements in the care of patients with advanced disease, the majority of patients will not survive 2 years. For those patients diagnosed with earlier stages of disease, a substantial portion (up to 50%) will ultimately die from recurrent/progressive disease

despite curative surgical attempts. These patients likely already harbor distant micrometastatic disease not seen by conventional CT scanning at initial staging.

PET scanning has emerged as a valuable tool in the initial staging of patients diagnosed with lung cancer [1]. The sensitivity and specificity of PET for the detection of mediastinal disease has been estimated at 91% and 86%, respectively. The corresponding estimates using CT are 75% and 66%. PET can find distant metastases not seen using CT scanning. More accurate staging at diagnosis potentially could spare many patients unnecessary (noncurative) surgery, as well as identify others who may benefit more from preoperative chemoradiotherapies.

Viney et al hypothesized that PET scanning may reduce the number of unnecessary surgeries in patients with conventionally staged I-II NSCLC by identifying those patients with more advanced disease. Indeed, in their study, PET scanning "upstaged" 24% of patients. However, in terms of number of thoracotomies performed, there was no statistical difference between the group who underwent PET staging and the group conventionally staged with CT scanning alone.

This is an important study because it represents one of the few prospective, randomized studies assessing the role of PET scanning in the care of patients with lung cancer. It is worth noting that in one of the few other prospective, randomized studies (similarly sized), PET was associated with a 51% relative reduction in so-called "futile" thoracotomies [2]. Some reasons for the discrepant findings may have to do with the populations studied. In the Viney et al study, most of the patients upstaged were stage I at enrollment, and most were upstaged to stage IIIA (predominantly because of ipsilateral mediastinal node involvement)—a stage where

surgery still can play an important role in care. In the van Tinteren et al study [2], only 64% had stage I disease at enrollment. As well, van Tinteren and colleagues worked with a broader definition of futile surgery. It also is important to consider that the majority of patients in the Viney et al study were assessed by 1 surgeon, potentially introducing bias in terms of who went to surgery despite the PET results.

Somewhat overshadowed in the Viney study was the fact that PET could have affected the care of 26% of patients (thoracotomies avoided, preoperative chemotherapy more carefully used). As the authors point out, the value of FDG-PET for patients with clinical stage I-II NSCLC is dependent on the management strategy for stage IIIA disease. Newer combination CT/PET scanners now in use since this study was conducted likely enhance our ability to accurately stage patients at diagnosis and optimize their care.

### Applications for Clinical Practice

PET scanning is an important tool in the initial staging of patients with NSCLC and should be performed where available.

—Review by David R. Spigel, MD

### References

1. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med* 2000;343:254–61.
2. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: The PLUS multicentre randomised trial. *Lancet* 2002;359:1388–93.