Video-assisted wedge resection and local radiotherapy for peripheral lung cancer in high-risk patients: The Cancer and Leukemia Group B (CALGB) 9335, a phase II, multi-institutional cooperative group study

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Objectives: This study examined the feasibility of thoracoscopic wedge resection and radiotherapy for clinical T1 lesions in patients with compromised cardiopulmonary status.

Methods: In this phase II, prospective, multicenter, cooperative group trial, high-risk patients had one or more of the following risk factors: forced expiratory volume in 1 second less than 40%, carbon monoxide diffusing capacity in lung less than 50%, and maximum oxygen consumption less than 45 mm Hg. Patients underwent video-assisted wedge resection followed by local (56 Gy) radiotherapy. The primary end point was the proportion of patients whose disease could be completely resected and who received radiotherapy without treatment complications.

Results: Between September 1995 and September 1999, a total of 65 patients were accrued, of which 58 were eligible (52% male, median age 69 years). Pathologic staging resulted in upgrading to T2 or greater in 16 of 58 cases (28%) and in reassessment as benign in 10 of 58 cases (17%). Conversion to thoracotomy was required in 10 cases (17%), including 1 of 10 benign T1-size lesion (10%), 4 of 35 non–small cell lung cancer T1 lesions (13%), and 5 of 14 non–small cell lung cancer T2 lesions (31%). Resection margins were positive in 5 patients: 6% of T1 and 23% of T2. Surgery was aborted in 2 cases (3.5%), and operative mortality was 4%. Overall operative failure rates of video-assisted wedge resection were 20% for benign T1-size lesions, 22% for T1 non–small cell lung cancer, 21% for all T1 lesions, 50% for T2 non–small cell lung cancer, and 29% for all lesions in this study (clinical T1). Prolonged air leaks occurred in 10%, pneumonia in 6%, and respiratory failure in 4%. Thirty-one patients were eligible for radiotherapy; 3 of them refused, and 1 died before treatment. Among the 28 patients who received radiotherapy, severe dyspnea was noted in 3 patients (11%) and moderate pneumonitis in 4 (14%).

Conclusions: Clinical staging in high-risk patients is often inaccurate (45% difference from pathologic staging). Intention to treat clinically staged T1 disease by video-assisted wedge resection is associated with a high failure rate. Pathologically staged T1 lesions can be successfully resected in 75% of cases; however, narrow resection margins remain a concern.

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Major surgical resection (lobectomy) has been proved to be the best therapeutic modality for T1 non–small cell lung cancer (NSCLC).[1] Though only a few single-center studies have examined the role of limited resection in treating high-risk patients, several uncontrolled studies reported during the last decade have suggested a potential benefit of limited surgical resection (wedge resection and segmentectomy) alone or with adjuvant radiotherapy in treating patients with compromised cardiopulmonary status.[2,3]These studies suggest that limited lung resection in select groups of NSCLC patients is safe and effective.

The emergence of innovative surgical technologies that permit the performance of surgical procedures by less-invasive endoscopic techniques have gained increasing acceptance by surgeons. Such treatments are sought by many patients, who are lured by the potential for a faster recovery with less pain and morbidity. Thoracic surgeons have rapidly adopted video-assisted thoracoscopic wedge resection (VAR) techniques for the treatment of lung cancer, but without proper validation. Despite evidence for some early postoperative advantages, several studies have failed to show substantial benefits of endoscopic and other minimally invasive cancer resection techniques. In fact, innovative surgical technology in general has not been subjected to the same rigor of clinical trials required for other cancer therapies. This study was designed to evaluate the feasibility of treating patients with poor cardiopulmonary status and peripheral T1 NSCLC with VAR and local radiotherapy. The study (The Cancer and Leukemia Group B [CALGB] 9335) was conducted as a phase II, multi-institutional, cooperative group trial.

