Thirty- and ninety-day outcomes after sublobar resection with and without brachytherapy for non–small cell lung cancer: Results from a multicenter phase III study

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Objective: Sublobar resection (SR) is commonly used for patients considered high risk for lobectomy. Nonoperative therapies are increasingly being reported for patients with similar risk because of perceived lower morbidity. We report 30- and 90-day adverse events (AEs) from American College of Surgeons Oncology Group Z4032, a multicenter phase III study for high-risk patients with stage I non–small cell lung cancer.

Methods: Data from 222 evaluable patients randomized to SR (n = 114) or SR with brachytherapy (n = 108) are reported. AEs were recorded using the Common Terminology Criteria for Adverse Events, Version 3.0, at 30 and 90 days after surgery. Risk factors (age, percent baseline carbon monoxide diffusion in the lung [DLCO%], percent forced expiratory volume in 1 second [FEV1%], upper lobe vs lower lobe resections, performance status, surgery approach, video-assisted thoracic surgery vs open and extent, and wedge vs segmentectomy) were analyzed using a multivariable logistic model for their impact on the incidence of grade 3 or higher (G3+) AEs. Respiratory AEs were also specifically analyzed.

Results: Median age, FEV1%, and DLCO% were similar in the 2 treatment groups. There was no difference in the location of resection (upper vs lower lobe) or the use of segmental or wedge resections. There were no differences between the groups with respect to "respiratory" G3+AEs (30 days: 14.9% vs 19.4%, $P = .35$; 0–90 days: 19.3% vs 25%, $P = .31$) and "any" G3+ AEs (30 days: 25.4% vs 30.6%, $P = .37$; 0–90 days: 29.8% vs 37%, $P = .25$). Further analysis combined the 2 groups. Mortality occurred in 3 patients (1.4%) by 30 days and in 6 patients (2.7%) by 90 days. Four of the 6 deaths were thought to be due to surgery. When considered as continuous variables, FEV1% was associated with "any" G3+ AE at days 0 to 30 ($P = .03$; odds ratio [OR] = 0.98) and days 0 to 90 ($P = .05$; OR = 0.98), and DLCO% was associated with "respiratory" G3+ AE at days 0 to 30 ($P = .03$; OR = 0.97) and days 0 to 90 ($P = .05$; OR = 0.98). Segmental resection was associated with a higher incidence of any G3+ AE compared with wedge resection at days 0 to 30 (40.3% vs 22.7%; OR = 2.56; $P < .01$) and days 0 to 90 (41.5% vs 29.7%; OR = 1.96; $P = .04$). The median FEV1% was 50%, and the median DLCO% was 46%. By using these median values as potential cutpoints, only a DLCO% of less than 46% was significantly associated with an increased risk of "respiratory" and "any" G3+ AE for days 0 to 30 and 0 to 90.

Conclusions: In a multicenter setting, SR with brachytherapy was not associated with increased morbidity compared with SR alone. SR/SR with brachytherapy can be performed safely in high-risk patients with non–small cell lung cancer with low 30- and 90-day mortality and acceptable morbidity. Segmental resection was associated with increased "any" G3+ AE, and DLCO% less than 46% was associated with "any" G3+ AE and "respiratory" G3+ AE at both 30 and 90 days. (J Thorac Cardiovasc Surg 2011;142:1143-51)

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Sublobar resection (SR) is usually reserved for patients with non–small cell lung cancer (NSCLC) who are considered high risk for lobectomy. The principal reason for selective use in higher-risk patients is the higher locoregional

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Abbreviations and Acronyms
ACOSOG = American College of Surgeons
            Oncology Group
AE   = adverse event
ASA   = American Society of
            Anesthesiologists
CI   = confidence interval
CTC   = Common Terminology Criteria
DLCO   = carbon monoxide diffusion in the
            lung
FEV_1 = forced expiratory volume in 1 second
NSCLC   = non–small cell lung cancer
OR   = odds ratio
SBRT   = stereotactic body radiation therapy
SR   = sublobar resection
SRB   = sublobar resection with
            intraoperative brachytherapy

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recurrence rate after SR compared with lobectomy.[1] One approach that may reduce the incidence of local recurrence is the addition of adjuvant brachytherapy.[2-4] Z4032 is a prospective randomized clinical trial by the American College of Surgeons Oncology Group (ACOSOG) that compares SR with intraoperative brachytherapy (SRB) with SR alone. This study has recently completed accrual. The primary outcome of interest of the study is 2-year local control, and this end point will be reported when sufficient follow-up becomes available. The current report examines the incidence and severity of adverse events (AEs) occurring at both 30 and 90 days after surgery from this multicenter randomized prospective study. This is of particular importance because nonoperative therapies, such as stereotactic body radiation therapy (SBRT) and radiofrequency ablation, are gaining increasing attention within the medical community, even for patients who are candidates for operation.[4,5] The toxicity profiles of the various lung cancer therapies are important considerations when discussing treatment options with patients. We report the incidence and severity of AEs after SR in the high-risk population selected for Z4032.

