The impact of adjuvant brachytherapy with sublobar resection on pulmonary function and dyspnea in high-risk patients with operable disease: Preliminary results from the American College of Surgeons Oncology Group Z4032 Trial

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Background: Z4032 was a randomized study conducted by the American College of Surgeons Oncology Group comparing sublobar resection alone versus sublobar resection with brachytherapy for high-risk operable patients with non-small cell lung cancer (NSCLC). This evaluates early impact of adjuvant brachytherapy on pulmonary function tests, dyspnea, and perioperative (30-day) respiratory complications in this impaired patient population.

Methods: Eligible patients with stage I NSCLC tumors 3 cm or smaller were randomly allocated to undergo sublobar resection with (SRB group) or without (SR group) brachytherapy. Outcomes measured included the percentage predicted forced expiratory volume in 1 second (FEV1%), percentage predicted carbon monoxide diffusion capacity (DLCO%), and dyspnea score per the University of California San Diego Shortness of Breath Questionnaire. Pulmonary morbidity was assessed per the Common Terminology Criteria for Adverse Events version 3.0. Outcomes were measured at baseline and 3 months. A 10% change in pulmonary function test or 10-point change in dyspnea score was deemed clinically meaningful.

Results: Z4032 permanently closed to patient accrual in January 2010 at 224 patients. At 3-month follow-up, pulmonary function data are currently available for 148 (74 SR and 74 SRB) patients described in this report. There were no differences in baseline characteristics between arms. In the SR arm, 9 patients (12%) reported grade 3 respiratory adverse events, compared with 12 (16%) in the SRB arm ($P = .49$). There was no significant change in percentage change in DLCO% or dyspnea score from baseline to 3 months within either arm. In the case of FEV1%, percentage change from baseline to 3 months was significant within the SR arm ($P = .03$), with patients reporting improvement in FEV1% at month 3. Multivariable regression analysis (adjusted for baseline values) showed no significant impact of treatment arm, tumor location (upper vs other lobe), or surgical approach (video-assisted thoracoscopic surgery vs thoracotomy) on 3-month FEV1%, DLCO%, and dyspnea score. There was no significant difference in incidence of clinically meaningful (10% pulmonary function or 10-point dyspnea score change) change between arms. Twenty-two percent of patients with lower-lobe tumors and 9% with upper-lobe tumors demonstrated 10% decline in FEV1% (odds ratio, 2.79; 95 confidence interval, 1.07–7.25; $P = .04$).

Conclusions: Adjuvant intraoperative brachytherapy in conjunction with sublobar resection did not significantly worsen pulmonary function or dyspnea at 3 months in a high-risk population with NSCLC, nor was it associated with increased perioperative pulmonary adverse events. Lower-lobe resection was the only factor significantly associated with clinically meaningful decline in FEV1%. (*J Thorac Cardiovasc Surg* 2011;142:554-62)

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Z4032 is a prospective, randomized clinical trial by the American College of Surgeons Oncology Group intended to compare sublobar resection with intraoperative brachytherapy (SRB group) with sublobar resection alone (SR group) for patients with stage I non-small cell lung cancer

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Abbreviations and Acronyms

CTCAE	= Common Terminology Criteria for Adverse Events version 3.0
DLCO%	= percentage predicted carbon monoxide diffusing capacity of the lung
FEV1%	= percentage predicted forced expiratory volume in 1 second
FVC	= forced vital capacity
NSCLC	= non-small cell lung cancer
SBRT	= stereotactic body radiation therapy
SR	= sublobar resection alone [group]
SRB	= sublobar resection with intraoperative brachytherapy [group]
UCSD	= University of California San Diego
VATS	= video-assisted thoracoscopic surgery

(NSCLC) who considered to be at increased risk for lobectomy. This study has recently completed accrual. The primary aim of the study is local control, and results will be reported when sufficient follow-up becomes available. This initial report examines the effects of these procedures on pulmonary function, dyspnea symptoms, and perioperative respiratory complications to determine in particular any adverse effects that brachytherapy might have in a patient group that is already compromised from a pulmonary standpoint.

