
DAVID P. MASON, MD

Department of Thoracic and Cardiovascular Surgery,
Transplantation Center, Cleveland Clinic,
Cleveland, OH

The role of surgery for locally advanced non–small cell lung cancer

■ ABSTRACT

Accurate clinical staging of patients with locally advanced non–small cell lung cancer (NSCLC) is critical in identifying surgical candidates, who are typically patients with stage N2 disease. Preoperative staging by ^{18}F -fluorodeoxyglucose–positron emission tomography can alter staging and therefore influence the selection of therapy. The staging evaluation should include an assessment of the mediastinal lymph nodes; mediastinal lymph node involvement is a negative prognostic indicator. When the treatment plan potentially includes surgery, multidisciplinary evaluation including physiologic evaluation is essential, as surgery is aggressive with potential morbidity. Multimodality therapy offers the best chance for improved progression-free and overall survival. Patients with potentially resectable NSCLC who are downstaged following induction chemotherapy have a superior prognosis compared with those whose stage is unaltered.

Although not every patient with locally advanced non–small cell lung cancer (NSCLC) is a surgical candidate, surgery is worth considering for a subpopulation of patients who can benefit. For patients with stage III disease, choosing the optimal treatment is difficult and best done by a team skilled in managing this type of cancer.

Accurate clinical staging is extremely important to optimize treatment and outcome. The most common staging system used is the tumor, node, metastasis (TNM) system, which was revised in 2009. Surgery as a potential option for patients with lung cancer is becoming more accepted for patients with N2 disease

but is still controversial for N3 disease. For the most part, surgical candidates are those with N2 or T4N1 disease. This article therefore focuses on staging and the utility of surgery in patients with N2 disease.

■ NONINVASIVE STAGING

Computed tomography (CT) of the chest and upper abdomen with intravenous contrast, including the liver and adrenal glands, is standard procedure for noninvasive staging of NSCLC. Contrast CT or magnetic resonance imaging of the brain is necessary to rule out brain metastasis in the patient with NSCLC for whom surgery is being considered.

Fused ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) is being used increasingly for staging patients with NSCLC. Preoperative staging by FDG-PET improves the detection of occult metastatic disease and alters staging (**Figure 1**). Pieterman et al¹ demonstrated that the use of PET for clinical staging resulted in downstaging of 20 patients and upstaging of 42 patients compared with standard approaches (CT, ultrasonography, bone scanning, and needle biopsies) in a series of 102 patients with potentially resectable NSCLC. For mediastinal lymph node staging, the sensitivity and specificity of FDG-PET were 91% and 86%, respectively, compared with 75% and 66%, respectively, with CT.

At Cleveland Clinic, we have found that PET stage and pathologic stage correlate less than 70% of the time, which reflects the high incidence of histoplasmosis and other endemic inflammatory diseases of the mediastinum.

■ MEDIASTINAL SAMPLING

The staging evaluation includes an assessment of the mediastinal lymph nodes. Nodal sampling of the mediastinum is advised for every patient with potentially resectable NSCLC, even in the absence of an enlarged mediastinal lymph node on CT, because mediastinal lymph node involvement is a negative prognostic indicator; absence of tumor involvement of the mediasti-

Dr. Mason reported that he has no financial relationships that pose a potential conflict of interest with this article.

This article was developed from an audio transcript of Dr. Mason's presentation at the "Advances in Lung Cancer Evaluation and Management" symposium held in Cleveland, Ohio, on April 30, 2011. The transcript was formatted and edited by *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness and was then reviewed, revised, and approved by Dr. Mason.

doi:10.3949/ccjm.79.s2.08

nal lymph nodes confers a more favorable prognosis.

Cervical mediastinoscopy was first introduced for lung cancer staging in 1959 and is considered the gold standard in mediastinal staging. The sensitivity and specificity approach 100% in experienced hands. A single-center experience of 2,137 cervical mediastinoscopies revealed a complication rate of 0.6% and death from mediastinoscopy in 0.05%.² Node stations obtainable with cervical mediastinoscopy are 2R, 4R, 3, 2L, and 4L, and sometimes 10R. These are central mediastinal nodal stations.

