Comparison of Survival after Sublobar Resections and Ablative Therapies for Stage I Non−Small Cell Lung Cancer

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BACKGROUND: Lobectomy is the standard therapy for patients with stage I non−small cell lung cancer (NSCLC). Recently, sublobar resections (SLR), radiofrequency ablation (RFA), and percutaneous cryablation therapy (PCT) for high-risk patients unfit for standard resection have been reported. This study compares all 3 modalities in stage I NSCLC.

STUDY DESIGN: Patients with biopsied stage I NSCLC determined by PET/CT deemed medically unfit for standard resection were reviewed by a tumor board according to American College of Surgeons Oncology Group/NIH inoperability criteria before being offered SLR, RFA, or PCT under anesthesia. Patients were followed with CT scans alternating with PET scans. The primary end points were overall survival, cancer-specific survival, and cancer-free survival. Kaplan-Meier analysis and log-rank tests were used.

RESULTS: Sixty-four patients underwent SLR (n = 25; 11 men, 13 women; median age 66 years, range 49 to 85 years), RFA (n = 12; 8 men, 4 women; median age 74 years, range 62 to 83 years), and PCT (n = 27; 16 men, 11 women; median age 74 years; range 59 to 88 years). The probability of 3-year survival for the SLR, RFA, and PCT groups was 87.1%, 87.5%, and 77%, respectively ($p > 0.05$). The 3-year cancer-specific and cancer-free survival for SLR, RFA, and PCT groups was 90.6% and 60.8% versus 87.5% and 50% versus 90.2% and 45.6%, respectively.

CONCLUSIONS: This experience suggests comparable survival after sublobar resections and ablative therapies at 3 years. Ablative therapies appear to be a reasonable alternative in high-risk patients not fit for surgery. However, larger randomized studies with longer follow-up are needed to make recommendations for therapy. (J Am Coll Surg 2010;211:68–72. © 2010 by the American College of Surgeons)

Since the Lung Cancer Study Group performed its often-quoted trial comparing lobectomy versus lesser resections for stage I non−small cell lung cancer, lobectomy has been established, at least in the United States, as the standard of care for resectable patients.[1] This study showed a 75% increase in local recurrence rates, as well as a trend toward lower survival in the sublobar resection group compared with lobectomy. Five-year survival for patients with stage I non−small cell lung cancer ranges between 60% and 80% in most studies.[2,3] However, there remains a large population of patients who cannot tolerate lobectomy secondary to their medical comorbidities. The experience with sublobar resections (SLR) has been fairly extensive in a wide range of applications, with 5-year survival reported between 40% and 80%.[1] For patients who cannot tolerate surgery, or refuse an operative intervention, the guidelines as reported by the American College of Chest Physicians recommends radiation therapy, with the best 5-year survival reported around 40%.[4,5] This therapy is clearly seen as palliative because of the relatively low success rate with considerable long-term side effects. This has prompted a search for other minimally invasive options, including ablative therapy and stereotactic radiation. In this study, we have compared outcomes in a retrospective fashion of 3 different alternative modalities, namely radiofrequency ablation (RFA), percutaneous cryoablation (PCT), and SLR for stage I non−small cell lung cancer (NSCLC).

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METHODS

Our study included 64 patients with stage I non−small cell lung cancer who were treated at Stony Brook University Hospital between 2003 and 2008. Our IRB-approved da-

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Abbreviations and Acronyms

NSCLS = non−small cell lung cancer
PCT = percutaneous cryablation therapy (PCT)
RFA = radiofrequency ablation
SLR = sublobar resections

tabase comprises patients with a diagnosis of NSCLC who were treated with surgical or radiologic interventions. The information entered into the database includes baseline characteristics of the patients (Table 1), biopsy and/or pathology results, stage of cancer, date of diagnosis, kind of treatment received and date of treatment, date of death, cause of death, and date of diagnosis of recurrence. We included patients with stage I NSCLC who underwent either SLR (n = 25; wedge resection or segmentectomy), RFA (n = 12), or PCT (n = 27). Regardless of methods chosen, the senior surgeon attended all patients. All patients were diagnosed with bronchoscopic or percutaneous biopsy and were staged by PET/CT. All patients were reviewed by a tumor board and deemed medically inoperable according to American College of Surgeons Oncology Group/NIH criteria (Table 2). Patients who qualified for a lobectomy were excluded from the study. Patients who could not tolerate general anesthesia were also excluded from the study because all interventions were performed under general anesthesia. In addition, all recurrences were again reviewed by the tumor board and adjudicated between second primary versus recurrence.

Group assignment was subjective and based on the judgment of the senior surgeon using information from best practices reported and taking into consideration wishes of the patient. The SLR group included mostly patients with central lesions because percutaneous methods are not easily applicable to those anatomic locations. Also, these patients had to be able to tolerate 1-lung anesthesia. Therefore, the ablation group consisted of more patients with peripheral lesions. The RFA group included patients with larger lesions (≥3 cm) and relatively healthy lung parenchyma who were believed to be better and safer treated with the multitine RFA probes. Extensive emphysema patients and patients in general with lesions <3 cm made up the PCT group. This is based on our previous experience that with PCT probes, we could lower the incidence of postprocedural pneumothoraces. We kept all patients in the hospital overnight.