MATERIALS AND METHODS

Eligible patients for this study included patients with stage I lung cancers 3 cm or less in maximum diameter (stage IA or the subset of stage IB with visceral pleural involvement) on preoperative computed tomographic scan. Patients were considered to be at high risk for lobectomy if they met at least 1 major criterion or 2 minor criteria, as described in Table 1. To facilitate enrollment, preregistration and random assignment occurred before surgery to allow a diagnostic wedge resection to be performed on the day of surgery. To confirm that patients did not have nodal involvement, all suspicious lymph nodes seen on positron emission tomographic or computed tomographic scan required biopsy by mediastinoscopy, by endobronchial or esophageal ultrasonography, or at the time of resection. Sublobar resection included wedge or segmental resection and could be performed by video-assisted thoracoscopic surgery (VATS) or through a thoracotomy. The type of sublobar resection and approach (VATS vs thoracotomy) was at the discretion of the treating surgeon. Lymph node dissection or sampling was strongly encouraged but was not mandatory in this high-risk population. Two methods of brachytherapy were allowed.^{1,2} In the first technique, polyglactin sutures containing iodine 125 seeds (Oncura Inc, Arlington Heights, Ill) 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 iodine 125 suture strands were woven into a piece of polyglactin. The strands were placed at 1-cm intervals. The mesh was then sutured over the staple line with 2.0 or 3.0 sutures. The goal of the brachytherapy was to deliver 100 Gy at 5 to 7 mm along the central axis of the resection margin.

The primary objective of this phase III trial was to ascertain whether patients treated by sublobar resection with intraoperative brachytherapy would have longer time to local recurrence than would patients treated with sublobar resection alone. A secondary aim of this study was to assess the effects of brachytherapy on pulmonary function, dyspnea symptoms, and perioperative respiratory complications. In this article, we focus on the pulmonary function results to month 3 by analyzing data from patients for whom complete pulmonary function data were available at both baseline and 3 months after surgery.

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 United States Department of Health and Human Services.

Data

Pulmonary function tests included percentage predicted forced expiratory volume in 1 second (FEV1%) and percentage predicted carbon monoxide diffusing capacity of the lung (DLCO%), both of which were measured preoperatively (baseline, day 0) and at 3 months after intervention. These data will continue to be collected at 12 and 24 months post intervention. Dyspnea score was measured with the University of California San Diego (UCSD) Shortness of Breath Questionnaire at the same intervals as the pulmonary function tests.³ The 24-item UCSD questionnaire uses a 6-point scale (0 for not at all breathless to 5 for maximally breathless or too breathless to do the activity) to assess the severity of each patient's self-reported shortness of breath. Dyspnea was also assessed with the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) at day 0 (baseline) and at 30 days and 3, 6, and 12 months after intervention. Pulmonary and respiratory complications were assessed with the CTCAE and included pneumonia from the infection category. It should be noted that the CTCAE definition of prolonged intubation (>24 hours) is shorter in duration than the definition used in the Society of Thoracic Surgeons general thoracic surgery database (>48 hours).

Statistical Analysis

Both χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables were used to compare the baseline patient characteristics between the SR and SRB arms. The grade 3 or higher perioperative respiratory complications were compared between treatment arms with the Fisher's Exact test. The UCSD scale was reversed and scored by summing responses across all 24 items to form a total score ranging from 0 to 120. The total score was then transformed into a 0 to 100 scale, in which 0 represented worst dyspnea (poor quality of life) and 100 represented no dyspnea (best quality of life). The median percentage changes in the transformed UCSD dyspnea score, DLCO%, and FEV1% from baseline to month 3 were compared within the SR and the SRB arms with a Wilcoxon signed rank test. Additionally, a 10-point increase or decrease in dyspnea score and a 10% increase or decrease in DLCO% or FEV1% was deemed clinically meaningful and compared between the arms with the Fisher's Exact test. Exploratory logistic regression models were used to assess the impact of surgical approach (VATS vs thoracotomy) and tumor location (upper lobe vs other lobes) on clinically significant increases or decreases in DLCO%, FEV1%, and UCSD dyspnea score. In addition, general linear models adjusting for baseline values were used to assess the effects of treatment arm, surgical approach, and tumor location on the 3-month FEV1%, DLCO%, and dyspnea score, all considered as continuous variables.

RESULTS

This trial met its target accrual and was permanently closed as of January 22, 2010. A total of 224 patients were registered. One patient in the SR arm had the

TABLE 1. Major and minor eligibility criteria for Z4032 trial**Major criteria**

1. Forced expiratory volume in 1 second $\leq 50\%$ predicted
2. Diffusing capacity of the lung for carbon monoxide $\leq 50\%$ predicted

Minor criteria

1. Age ≥ 75 y
2. Forced expiratory volume in 1 second 51%–60% predicted
3. Diffusing capacity of the lung for carbon monoxide 51%–60% predicted
4. Pulmonary hypertension (defined as pulmonary artery systolic pressure >40 mm Hg), as estimated by echocardiography or right heart catheterization
5. Poor left ventricular function (defined as ejection fraction $\leq 40\%$)
6. Resting or exercise $Pao_2 \leq 55$ mm Hg or peripheral oxygen saturation $\leq 88\%$
7. $Pco_2 > 45$ mm Hg
8. Modified Medical Research Council Dyspnea Scale score ≥ 3 .