De Leyn et al³ demonstrated that even small tumors can have lymph node involvement. Cervical mediastinoscopy was positive in their series in 9.5% of stage T1 tumors, 17.7% of T2, 31.2% of T3, and 33.3% of T4.

■ ENDOBRONCHIAL ULTRASOUND (EBUS) AND EBUS STAGING

Endobronchial ultrasound involves the use of a bronchoscope with an ultrasound probe mounted on it to evaluate nodal stations for suspicious lesions that require biopsy. Needle aspiration biopsy is performed by advancing a needle housed in a sheath of the endoscope, using ultrasound to identify target nodal tissue and obtain sample tissue for evaluation.

■ BRAIN IMAGING

Although brain metastases are uncommon, occurring in only 1% to 5% of asymptomatic patients with NSCLC, their identification is paramount when the treatment for stage III NSCLC is potentially high-morbidity surgery.

■ PHYSIOLOGIC EVALUATION

When the treatment plan potentially includes surgery, a multidisciplinary evaluation is essential and should involve specialists in medical oncology, radiation oncology, pulmonary medicine, thoracic surgery, and pathology.

Because surgery for stage III NSCLC is aggressive, prior physiologic evaluation is necessary to assess operative risk. Pulmonary function evaluation should include spirometry, measurement of arterial blood gas values, diffusion capacity (transfer factor of the lung for carbon monoxide), 6-minute walk test, and cardiopulmonary exercise testing.

Stress testing, whether by nuclear imaging or dobutamine echocardiogram, is also indicated, especially if considering pneumonectomy. A quantitative ventilation-perfusion scan is indicated for a more definitive evaluation of pulmonary function.



FIGURE 1. Fused ¹⁸F-fluorodeoxyglucose-positron emission tomography is used for staging patients with non-small cell lung cancer. This image shows an N2-node.

■ RESULTS OBTAINED WITH MULTIMODALITY THERAPY

Southwest Oncology Group 8805

The Southwest Oncology Group (SWOG) study 8805 used a trimodality approach in patients with bulky stage III NSCLC: induction chemoradiation with concurrent cisplatin, etoposide, and radiotherapy (45 Gy) followed by surgical resection.⁴ The 3-year survival rate with this treatment strategy was 26%. Patients in this trial who were downstaged following induction therapy so that they had node-negative disease at the time of surgery had a superior prognosis, with a 3-year survival rate of 41%. Therefore, a subset of patients with stage III NSCLC stands to benefit from surgery, but identifying this group prior to surgery may not be possible.

Trial of accelerated multimodality therapy

An accelerated multimodality induction regimen given over 12 days was tested in 105 patients with stage IIIa (n = 78) and stage IIIb (n = 27) NSCLC, 97% of whom had mediastinal involvement.⁵ Seven patients had T4 disease. The induction regimen consisted of a 12-day course of concurrent cisplatin, paclitaxel, and radiotherapy. A 4-day continuous infusion of cisplatin (20 mg/m²/day) and a 24-hour continuous infusion of paclitaxel (175 mg/m²) were administered on day 1. Concurrent accelerated fractionated radiotherapy consisted of twice-daily fractions of 1.5 Gy.

All patients completed induction therapy. Of the 105 patients, 98 were candidates for surgical treatment and 83 underwent curative resections (lobectomy, n = 42; pneumonectomy, n = 36; and bilobectomy, n = 5).

Surgical mortality was 7% and morbidity was 31% (supraventricular arrhythmia, 18%; recurrent laryngeal nerve palsy, 6%; pneumonia or adult respiratory

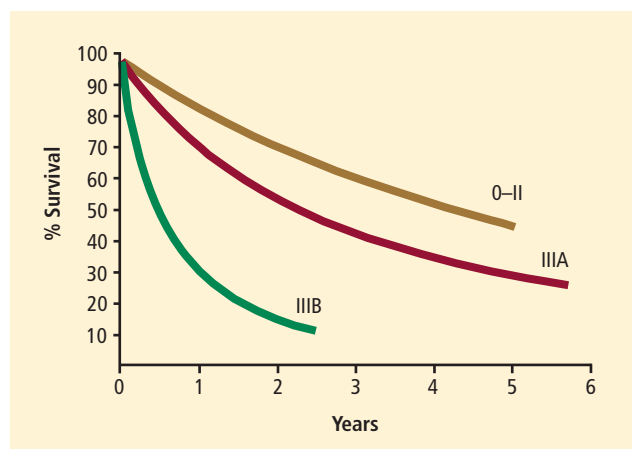


FIGURE 2. Pathologic stage is the most powerful predictive factor in patients with resectable non-small cell lung cancer. Survival among patients with pathologic stages 0 to II is superior to those with residual N2 (stage IIIA) disease. Nonresponders (stage IIIB) have the poorest survival.