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Patients and Methods

Objectives

The primary objective of CALGB 9335 was to determine the feasibility of treating patients with cardiopulmonary dysfunction and T1 peripheral NSCLC by VAR and radiotherapy. The basis for determining feasibility and safety was the proportion of patients who could not have complete resection with video-assisted thoracoscopic technology or who had any of the following complications: (1) major operative complications occurring within 30 days after surgery, including death, myocardial infarction, and cardiac or respiratory failure necessitating mechanical ventilation for more than 72 hours; (2) delayed complications related to surgery or radiotherapy (within 6 months), including progressive dyspnea, hypoxia or hypercarbia, and decline in measured lung functions; (3) conversion to thoracotomy for any reason, including extent of tumor, adhesions, technical difficulty, and complications; and (4) positive resection margins at completion of final resection. Secondary objectives of this study included the following: (1) to describe the incidence of locoregional recurrence among high-risk patients with T1 peripheral NSCLC treated by VAR and radiation therapy, (2) to describe pattern of survival and disease-free survival in high-risk patients treated with VAR and radiotherapy, (3) to determine the technical feasibility of ipsilateral lymph node sampling and complete resection with VAR, (4) to describe the rate and causes of conversion to open thoracotomy, (5) to describe the short- and long-term complications associated with VAR, and (6) to describe the toxicity associated with adjuvant radiotherapy after VAR.

Inclusion and Exclusion Criteria

Patients were required to fulfill the following criteria to be eligible: (1) tumor characteristics of single T1-size lung nodule on computed tomography (CT) located peripherally and judged to be surgically accessible for thoracoscopic resection by the surgeon; and (2) patient characteristics of forced expiratory volume in 1 second of less than 40%, carbon monoxide diffusing capacity in lung of less than 50%, maximum oxygen consumption of less than 15 mL/(kg · min), oxygen requirement, or arterial carbon dioxide level of more than 45 mm Hg. In addition, the following were considered exclusion criteria: (1) evidence of distant metastasis, pleural effusion, or N2 disease by CT scan, with patients with lymph nodes larger than 1 cm on CT scan required to undergo mediastinoscopy to role out lymph node metastasis; (2) previous chest radiotherapy; and (3) previous cancer other than nonmelanoma skin cancer and in situ cervical cancer, with patients with other cancer but more than 5-year disease-free interval considered eligible.

Schema of Protocol

Patients meeting selection criteria were registered and subjected to VAR of the suspect nodule. After complete resection and pathologic documentation of T1 NSCLC, patients were reregistered and subjected to radiation therapy (56 Gy) per protocol. Those with incomplete resection or positive resection margins underwent radiation therapy with a higher dose of 66 Gy.

Technique of VAR

Preparation, positioning of patients and method of administering anesthesia were left to the discretion of the treating team. Wedge resection was to be performed with endostaplers or other means under indirect thoracoscopic vision, either totally endoscopically or with the addition of a working incision not exceeding 8 cm and without the use of retractors. Systematic attempt at intraoperative thoracoscopic identification and sampling of ipsilateral lymph nodes before commencement of resection was incorporated

as part of this study to gauge the capacity of thoracoscopic techniques in performing adequate lymph node staging.

Intraoperative pathologic examination of frozen sections of resection margins was required. Additional resection was to be performed if margins were shown to have malignant cells, unless this was not feasible for technical or other, patient-related reasons.

Technique of Radiotherapy

A radiation oncologist saw patients at re-registration time, and radiation treatment started between 14 and 56 days after surgery. Patients with complete resection received a total of 56 Gy in 28 fractions of 2.0 Gy/d and 5 fractions/wk. Those with incomplete resection were treated with a total dose of 66 Gy in 33 fractions of 2.0 Gy in 5 fractions/wk. The target volume was defined by the staple line or clip markings with an additional 2 cm margin, to a maximum total field of 7 × 7 cm for completely resected tumors and one of 8 × 8 cm for incompletely resected tumors. The prescription point was the center of the target volume.

Statistical Methods

The primary end point of CALGB 9335 was the proportion of patients with cardiopulmonary dysfunction and a single peripheral T1 N0 NSCLC or suspected lung cancer who could be completely resected and receive radiotherapy without acute operative complication or delayed complications from the resection or radiotherapy. The study hypothesis assumed that the treatment regimen was unacceptable if failure, defined as inability to completely resect tumor or presence of complications, occurred in 30% or more of patients, whereas the regimen was acceptable if this proportion was 15% or less. To estimate the unknown proportion of failures, p, it was necessary to define and estimate the following unknown parameters: $P1$, the proportion of patients with acute postoperative and intraoperative complications or incomplete resection, and $P2$, the proportion of patients with delayed complications among those with complete resection and have no acute complications. This proportion is the conditional probability of delayed complications for a patient who underwent complete resection without acute complications.