Eligible patients must have met either 1 major criterion or 2 minor criteria.

intervention at an institution not approved by the institutional review board and thus was deemed not evaluable. Sublobar resection alone was performed in 114 patients, and sublobar resection with brachytherapy was performed in 109 patients. Figure 1 shows the patient cohort diagram.

Data collection was frozen on March 9, 2010, for this analysis. At 3-month follow-up, complete pulmonary function test data were available for 148 patients ($n = 74$ SR, $n = 74$ SRB). Of the 148 patients with baseline and 3-month follow-up data, 12-month data were available for only 91 patients ($n = 40$ SR, $n = 51$ SRB); therefore, the 3-month cohort is this review's focus. Adjuvant chemotherapy was not allowed with this protocol. If a patient was found after resection to have a stage more advanced than IA, however, adjuvant chemotherapy could be given at the treating physician's discretion. At 3-month follow-up, only 3 patients (4%) in the SR arm had received nonprotocol cancer therapy. One patient received leuprolide acetate (Lupron, INN leuprorelin) injections for prostate cancer, and 2 patients received adjuvant cancer therapy for their primary NSCLC.

Baseline patient characteristics are summarized in Table 2. There were no differences between the arms. VATS was undertaken in 51 SR group patients (69%) and 46 SRB group patients (62%, $P = .39$). There were similar numbers of upper-lobe tumors in each group, specifically 46 cases in the SR group (62%) and 42 cases in the SRB group (57%, $P = .50$). The 3-month cohort was also similar to the remaining patients not included in this preliminary analysis for both the SR and the SRB arms.

Data on grade 3 or higher perioperative (30-day) respiratory complications by arm are presented in Table 3. No grade 5 respiratory complications were reported in either arm. In the SR arm, 9 patients (12%) reported 11 grade 3 respiratory adverse events. In the SRB arm, 12 patients (16%) reported 17 grade 3 respiratory adverse events; of these, 1 patient also reported grade 4 hypoxia. This was

*Complete PFT (Pulmonary Function Test) data refers to having both DLCO (%) and % Predicted FEV1

FIGURE 1. Patient cohort diagram. *PFT*, Pulmonary function test; *IRB*, institutional review board; *DLCO* (%), percentage predicted diffusing capacity of the lung for carbon monoxide; % *Predicted FEV1*, percentage predicted forced expiratory volume in 1 second.

not statistically significant (Fisher's Exact test $P = .49$). There were 3 perioperative deaths ($n = 1$ SR, $n = 2$ SRB), 2 of patients who had lower-lobe resections. Two deaths were attributed to cardiovascular events and 1 to pulmonary embolus. One patient who died after a lower-lobe sublobar resection had a baseline FEV1% of 25%.

Twenty-seven patients ($n = 13$ SR, $n = 14$ SRB) had baseline FEV1% or DLCO% values less than 30%, with 6 patients ($n = 1$ SR, $n = 5$ SRB) having a value not greater than 20%. Among these 27 patients, 2 patients reported grade 3 respiratory complications (dyspnea) on day 30, 7 patients had a 10% decline in FEV1% or DLCO% at month 3, and 6 patients had undergone lower-lobe resection. One patient had grade 3 hypoxia (required continuous home oxygen therapy) at baseline. This patient had grade 4 hypoxia at 30 days. Seven additional patients had grade 3 hypoxia at 30 days, thus becoming oxygen dependent immediately after treatment; however, no grade 3 or higher hypoxia was reported at 3 months.

Baseline and 3-month pulmonary function test values and dyspnea scores for the SR and SRB arms are provided in Table 4. There was no significant change in the percentage change in DLCO% or dyspnea score from baseline to 3 months within either arm. In the case of FEV1%, the percentage change from baseline to 3 months was significant within the SR arm ($P = .03$), with patients reporting an improvement in the median FEV1% from 49% to 53% at month 3. Results from the general linear models (adjusted for baseline values) showed no significant impact of treatment arm, tumor location, or surgical approach on the 3-month values for FEV1%, DLCO%, and dyspnea score.