Follow-up for all patients consisted of whole-body PET/CT scans at 6 months and contrast-enhanced CT every 3 months for the first year and annually thereafter. Radiologic evidence of recurrence was confirmed by biopsy. Primary end points in our study were 3-year overall survival, cancer-specific survival (only cancer-related deaths were counted as events), and cancer-free survival (cancer recurrences and all deaths were counted as events). We used the Kaplan-Meier method and log rank test to compare survival curves for these groups. Baseline characteristics of the 3 groups were compared using *t*-test and chi-square test. Secondary outcomes were the number of local recurrences, metastatic disease, time to local recurrence, postprocedure complications, and length of hospital stay.

RESULTS

There were 25 patients in the SLR group, 12 patients in the RFA group, and 27 patients in the PCT group. Baseline characteristics of all 3 groups were comparable (Table 1). The only statistically significant difference was diffusion capacity of the lung for CO, which was lower in the PCT group than in the other 2 groups. Eighty-nine percent of patients who underwent SLR had lymph nodes sampled (2 to 7 lymph node stations per case were sampled) and none of the lymph nodes were positive for cancer. Mean follow-up was 33 months. There were no patients lost to follow-up. We found overall 3-year survival of 87.1%, 87.5%, and 77% for SLR, RFA, and PCT, respectively, with no statistically significant difference between groups (see Fig. 1 for SEM values). The 3-year cancer-specific survival was also comparable between the 3 groups at 90.6%, 87.5%, and 90.2% (Fig. 2). There was a tendency toward higher cancer-free survival at 3 years for the SLR group (60.8%) and for RFA and PCT groups (50% and 45.6%, respectively) (Fig. 3). However, this difference did not reach statistical significance ($p > 0.05$). There was a trend

Table 1. Baseline Characteristics

Demographics	SLR (n = 25)	RFA (n = 12)	PCT (n = 27)	p Value
Age, y, mean (range)	66 (49−85)	74 (62−83)	74 (59−88)	>0.05
Female, n (%)	16 (64)	5 (44)	16 (60)	
FEV_1, n (% predicted range)	65 (40−104)	64 (36−100)	64 (23−119)	>0.05
DLCO, n (% predicted range)	73 (53−110)	62 (36−107)	57 (12−94)	0.02
EF, n (% range)	60 (44−75)	62 (23−75)	54.50 (35−74)	>0.05

DLCO, diffusion capacity of the lung for CO; EF, ejection fraction; FEV_1, forced expiratory volume in 1 second; PCT, percutaneous cryoablation; RFA, radiofrequency ablation; SLR, sublobar resections.

Table 2. American College of Surgeons Oncology Group/NIH Inoperability Criteria for Lung Surgery

Major criteria (need at least 1)
FEV_1 ≤50% of predicted
DLCO ≤50% of predicted
OR
Minor criteria (need at least 2)
Age 75 y and older
FEV_1 51−60% of predicted
DLCO 51−60% of predicted
Pulmonary hypertension, defined as pulmonary artery systolic pressure >40 mmHg by echocardiography or right heart catheterization
LVEF ≤40%
Resting or exercise arterial oxygen partial pressure ≤55 mmHg or oxygen saturation ≤88% by pulse oximetry
Arterial carbon dioxide partial pressure >45 mm Hg
Modified Medical Research Council Dyspnea Scale ≥3

DLCO, diffusion capacity of the lung for CO; FEV_1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction.

toward higher local recurrence and high regional and distant recurrence in the RFA group (Table 3). We have also observed longer times to local recurrence for the resection group than for the ablation group (Table 3). However, none of these data reaches statistical significance secondary to the small sample size ($p > 0.05$). The major complications that were observed for the ablation group were pneumothorax and hemoptysis, and there were no postsurgical complications in the resection group (Table 3). None of these complications resulted in cardiorespiratory compromise or required an operative intervention. Two of seven cases of hemoptysis required bronchoscopy. In 47% of patients with radiographic pneumothorax, the size warranted chest tube insertion. Length of hospital stay was considerably shorter for the 2 ablation groups than for the SLR group (Table 3).

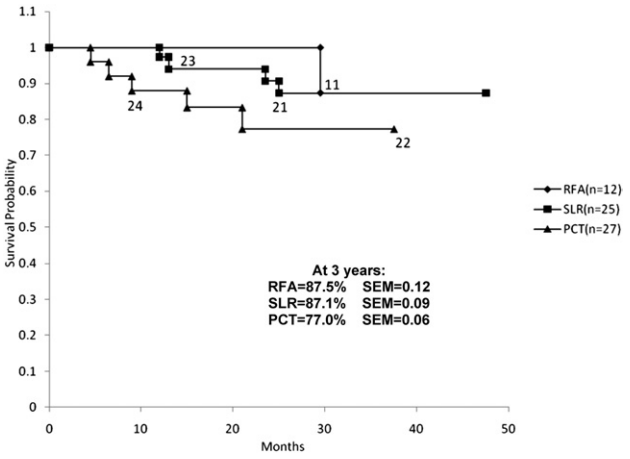

Figure 1. Probability of overall survival. PCT, percutaneous cryoablation; RFA, radiofrequency ablation; SLR, sublobar resections.