The numbers of patients on which estimates of P1 and P2 are based differ because of patient withdrawal, ineligibility after resection, occurrence of acute postoperative complications, and incomplete resections. The denominator of P1 was all patients accrued to this study, including those who were subsequently discovered to be ineligible according to histologic criteria. The denominator of P2 was the number of patients who received radiation after complete resection without acute operative complications. With an accrual goal of 65 patients, simulation studies were conducted that showed that the study design had a type I and II error rate of 10% under the following assumptions: (1) 10% to 20% of patients who undergo resection would withdraw before radiotherapy or not be eligible for radiotherapy, and (2) the proportion of patients who would not undergo radiotherapy after complete resection without acute operative complications was 20%.

TABLE 1. Operative outcomes in relation to pathologic staging

	Total	Failure	Success
Benign T1-size lesions	10	2 (20%)	8 (80%)
T1 NSCLC	32	7 (22%)	25 (78%)
All T1	42	9 (21%)	33 (79%)
T2 and other	16	8 (50%)	8 (50%)
Total	58	17 (29%)	41 (71%)

The product limit estimator developed by Kaplan and Meier was used to describe the survival and failure-free survival from study entry and after surgery for patients enrolled in CALGB 9335. Survival was defined as time from study entry until death, whereas survival after surgery was defined as the time between surgery and death. Failure-free survival and failure-free survival after surgery were computed from study entry or time of surgery until initial failure (death, disease progression, or relapse).

Analyses were based on all data available as of February 2002.

Results

Between September 1995 and September 1999, a total of 65 patients were accrued, consistent with the target. CALGB institutions accrued 54 patients and The Eastern Cooperative Oncology Group institutions accrued 11 patients. Of the 65 patients accrued, 7 patients were retrospectively determined by the study chair to have been ineligible to enroll in CALGB 9335. Reasons for ineligibility included prestudy chest images confirming T2 disease in 3 patients, preoperative workup of suspected mediastinal involvement in 1 patient, N2 or N3 lymph nodes in 2 patients, and suspected extensive local thoracic disease before surgery in 1 patient. These 7 patients are therefore excluded from all analyses. Among the remaining 52 patients, 58% were male, the age median was 69 years (49-82 years), and 77% had a performance status of 0 or 1. The median forced expiratory volume in 1 second for all patients was 37% predicted, carbon monoxide diffusing capacity in lung was 44% predicted, the maximum oxygen consumption was 13 mL/(kg · min), and 10% of patients were oxygen dependent.

Table 1 summarizes the operative success or failure of VAR for all patients and for each of the specific pathologic stages. Patients with benign T1-size lesions had an 80% success rate (8/10). The T1 NSCLC success rate was 78% (25/32), whereas that for all T1 lesions was 79% (33/42).

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TABLE 2. Reasons for failure and relationship to operative staging

Patient	T2 pathologic stage	Converted	Problem
60446	Yes		Positive margins after resection
61734		Abort	Extensive adhesions
63197		Yes	Exposure, tumor rupture
63567	Yes	Yes	Large tumor, positive margins
66724		Yes	Localization
66767		Yes	Exposure, adhesions
66843		Yes	Adhesions, bleeding
67247			Positive margins after resection
67953	Yes	Yes	Exposure, localization
68588	Yes	Yes	Large tumor, exposure, positive margins
69013		Abort	Deep tumor
69745	Yes	Yes	Secondary malignancy detected
71029	Yes	Yes	Large tumor, technical difficulties
71744			Positive margins after resection
71763			Intraoperative death, respiratory failure
73901	Benign		Intraoperative bleeding, died day 2
73988	Benign	Yes	Extensive adhesions

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Patients with T2 or higher NSCLC had a low operative success rate of 50% (8/16). The total success rate for all VAR procedures in this study was 71% (41/58). Table 2 describes the reasons for conversion to open thoracotomy or abortion of surgery altogether and its association with increase in staging to T2 or higher.