Table 5 summarizes the clinically meaningful changes (increases or decreases of 10% or 10 points) from baseline

TABLE 2. Baseline patient characteristics

Factors	Month 3-cohort			Non-month 3 SR (n = 40) vs month 3 SR (n = 74)	Non-month 3 SRB (n = 35) vs month 3 SRB (n = 74)
	SR (n = 74)	SRB (n = 74)	P value	P value	P value
Age (y, median and range)	70 (49–85)	71 (53–87)	.69*	.68*	.18*
Sex (no.)			>.999	.63	.91
Female	41 (55%)	41 (55%)			
Male	33 (45%)	33 (45%)			
Performance status (no.)			.29	.51	.26
0	13 (18%)	21 (28%)			
1	45 (61%)	39 (53%)			
2	16 (21%)	14 (19%)			
T stage (no.)			.15	NA	.34
T1	74 (100%)	72 (97%)			
T2	0 (0%)	2 (3%)			
M stage (no.)			NA	NA	NA
M0	74 (100%)	74 (100%)			
N stage (no.)			.32	.17	.49
N0	74 (100%)	73 (99%)			
N1	0 (0%)	1 (1%)			
N2	0 (0%)	0 (0%)			
Surgery in upper lobe (no.)			.50	.17	.42
Yes	46 (62%)	42 (57%)			
No	28 (38%)	32 (43%)			
Surgery type (no.)			.39	.90	.54
VATS	51 (69%)	46 (62%)			
Thoracotomy	23 (31%)	28 (38%)			
Surgery extent (no.)			.07	.58	.07
Segmentectomy	26 (35%)	16 (22%)			
Wedge resection	48 (65%)	58 (78%)			

P values by χ^2 test except as marked. SR, Sublobar resection; SRB, sublobar resection with intraoperative brachytherapy; VATS, video-assisted thoracoscopic surgery; NA, not applicable. *By Wilcoxon rank sum test.

to 3 months in FEV1%, DLCO%, and dyspnea score. There were no statistically significant differences between the groups with regard to the fractions of patients who had meaningful changes in these parameters. At 3 months, clinically meaningful declines in FEV1%, DLCO%, and dyspnea score, respectively, occurred in 14%, 19%, and 21% of the SR group and in 15%, 30%, and 27% of the SRB group. Clinically meaningful improvements in FEV1%, DLCO%, and dyspnea score, respectively, occurred in 19%, 19%, and 27% of the SR group and in 20%, 19%, and 34% of the SRB group. Most patients' conditions remained stable. Specifically, 68%, 62%, and 51% of patients in the SR arm and 65%, 51%, and 38% in the SRB arm had neither a clinically meaningful improvement nor a clinically significant decline in FEV%, DLCO%, and dyspnea score, respectively.

The effects of surgical approach (VATS vs thoracotomy), tumor location, and development of grade 3 or 4 perioperative respiratory complications on 3-month decline in DLCO %, FEV%, and dyspnea score are summarized here. Of the 36 patients (n = 14 SR, n = 22 SRB) who had 10% decrease in DLCO%, 21 patients (58%) had surgery in the upper-lobe area, 14 (39%) had thoracotomy, and 5 (14%) had

grade 3 or 4 perioperative respiratory complications. Of the 21 patients (n = 10 SR, n = 11 SRB) who had a 10% decrease in FEV1%, 8 patients (38%) had surgery in the upper-lobe area and 7 (33%) had thoracotomy. No grade 3 or 4 respiratory complications were reported among these patients. Thirty-five patients (n = 15 SR, n = 20 SRB) reported a 10-point decrease in dyspnea score; of these, 25 patients (71%) had surgery in the upper-lobe area, 12 (34%) had thoracotomy, and 4 (11%) had grade 3 or 4 respiratory complications. There was no statistically significant impact of the surgical approach or tumor location on clinically significant changes in DLCO% and UCSD dyspnea scores from baseline to month 3. There was, however, a significant association between tumor location and a 10% decline in FEV1%. Twenty-two percent of patients with lower-lobe tumors versus only 9% of patients with upper-lobe tumors had a 10% decline in FEV1% (odds ratio, 2.79; 95% confidence interval, 1.07–7.25; *P* = .04).