Adapted from *The Journal of Thoracic and Cardiovascular Surgery* (DeCamp MM, et al. Value of accelerated multimodality therapy in stage IIIA and IIIB non-small cell lung cancer. *J Thor Cardiovasc Surg* 2003; 126:17–27), copyright © 2003, with permission from The American Association for Thoracic Surgery. www.sciencedirect.com/science/journal/00225223

distress syndrome, 3%; bronchopleural fistula, 3%; wound infection, 2%; reoperation for bleeding, 1%).

Survival after resection was 70% at 1 year, 42% at 3 years, and 26% at 5 years. As with SWOG 8805, nodal downstaging was associated with improved survival. Patients with disease that was downstaged to pathologic stage 0 to II had a 5-year survival that approached 50%, whereas patients with persistent stage IIIB disease had a 2-year survival of just 18% (Figure 2). Patients with postresection N0 to N1 status had a 5-year survival of 55%, which declined to approximately 31% with N2 status. Few patients with N3 status survived to 3 years.

Profiles of patients with favorable and unfavorable prognoses were developed. A younger patient with adenocarcinoma whose disease was downstaged with induction therapy had a favorable prognosis, whereas an older patient with squamous carcinoma that did not respond to treatment and continued in pathologic stage IIIB had an unfavorable prognosis.

SURVIVAL DATA FAVOR SURGERY

An accurate head-to-head comparison of chemoradiation with or without surgery in patients with resectable NSCLC is difficult because patients selected for surgery must meet performance status criteria, whereas an evaluation of performance status is not mandated for patients treated with definitive chemoradiation alone. The quality of postoperative care and

the management of postoperative complications also differ from institution to institution.

A controlled trial in which patients with stage IIIa NSCLC were randomized to chemoradiation with or without surgical resection was performed by Albain et al.⁶ The induction regimen consisted of 2 cycles of cisplatin and etoposide plus radiotherapy (45 Gy). At 5 years, overall survival was 27% in patients who underwent resection and 20% in those who continued radiotherapy without resection, a difference that did not achieve statistical significance. Progression-free survival was superior in the group assigned to surgery compared with those not undergoing resection (median: 12.8 months vs 10.5 months).

A Surveillance Epidemiology and End Results registry of more than 48,000 patients with stage III NSCLC revealed significantly better overall survival in those who received neoadjuvant radiotherapy plus surgery compared with radiation therapy alone, postoperative radiation therapy, and surgery alone.⁷

CLEVELAND CLINIC EXPERIENCE WITH ACCELERATED PROTOCOL

At Cleveland Clinic, the current protocol for stage IIIa and IIIB NSCLC is an accelerated multimodality regimen consisting of paclitaxel, 50 mg/m² twice weekly for 3 weeks; carboplatin (target area under the concentration vs time curve dosing) twice weekly for 3 weeks; and daily erlotinib (phase 1 dose escalation protocol) with concurrent radiotherapy, 1.5 Gy twice daily, as induction therapy, followed by a preoperative evaluation and surgery if local control is achieved with induction treatment.

This protocol has been used in 30 patients with stage IIIa disease (median age: 61 years) with no operative mortality (62% lobectomy, 38% pneumonectomy) and a median length of stay of 6.2 days. Forty percent of patients had their disease downstaged following induction therapy. Three-year survival is approximately 60% and, at 5 years, survival is still 55%.

CONCLUSION

Multimodality therapy for NSCLC is effective and achieves favorable survival. Pathologic downstaging is an important predictor for survival but patients with residual N2 disease still have meaningful survival with resection.

A team approach to evaluation and treatment among medical oncology, radiation oncology, pulmonary medicine, and thoracic surgery is critical to successful outcome.

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Correspondence: David P. Mason, MD, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Avenue, J4-1, Cleveland, OH 44195; masond2@ccf.org