MATERIALS AND METHODS

Eligible patients for this study included patients with stage I lung cancers 3 cm or less in maximum diameter (ie, stage IA or the subset of stage IB with visceral pleural involvement) on preoperative computed tomography scan. Patients were defined as high risk for lobectomy if they met at least 1 major criterion or 2 minor criteria as described in Table 1. In addition to meeting these criteria, patients had to be evaluated by an ACOSOG-approved thoracic surgeon and considered not to be a candidate for lobectomy or to be too high risk for any form of pulmonary resection. Patients considered medically inoperable (but who met these criteria) were usually referred for nonoperative therapies, such as radiofrequency ablation or SBRT. We did not record the details of screened patients who

met the major and minor criteria described above who were not offered participation in this study. To confirm that patients did not have nodal involvement, all suspicious lymph nodes seen on positron emission tomography or computed tomography scan required biopsy by mediastinoscopy, endobronchial ultrasound, or sampling at the time of resection. SR included wedge or segmental resection and could be performed by video-assisted thoracic surgery or thoracotomy. Two methods of brachytherapy were allowed.[6,7] The method used was at the discretion of the treating surgeon. In the first technique, polyglactin sutures containing ^{125}I seeds (Oncura, Inc, Princeton, NJ) were placed parallel to and 5 mm away from the staple line on each side of the resection margin. The suture strands were fixed to the lung surface with several 3.0 silk or polyglactin sutures placed 1 to 2 cm apart. With the second brachytherapy technique, a polyglycolic mesh implant was created during the procedure. The same ^{125}I suture strands were woven into a piece of Vicryl mesh. The strands were placed at 1-cm intervals. The mesh was then sutured over the staple line. The dosimetry goal of the brachytherapy was to deliver 100 Gy at 5 to 7 mm along the central axis of the resection margin.

AEs were recorded using the Common Terminology Criteria (CTC) for Adverse Events Version 3.0.[8] The CTC is a broad classification of AE with several defined categories. Within each category, AEs are listed and accompanied by a description of severity (grade). Grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life-threatening or disabling AE, and grade 5 is death related to the AE.

AEs were analyzed at 0 to 30 days and again at 0 to 90 days. For the purpose of this report, we limit discussion to grade 3 and higher (3+) AE. Because this group was considered high risk primarily on the basis of lung function, 2 groups of AE were studied: "any AE" or "respiratory AE", where "respiratory AE" included adult respiratory distress syndrome, aspiration, bronchospasm, bronchostenosis, dyspnea, hypoxia, pleural effusion, pneumonitis, chest tube drainage or leak, prolonged intubation, pulmonary-other, and pneumonia as defined by the CTC.

All patients provided written informed consent before trial enrollment in accordance with applicable guidelines. At each participating site, institutional review board approval was obtained in accord with an assurance filed with and approved by the US Department of Health and Human Services.

Statistical Analysis

Chi-square tests for categoric variables and Wilcoxon rank-sum tests for continuous variables were used to compare the baseline patient characteristics between the SR and the SRB arms. We compared the 2 treatment arms for the incidence of any grade 3+ AE and any grade 3+ respiratory AE using a Fisher exact test. Risk factors for AEs (age, baseline carbon monoxide diffusion in the lung [DLCO]%, and forced expiratory volume in 1 second [FEV_1]% considered as continuous variables, upper lobe vs lower lobe resection, and performance status) were analyzed using a multivariable logistic model for any grade 3+ and grade 3+ respiratory AEs at 0 to 30 days and 0 to 90 days. In addition to these factors, surgery extent (wedge vs segmentectomy) and type (thoracotomy vs video-assisted thoracic surgery) were also considered for any grade 3+ AEs outcomes at 0 to 30 days and 0 to 90 days. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported, where the OR estimates for a continuous covariate correspond to a 1-unit increase. Optimal cutpoints were therefore explored to define the high-risk versus low-risk categories for the baseline DLCO% and FEV_1% using data-dependent methods (mean or median) and outcome-based approaches (graphic diagnostic plots and the minimum P value approach).[9] Subsequently, univariable logistic regression models using the categorized DLCO% and FEV_1% were explored. In addition, the entry criteria used to define the high-risk subset were explored further by first analyzing patients eligible by at least 2 minor criteria and by including