DISCUSSION

Since the publication of the Lung Cancer Study Group's randomized comparison of lobectomy and sublobar

TABLE 3. Grade 3 or higher perioperative (30-day) respiratory complications by arm

Adverse Event	Arm	Grade						All No.
		3		4		5		
		No.	%	No.	%	No.	%	
Infection or febrile neutropenia								
Pneumonia*	SR	1	1.4	0	0	0	0	1
	SRB	3	4.1	0	0	0	0	3
Pulmonary								
Adult respiratory distress syndrome	SR	1	1.4	0	0	0	0	1
	SRB	0	0	0	0	0	0	0
Dyspnea	SR	5	6.9	0	0	0	0	5
	SRB	7	9.5	0	0	0	0	7
Hypoxia	SR	2	2.8	0	0	0	0	2
	SRB	5	6.8	1	1.4	0	0	6
Pneumothorax	SR	1	1.4	0	0	0	0	1
	SRB	1	1.4	0	0	0	0	1
Prolonged air leak	SR	1	1.4	0	0	0	0	1
	SRB	0	0	0	0	0	0	0
Pulmonary, other	SR	0	0	0	0	0	0	0
	SRB	1	1.4	0	0	0	0	1

SR, Sublobar resection alone; SRB, sublobar resection with brachytherapy. *Pneumonia both with and without absolute neutrophil count specified.

resection,⁴ lobectomy has been the standard of care for patients with stage I NSCLC. Currently, sublobar resection is generally reserved as a compromise approach for high-risk patients with impaired lung function. The impact of surgical resection on these patients with baseline emphysema is a significant concern. These considerations become even more significant for treatment planning as nonresectional therapies, such as stereotactic body radiation therapy (SBRT) and radiofrequency ablation, become more widely available.⁵⁻⁷

Miyazima and colleagues⁸ reported the effects of pulmonary resection on early (4–6 months) and late (42–48 months) cardiopulmonary function. In their small patient cohort (n = 8), forced vital capacity (FVC) and maximum voluntary ventilation were found to be significantly decreased at late follow-up. Interestingly, DLCO% decreased from 85.4% to 79.5% at early follow-up but was

significantly increased to 106.9% at late follow-up. In the much larger randomized Lung Cancer Study Group study,⁴ pulmonary function tests were measured preoperatively and at 6-month intervals; however, values were only obtained for 60% of eligible patients who had at least 9-month follow-up. At 6 months the changes from baseline for forced expiratory volume in 1 second, FVC, and maximum voluntary ventilation were significantly better in patients undergoing sublobar resection than in those undergoing lobar resection. At 12 to 18 months, only the forced expiratory volume in 1 second was statistically different between patients undergoing lobar and sublobar resection. Diffusing capacity of the lung for carbon monoxide was not measured in that study.

Keenan and associates⁹ compared pulmonary function test values between 147 patients who underwent lobectomy and 54 patients treated with segmental resection. At 1 year,

TABLE 4. Baseline and 3-month pulmonary function tests and dyspnea scores by arm

Factor	No.	SR			P value*	No.	SRB			P value*
		Baseline	Month 3				Baseline	Month 3		
Forced expiratory volume in 1 s (% predicted, median and range)	74	49% (22%–117%)	53% (24%–101%)	.03	74	51% (25%–110%)	53% (24%–104%)		.18	
Diffusing capacity of lung for carbon monoxide (% predicted, median and range)	74	46% (18%–97%)	48% (14%–144%)	.38	74	46% (10%–137%)	43% (5%–96%)		.16	
UCSD Shortness of Breath Questionnaire score (median and range)	73	75 (18–100)	79 (17–100)	.13	73	71 (6–98)	73 (27–100)		.10	

SR, Sublobar resection; SRB, sublobar resection plus brachytherapy; UCSD, University of California San Diego. *Percentage change from baseline to 3-month value, Wilcoxon signed rank test.

TABLE 5. Distribution of clinically meaningful changes (10% change in diffusion capacity of the lung for carbon monoxide percentage predicted, 10% change in forced expiratory volume in 1 second percentage predicted, and 10-unit change in University of California San Diego Shortness of Breath Questionnaire score) from baseline to month 3

Factor	SR (n = 74)	SRB (n = 74)	P value*
Diffusing capacity of lung for carbon monoxide, percentage predicted			.29
Increase of 10%	14 (18.9%)	14 (18.9%)	
Decrease 10%	14 (18.9%)	22 (29.7%)	
Neither increase nor decrease of 10%	46 (62.2%)	38 (51.4%)	
Forced expiratory volume in 1 s, percentage predicted			.94
Increase of 10%	14 (18.9%)	15 (20.3%)	
Decrease of 10%	10 (13.5%)	11 (14.9%)	
Neither increase nor decrease of 10%	50 (67.6%)	48 (64.9%)	
University of California Shortness of Breath score (0–100)			.30
Missing	4 (5.4%)	1 (1.4%)	
Increase of 10 units	19 (25.7%)	25 (33.8%)	
Decrease of 10 units	15 (20.3%)	20 (27.0%)	
Neither increase nor decrease of 10 units	36 (48.6%)	28 (37.8%)	