Conversion to thoracotomy occurred in 10 cases (17%), including 1 patient with benign T1-size disease (10%), 4 patients with T1 NSCLC (13%), and 5 patients with T2 NSCLC (31%). Resection margins were found to be positive in 5 patients (8.6%): 2 patients with T1 NSCLC (6%) and 3 patients with T2 NSCLC (19%). Surgery was aborted in 2 cases, and 2 other patients died early after the operation.

Table 3 describes the relationship of pathologically determined tumor size to the width of resection margins. A wide resection margin of 1 cm or more was present in 7 of 9 patients with benign T1-size lesions (78%), in 14 of 32 patients with T1 NSCLC lesions (44%), and in 5 of 15 patients with T2 NSCLC and other lesions (33%). Overall, only 46% of patients undergoing VAR in this study had a surgically wide ($\geq$1 cm) resection margin. VAR was performed equally on both sides (52% on right, 48% on left). The numbers of incisions used per procedure were 2 in 9% of all cases, 3 in 79%, and 4 in 11%. Lung deflation permitting ease of exposure was partial in 38% of cases, full in 55%, and not performed in 4%. Adhesions were absent in 50%, of cases minimal in 21%, moderate in 21%, and extensive in 7%. Pulmonary lobes were reported to be anatomically separate in 59% of patients and not separate in 34%.

Compliance with systematic ipsilateral lymph node sampling was rather poor in this study. Only lymph nodes R4, R7, and R13 were explored, and only in a total of 21 patients. Because the accessibility of lymph nodes was limited, no meaningful data could be additionally gained from attempting to sample these lymph nodes. Sampling ranged from 2% for R13 lymph node station to 47% for R4 and R7 lymph nodes stations. Nonanatomic wedge resection was performed with automated stapler devices in 89% of procedures, cautery dissection in 14%, and laser dissection in 2%. Intraoperative bleeding was noted to be absent in 57% of VAR procedures, minimal in 41%, and moderate in 2%. Surgeons used only one chest tube for drainage in most cases (73%) and 2 tubes in 27% of cases. The duration of VAR procedures was a median of 100 minutes, ranging between 40 and 255 minutes.

Postoperative complications (Table 4) were low, with 2 deaths from cardiorespiratory failure (4%), respiratory failure requiring mechanical ventilation in 4%, pneumonia in 6%, arrhythmia in 6%, and prolonged air leak in 10%. Of the total number of patients registered in the study, 32 patients were found to have pathologically staged T1 NSCLC. Three patients refused radiotherapy, and another died of underlying lung disease before commencement of radiotherapy. Twenty-eight patients completed radiotherapy. Toxicity from this treatment is reported in Table 5.

As of October 2001, survival of patients with pathologic T1 disease was determined from the time of surgical resection until death. With 18 of the 31 patients dead, the median survival after surgery was 32 months (95% confidence interval 4-20.7).

Failure-free survival after surgery was determined from the time of surgery until first failure (relapse, disease progression, or death). With 18 of 31 patients having failure, the median failure free survival was 30.5 months (95% confidence interval 4-13.4).

TABLE 3. Pathologic staging and effect on width of surgical resection margins

Margins	Benign	T1	T2 and other	All (n = 56)
Widely resected	7 (78%)	14 (44%)	5 (33%)	26 (46%)
Narrowly resected	2 (22%)	14 (44%)	6 (40%)	22 (39%)
Positive margins	0 (0%)	2 (3%)	2 (13%)	4 (7%)
Unknown	0 (0%)	2 (3%)	2 (13%)	4 (7%)

TABLE 4. Postoperative complications of VAR

Complication	%
Surgical death	4
Postoperative fever	14
Air leak	10
Pneumonia	6
Respiratory failure	4
Arrhythmia	6
Myocardial infarction	0

TABLE 5. Complications associated with radiotherapy after VAR

	Mild	Moderate	Severe
Dyspnea	11%		11%
Pneumonitis		4%	
Neurologic	4%	4%	
Soft tissue	11%		

Median survival after radiotherapy for pathologically staged T1 NSCLC, with 16 of 28 patients dead, was 27.2 months (95% confidence interval 4-17.2). Median failure-free survival after radiotherapy completion, with 16 of 28 patients dead, was 26.8 months (95% confidence interval 4-9.93).

