

# Initiating the Era of “Precision” Lung Cancer Surgery

Valerie W. Rusch, M.D.

Surgical resection for lung cancer dates to the early 20th century. Evarts Graham is credited with performing the first successful pneumonectomy in 1933 for what was then an uncommon disease. During the next 25 years, surgeons focused on improving outcomes through better resection techniques. In 1962, retrospective data suggested that lobectomy for early-stage non-small-cell lung cancer (NSCLC) yielded a 5-year overall survival similar to that reported after pneumonectomy,<sup>1</sup> and lobectomy gradually became the more commonly performed operation. By the 1980s, advances in imaging (e.g., computed tomography [CT]), staging by means of mediastinoscopy, and routine intraoperative lymphadenectomy enabled the identification of small, peripheral NSCLCs for which sublobar resection was potentially appropriate. Controversy over the preferred surgical management led to a landmark clinical trial by the Lung Cancer Study Group (LCSG) in which patients with peripheral stage T1N0 NSCLC (tumor size,  $\leq 3$  cm, without lymph-node metastases) were randomly assigned intraoperatively to undergo lobectomy or sublobar resection (segmentectomy or wedge resection).<sup>2</sup> In this equivalency trial involving 247 eligible patients, the difference in overall survival favored the lobectomy group but did not reach statistical significance. However, the incidence of locoregional recurrence was three times as high with sublobar resection as with lobectomy. Thereafter, lobectomy was the standard of surgical care for this group of patients, and sublobar resection was reserved for patients with limited pulmonary function.

Now we are in a completely different era. CT-based lung cancer screening routinely identifies “very early” NSCLC, defined as T1a–bN0 (measuring  $\leq 2$  cm, node negative) tumors. Adenocarcinoma is the most common form of lung cancer, with a preponderance of peripherally located tumors. Advances in preoperative staging (e.g., endobronchial ultrasonography) and the pathological classification of lung adenocarcinoma<sup>3</sup> have improved patient selection for treatment. Perioperative mortality, perioperative morbidity, and the median length of hospital stay after ei-

ther sublobar resection or lobectomy have steadily declined and are 0.5 to 1.1%, less than 10%, and 2 to 3 days, respectively, in a recent report from the Society of Thoracic Surgeons database.<sup>4</sup> At least 80% of resections are now performed by means of video- or robotic-assisted thoracic surgery, which has enhanced postoperative outcomes.<sup>4</sup>

In this issue of the *Journal*, Altorki et al.<sup>5</sup> report the results of a multicenter, noninferiority trial (CALGB 140503), which was similar in design to the LCSG trial but enrolled 697 eligible patients with peripheral T1aN0 NSCLC who were randomly assigned intraoperatively to undergo either lobectomy or sublobar resection (wedge resection or segmentectomy). After a median follow-up of 7 years, sublobar resection was noninferior to lobectomy with respect to disease-free survival, and overall survival was similar with the two procedures. The publication of this article comes shortly after that of a multicenter, noninferiority trial from Japan (JCOG0802)<sup>6</sup> in which 1106 patients with T1a–bN0 NSCLC were randomly assigned to undergo either lobectomy or segmentectomy (but not wedge resection). After a median follow-up of 7.3 years, no difference was noted in overall survival, and a lower relapse-free survival was seen after segmentectomy. Reasons for differences in 5-year overall survival between the two trials (80% in the CALGB 140503 trial and  $\geq 90\%$  in the JCOG0802 trial) are unclear and may relate to subtle variations in patient selection, intraoperative management, and tumor characteristics. However, these two landmark trials are practice-changing because they establish sublobar resection as the standard of care for a select group of patients with NSCLC.

Why is this important? As CT screening becomes more widespread, this patient population will increase in clinical practice. Although all these operations are now safe, sublobar resection is associated with an even lower risk than lobectomy. The LCSG, CALGB 140503, and JCOG0802 trials did not identify clinically significant long-term differences in pulmonary-function tests between lobectomy and sublobar resection, but testing was confined to spirome-

try measurements and did not include more sensitive or functional measurements, such as diffusion capacity and 6-minute walk tests. However, short-term differences in pulmonary-function tests occur and may affect perioperative and functional outcomes, especially for tumors in the lower lobe. Moreover, patients who are cured of their first NSCLC remain at high risk for metachronous primary NSCLC. Sublobar resections leave open more treatment options for such patients.

None of these results provide a license for suboptimal surgical care. The CALGB 140503 and JCOG0802 trials selected patients meticulously and included strict criteria for lymph-node staging and complete resection. Such safeguards must be preserved in routine practice outside clinical trials. Thoracic surgeons will need to expand their expertise in sublobar resections, especially complex segmentectomies, and will need to collaborate closely with pathologists in assessing margins of resection, adequacy of lymph-node staging, and tumor characteristics that may predict recurrence.<sup>7,8</sup> When appropriate, lobectomy should still be performed. The era of “precision” surgery for NSCLC has arrived.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York.

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