*By Fisher's Exact test.

significant declines were seen in FVC, FEV1%, maximum voluntary ventilation, and DLCO% in the lobectomy group. In contrast, in the segmentectomy group significant decline was only seen in DLCO% which dropped from a mean of 67.5% to 55% ($P = .0001$). A recent study from Japan measured pulmonary function before and after segmentectomy in 56 patients and compared these values with predicted values after virtual lobectomy.¹⁰ The predicted values were calculated by single-positron emission computed tomographic scan. FEV1% was significantly higher after segmentectomy (88%) than the value for virtual lobectomy (77%). Another interesting finding in this study was that preservation of FEV1% was superior if only 1 or 2 segments were removed relative to removal of 3 or more segments. Left–upper lobe upper-division segmentectomy (lingula-sparing lobectomy) also resulted in significantly lower forced expiratory volume in 1 second than seen in patients undergoing lingular segmentectomy. These findings suggest that segmental resection will preserve pulmonary function primarily if small sublobar resections are undertaken, whereas with larger sublobar resections (such as an upper-lobe division segmentectomy) the benefit is marginal. Thus these procedures perhaps should only be reserved for those patients with extremely compromised function.

The Cancer and Leukemia Group B¹¹ previously reported on a phase II trial of VATS wedge resection and local external beam radiotherapy for NSCLC. Although 65 patients were accrued, only 31 patients were ultimately eligible for radiotherapy, with 28 receiving the protocol treatment. Severe dyspnea was reported in 3 (11%) and moderate pneumonitis in 4 (14%). This study illustrates the difficulty in actually delivering planned external beam radiation postoperatively to a high-risk patient group and the potential for harm from the radiation when it is delivered. The advantage of intraoperative brachytherapy is that it can be delivered at the same time as the lung resection with, it is to be hoped, both lower radiation morbidity and improved local tumor control.¹² Sublobar resection with brachytherapy was initially reported in 1998 in a small series of 14 patients, 10 of whom required supplemental oxygen before surgery.² No significant radiation pneumonitis was observed at a mean follow-up of 7 months. In this series, no increased pulmonary morbidity was seen in the patient group randomly assigned to brachytherapy.

In another series, 23 patients who underwent sublobar resection with mesh brachytherapy had follow-up pulmonary function test measurements performed.¹³ No specific morbidity related to the mesh implant was noted. Pulmonary function was measured at baseline and 3 months but included forced expiratory volume and FVC only. There was no significant decline in either value at early follow-up. Our preliminary 3-month data are consistent with these findings. Relative to baseline values, there was no significant decrease in FEV1% or DLCO% in either group.

Therapies such as radiofrequency ablation and SBRT, which do not involve resection, are becoming increasingly popular for patients with NSCLC. There have been only a few reports documenting the effects of these therapies on pulmonary function. A multicenter, prospective, non-randomized trial of radiofrequency ablation included 22 patients with NSCLC who had pulmonary function test values recorded to 12 months.¹⁴ There was no significant decline in FEV1% or percentage predicted FVC. It should be noted, however, that baseline FEV1% was surprisingly high (68.8%) in this series, suggesting that this was not a group that most surgeons would regard as being at high risk. Another study reported on 20 patients who were treated with CyberKnife (Accuray Incorporated, Sunnyvale, Calif) and had serial measurements of pulmonary function tests recorded.¹⁵ Baseline FEV1% and DLCO% were 52% and 57%, respectively, which was consistent with this being a high-risk group. Posttreatment FEV% did not change significantly, although there were statistically significant declines of DLCO% of 9% and 11% seen at 6 and 12 months, respectively. In another series of 70 patients treated with SBRT, there was a 15.7% incidence of grade 3 to 5 toxicities, most of which were pulmonary-associated toxicities.¹⁶ Additionally, in that series 27.7% of patients

became oxygen dependent. The need for supplemental oxygen was not specifically reported in our series; however, the CTCAE defines grade 2 hypoxia as the need for intermittent oxygen and grade 3 as the need for continuous oxygen. Seven patients became oxygen dependent after treatment (at 30 days); however, by 3 months none of these patients were dependent on oxygen.