Discussion

VAR has been advocated as an attractive noninvasive approach to limited resection of lung cancer, particularly for patients with limited cardiopulmonary reserve who are feared to be unable to tolerate major lung resection. Until now there have not been any prospective examination of the advantages and limitations of applying new technology such as video-assisted techniques to the treatment of lung cancer. This multi-institutional study was conducted by surgeons who were required to show proficiency in thoracoscopic techniques. It exposes some serious limitations of the intention to treat high-risk patients with T1 NSCLC by means of VAR techniques.

First, it is clear from this study that preoperative clinical staging seriously overestimates or underestimates the extent of local disease. This may in part be attributable to the heterogeneity of underlying lung disease in this predominantly severely emphysematous study population. Additionally, this limitation may reflection the quality of CT scans used in the 1990s. Application of VAR in the treatment of patients with lesions pathologically proved to be larger than T1 was associated with 29% risk of failure from conversion, abortion of thoracotomy, or incomplete resection.

On the other hand, this study suggests that for high-risk patients with confirmed T1 NSCLC it is possible to use VAR with a low surgical morbidity. However, even patients with pathologically confirmed T1 disease are noted to be at risk for resection margins close to (<1 cm) from tumor margins when VAR is used. Thus there is a potentially increased risk of locoregional recurrence.

Although visualization and intraoperative surgical resection proceed uncomplicated in most cases, we are concerned with the limited ability to inspect and sample intrathoracic lymph nodes. This potential limitation of thoracoscopy in staging the locoregional extent of tumors, including ipsilateral lymph node status, may not have much impact on patients with limited life expectancy from cardiopulmonary dysfunction. However, it may be a serious consideration in the role of thoracoscopy in patient with a physiologic status that permits major resection or further adjuvant therapy.

Considering the high technical failure rate of thoracoscopic resection for all patients with clinically staged T1 lung cancer, including those who were later determined to have T2 or greater disease, one must conclude that VAR in its current form should not be considered the preferred treatment for patients with clinical T1 lung cancer. Improvements in imaging techniques for precise determination of tumor size and better VAR technology to permit wider resection margins may render thoracoscopic resection more acceptable in the future. Currently, however, we conclude that VAR is a compromising procedure that must be used only in compromised situations. Risks must be clearly indicated to patients. In the absence of better therapeutic alternatives, VAR may be advocated for the treatment of high-risk patients, patients who already have advanced underlying lung disease and thus a more limited survival expectance than the population at large, with an effort made to obtain wider resection margins. Consideration in the future must be given to examining the role of radiotherapy modalities alone or surgical resection, which would permit a wider resection margin.

In addition to McGill University Health Centre, the following persons and institutions participated in the study: Donald Burney (Secc-Moses, Greensboro, NC); Robert Cameron (SWOG, LosAngeles, Calif); A. Alan Conlan (University of Mass, Worcester, Mass); Malcolm Decamp (Cleveland Clinic, Cleveland, Ohio); Todd Demmy (University of Missouri, Ellis Fischel, Columbia, Mo); Kemp Kernstine (University of Iowa, Iowa City, Iowa); Leslie Kohman (SUNY Upstate, Syracuse, NY); Mark Krasna (University of Maryland, Baltimore, Md); Rudy Lackner (Long Island Jewish Medical Center, Hyde Park, NY); Thomas Lad (VAMC, Chicago, Ill); Michael Maddaus (University of Minnesota, Minneapolis, Minn); Stephen Myers (SUNY Upstate, Hyde Park, NY); Keith Shulman (Louis A. Weiss Memorial Hospital, Chicago, Ill); Joshua Sonett (Baltimore VAMC, Baltimore, Md); David Sugarbaker (Brigham & Womens Medical Center, Boston, Mass).

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