

Positron Emission Tomography to Improve Care for Patients with Suspected Non-Small Cell Lung Cancer

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;359:1388–92.

Study Overview

Objective. To compare conventional diagnostic methods with positron emission tomography (PET) in the preoperative staging of patients with suspected non-small cell lung cancer.

Design. Multicenter randomized prospective trial with intention-to-treat analysis.

Setting and participants. Between January 1998 and January 1999, 188 patients from 1 university and 8 community hospitals in the Netherlands with suspected or proven non-small cell lung cancer deemed medically operable and resectable on the basis of clinical staging were enrolled. Patients were randomly assigned to an evaluation using whole-body PET using 18-fluorodeoxyglucose followed by conventional workup (CWU) using invasive diagnostic and therapeutic procedures or to CWU alone. TNM staging was used. Outpatient clinic follow-up and data collection occurred for up to 1 year after randomization. Potential distant or nodal metastases were confirmed by other means.

Main outcome measures. The primary outcome measure was number of futile thoracotomies, classified as resections associated with benign lung lesions, pathologically proven mediastinal lymph-node involvement (stage IIIA-N2) other than minimal N2 disease (ie, intranodal involvement in a single node established at mediastinal dissection), stage IIIB disease, explorative intent for other reasons, or recurrent disease or death from any cause within 1 year after randomization. Number of futile thoracotomies with respect to total number of patients randomized in each group was tested by χ^2 analysis.

Main results. 92 patients were assigned to the CWU + PET group and 96 to the CWU group. 70% of patients in each group had clinical stage I/II disease at baseline. Most patients had received at least a chest computed tomography (CT) scan that included the liver and adrenal glands prior to randomization. The 2 groups shared similar baseline characteristics: mean age of 65 years, mostly men, good perfor-

mance status, and comorbidities (one third had chronic obstructive pulmonary disease). Approximately half in each group had a diagnosis of non-small cell lung cancer at baseline. Few patients had CT or magnetic resonance imaging of the brain.

A significantly greater proportion of futile thoracotomies occurred in the CWU group compared with the CWU + PET group (39 [41%] versus 19 [21%]; relative reduction, 51% [95% confidence interval {CI}, 32–80]; $P = 0.003$), which translates to 5 patients needing PET to avoid 1 futile thoracotomy. More patients in the CWU group underwent thoracotomy than in the CWU + PET group (81% versus 65%). Futile surgery occurred irrespective of clinical stage. Assessment of resectability by CT and PET was discordant in one third of the cases. In 37% of those undergoing PET, CT was incorrect with respect to the primary outcome. Most of the futile thoracotomies were based on recurrence or death within 1 year. PET correctly suggested surgery was justified in 81% of cases (95% CI, 68%–92%). Preoperative assessment using PET proved better than CWU alone before surgery with curative intent, at the time of surgery, and during follow-up.

Conclusion. Addition of PET to conventional workup prevented unnecessary surgery in 1 out of 5 patients with suspected non-small cell lung cancer.

Commentary

An estimated 157,000 people die from lung cancer in the United States each year, making it the number 1 cause of cancer-related mortality for both men and women [1]. Thoracotomy remains the most effective treatment for earlier stage disease but is associated with a high rate of relapse. Accurately staging patients prior to therapy can best predict prognosis and potentially prevent unnecessary surgical intervention in patients with more advanced disease. In the last

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several years, PET has become increasingly integrated into the baseline staging evaluation of patients with suspected lung cancer. PET previously has been shown to improve the rate of detection of both local and distant metastases in patients with non-small cell lung cancer as well as being accurate and cost-effective [2,3]. However, understanding how the improved rate of detection through PET translates into better outcomes for patients has been less clear.

van Tinteren et al conducted a well-designed study to assess the value of PET by looking at the number of futile thoracotomies after staging in 2 similar patient groups. Adding PET to the conventional preoperative evaluation led to a greater upstaging of patients, subsequently reducing the number of unnecessary resections. An impressive 20% of patients were spared futile surgeries. The multicenter randomized prospective design makes these results less prone to selection or investigator biases and more widely applicable.

While some might question the futility of surgery for stage III or even stage IV so-called oligometastatic disease (eg, solitary hepatic, brain, or bone metastases), the 5-year survival after resection is generally very poor. Neoadjuvant or combination chemo- or radiotherapies so far have not improved these survival rates. Whether emerging novel therapies may alter the surgical spectrum of lung cancer

remains to be seen. Indeed, how futility was defined in this trial seems appropriate and consistent with surgical practice.

Applications for Clinical Practice

PET previously has been shown to be a very sensitive and specific tool in evaluating patients with non-small cell lung cancer, improving the detection of both local and distant disease. Improved staging can lead to more appropriate treatment planning for these patients. PET plays an important role in the preoperative staging of patients with suspected non-small cell lung cancer and should be incorporated into current clinical practice.

—Review by David R. Spigel, MD

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