More recently, the Radiation Therapy and Oncology group¹⁷ completed a phase II study of SBRT in high-risk patients. Grade 3 and 4 protocol-specific toxicities were reported in 7 of 55 patients (12.7%) and 2 of 55 (3.6%), respectively. All but 1 of these (8/55, 14.5%) of these toxicities were respiratory associated. In our series, 21 of 148 patients (14.2%) had perioperative grade 3 or 4 respiratory complications, suggesting that even in a compromised patient population resection can be undertaken with similar outcomes to SBRT. Currently, the American College of Surgeons and the Radiation Therapy and Oncology Group are developing a randomized study to compare SR and SBRT in high-risk patients with lung cancer. Treatment-related toxicity and effects on pulmonary function will be key end points in this study.

In conclusion, in this randomized study of a patient cohort with stage I NSCLC at greater than average risk for lobectomy, brachytherapy had no significant effect on lung function at short-term follow-up. FEV1% and DLCO% were equally preserved in both groups. The 30-day incidences of grade 3 and 4 respiratory complications in the SR and SRB arms were not significantly different. Follow-up, including recording of pulmonary function, is ongoing at the 12- and 24- month time points to ascertain the long-term impact of brachytherapy on lung function.

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Discussion

Dr Walter Weder (Zurich, Switzerland). Fernando and colleagues are to be congratulated for having initiated and now finished a prospective, multicenter, randomized trial evaluating an important oncologic question. Today they report on a secondary study end point, lung function and dyspnea. Dr Fernando, congratulations on your clear presentation and thanks for sending me the manuscript long before the meeting. I have 3 questions. In your article, you discussed the Lung Cancer Study Group Trial, which evaluated lobectomy versus sublobar resection and you commented as follows about pulmonary function tests, "However, values were only obtained for 60% of eligible patients who had at least 9-month follow-up." My comment on your study is the same. Unfortunately, for only two thirds of the patients were the pulmonary function test values available at 3 months, and for less than half at 12 months. Why didn't you wait a few more months with your analysis and publication? This would have improved the value of this report significantly.

I will continue with my second question. The patients you included had either low forced expiratory volume in 1 second or low diffusing capacity of the lung for carbon monoxide. I assume this is typically the patient with emphysema. You also included, however, patients with either high pulmonary artery pressure or impaired left ventricular function, and the pulmonary function test values in these patients were normal. So these are completely different disease categories. My question is, why didn't you

analyze these 2 groups of patients separately? I assume that any effect of brachytherapy on lung function could vary by disease category. Finally, in your manuscript you mentioned that endobrachytherapy delivers 100 Gy. What is the depth of the radiation field of this locally applied radiation therapy?

Dr Fernando. Thank you very much. Those are great questions, and I appreciate the challenge. I think that you picked up a major point. We only have the 3-month data in detail. We debated how much we should put into the discussion of 12-month data that we had available. We decided that we could report what we have at the moment, but as we get the longer and more complete follow-up, we recognize that 12-month data results may change. Analyzing the 12-month data is important, because radiation pneumonitis can be seen up to 6 months afterward. Currently, we don't see a difference at 12 months; however, that may change, and that will be reported in detail when available.

In terms of analyzing the groups you mention separately, that's a good question. We didn't—

Dr Weder. Can I interrupt briefly? So what, then, is the value of the current analysis? You said that the major impact of radiation pneumonitis is at 3 to 6 months. If you are not waiting that time, we get the report that tells us, "Yes, it may not have an impact, but we are not really sure." If you would have waited another 6 months, we would have the relevant information.

Dr Fernando. Well, the 12-month data would help answer the question specifically about radiation pneumonitis, but not about other pulmonary complications, which typically you can see in the perioperative period up to 30 days. So I think that the 30-day information is still important. In previous studies, radiation pneumonitis has not really been reported with brachytherapy, although that is one of the things about which people remain concerned. We are taking a patient population at greater than average risk, we're suturing on the lung, we're not using Peri-Strips, for instance, to buttress the repair. Other surgeons are concerned about the risk of things like prolonged air leaks, pneumonia, and even empyemas. We didn't see any empyemas in this group. So I think the longer follow-up will really address the issue of radiation pneumonitis in its own right, and hopefully we can answer that question better then.

In terms of the second question, why we didn't analyze the groups separately, the data that we have on the data sheets that the various site clinical research associates sent to us did not specifically separate out those groups. I think that's a very interesting question. We do have access to the source documents (the pulmonary function test values), and so perhaps we will have to go back and analyze that information, so that we can try and separate those patients into those who maybe have more restrictive disease rather than emphysema. I think that's an excellent question, and something that we should address.

Can you remind me of the third question?

Dr Weder. You mention in the manuscript that a 100-Gy dose is delivered but say nothing about the depth of the radiation. Is it a few millimeters, or more?

Dr Fernando. It's about 5 to 7 mm or up to 1 cm, depending on how strong those radiation seeds are. So, in effect, what we're doing is improving our margins. I'm not sure which patients this benefits, but I suspect that the patients who will benefit are those patients who have close wedge resections or close margin wedge resections. If you do a wedge resection with a 1-cm margin or a margin at least

the diameter of the tumor, or you do a good segmental resection, probably the brachytherapy will not be as helpful.

Dr Weder. Thank you.

Dr Scott J. Swanson (*Boston, Mass*). Excellent paper. I thought it was really useful to hear that information at this point. Did your teams learn anything about how to put these seeds in, such that it got easier over the course of the trial? Can you share any of that technical information? Second, pertaining to that last point, can you share any information about margins? Did you measure margins? Do you have any data about margins?

Dr Fernando. I'll take the margin question first. I've gone through the reviews that I've done thus far. One of the secondary end points we had was to look at staple-line cytology. There are some Japanese data, I think by Sawabata, where he swiped the specimen on a glass slide and found differences between the staple-line cytology and the actual histology. He even identified patients who had positive staple-line cytology yet negative histology. So we put that in as a secondary end point that we're measuring, and those data will eventually be presented. But what's interesting, as I read through the reports, is that people are actually getting reads from their cytologists in there and they are going back and taking bigger and bigger margins. So I think as a group, the surgeons are actually doing better wedge resections or better segments than maybe in previous studies. So far I have not seen lot of local recurrences in the cases that I've analyzed.

The second thing, in terms of what have I learned, in terms of a thoracoscopic approach, I personally like to use the Endo-Stitch a lot, and I found with some of the Vicryl meshes that we have that the Endo-Stitch does not sew very well through the mesh, and the needle tends to get stuck. It's a blunter needle. So I changed to using a standard needle, and what I do is I place the stitch through the mesh and then into the lung, bring it up, and I have 2 long strands of suture. Rather than trying to do an endoscopic tie, what I do is I simply put a series of clips along the suture. So the clips serve as my tie on the suture, and that also avoids having to actually do an intracorporeal knot in the patient.

Dr Nasser K. Altorki (*New York, NY*). I enjoyed your presentation. I want to agree a little bit with you and a little bit with Walter. He made his point, but I think that there is a real issue of delivering 100 Gy to a fresh suture line, and I think all of us who do this worry about the issues that you described. I think in that sense your report is helpful. Can you share with us issues that relate to radiation exposure in the operating room? What do you do? What is the risk to people in the room? You sew it. Do you wear radioprotective gloves? Do you wear a shield?

Dr Robert J. Cerfolio (*Birmingham, Ala*). And any surgical team members who might be pregnant in the operating room, which is an issue.

Dr Fernando. That issue of radiation safety has been reported in another article, with data not from this study but from a previous single-center study (Smith RP, Schuchert M, Komanduri K, Burton S, Heron DE, Luketich JD, et al. Dosimetric evaluation of radiation exposure during I-125 vicryl mesh implants: implications for ACOSOG z4032. *Ann Surg Oncol*. 2007;14:3610-3). You have to follow the regulations in place in your own hospital and within your own state. I wear a lead apron when I do this. I try not to handle the seeds directly, for instance not tying right down into the knot with my fingers. When the implant is prepared,

what you do is basically to place all the sutures in place into the mesh with a lead shield over the active radiation seeds, and then when you're ready, you have all 4 sutures with the seeds into the mesh. You pull each suture through, so that you are minimizing radiation exposure. The radiation physicist is in the room measuring the radiation in the room and around the room. In terms of actual safety for the patient, it's really very safe. It's a low dose rate brachytherapy. And the falloff is rapid as you move away from the source. In the study I just mentioned, dosimeters placed on the patient's shoulder measured very low doses of radiation in these patients who had an implant placed. So it's actually a low dose of radiation exposure.

Dr Altorki. There is a glove that is lead impregnated that you could use.

Dr Daniel L. Miller (*Atlanta, Ga*). With regard to placement, what we at Emory and some other surgeons throughout the United States have been using is the pericardial Veritas strip, which is a little bit wider. They have a wider version, and it's very easy to handle. You bring the suture out, and you clip the radiation seed suture onto the buttress material. So you have no extra holes into the lung. When you have expansion of the lung, there's no tearing and so forth. It really minimizes the amount of time spent handling the radiation, and you're not suturing into the lung in a way that may produce prolonged air leaks and so forth. I know that wasn't allowed in this portion of the study, it's off-study; however, I think that in the future this is another way to look at that, to minimize other lung problems and so forth.

Dr Fernando. Thank you.