DISCUSSION

Ever since the widely quoted randomized trial from the Lung Cancer Study Group was published in 1995,[2] the standard of care for stage I NSCLC, at least in the United States, holds that a lobectomy is the most appropriate operation for early-stage lung cancer. That study compared lobectomy with sublobar resection and established that sublobar resections had higher local recurrence rates and a trend toward lower survival rates.[2] In the most recent recommendations by the American College of Chest Physicians, lobectomy is the standard of care for stage I NCLC.[1] However, sublobar resections have been around for quite some time as a treatment alternative to lobectomies for patients with limited cardiopulmonary reserve. Recently, there has been a resurgence of interest spawned by newer technological inventions and by observations made mainly

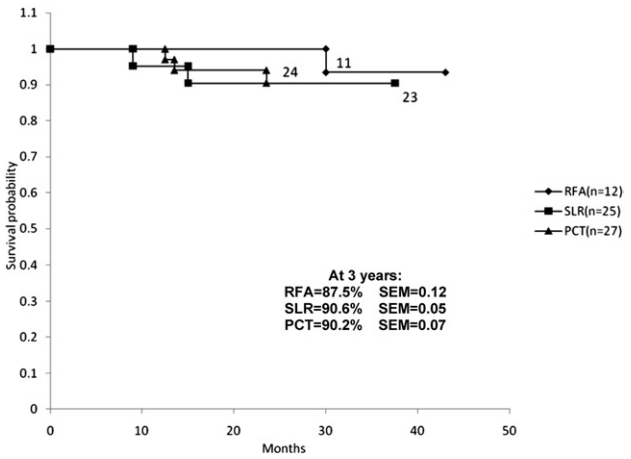

Figure 2. Probability of cancer-specific survival. PCT, percutaneous cryoablation; RFA, radiofrequency ablation; SLR, sublobar resections.

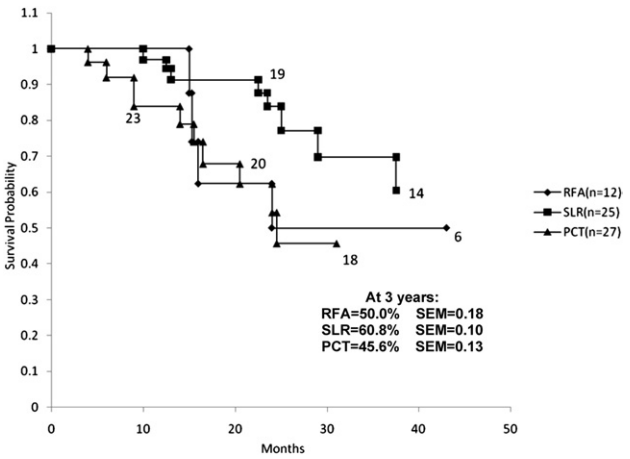

Figure 3. Probability of cancer-free survival. PCT, percutaneous cryoablation; RFA, radiofrequency ablation; SLR, sublobar resections.

Table 3. Secondary Outcomes

Secondary outcomes	SLR (n = 25)	RFA (n = 12)	PCT (n = 27)	p Value
Local recurrence, n (%)	3 (12)	4 (33)	3 (11)	>0.05
Any metastases, n (%)	3 (12)	3 (25)	2 (7.4)	>0.05
Time to local recurrence, mo	19	13	13	>0.05
Complications				
Pneumothorax, n (%)	0	7 (58)	10 (37)	>0.05
Hemoptysis, n (%)	0	1 (8.3)	6 (22)	>0.05
Length of stay, d	6	1.8	2	<0.05

PCT, percutaneous cryoablation; RFA, radiofrequency ablation; SLR, sublobar resections.

from our colleagues in Asia that some cancers might not need a full lobectomy to be controlled. In our series, 3-year survival rate for patients undergoing sublobar resections has been 80%, which is in the range of that reported by other authors. For example, a German study published in 2008 looked at wedge resections versus segmentectomies and reported 3-year cancer-related survival at around 60% for wedge resections and around 85% for segmentectomies.[6] A retrospective study from Pittsburgh showed an overall 3-year survival of around 60% for sublobar resections for stage I NSCLC.[3] Sublobar resections, although less morbid operations than lobectomies, do carry a lot of traditional down sides of surgical intervention for patients with compromised physiologic reserve. Patients who underwent a wedge resection or segmentectomy routinely stayed in the hospital an average of 6 days in our study. Also, all of them had chest tubes routinely placed during the operation, which, together with thoracic incisions, contributed to postoperative pain and sometimes inadequate pulmonary toilet. In addition, as has been pointed out by the study from Pittsburgh and is also true in our patients, sublobar resections tend to be associated with a lesser lymph node dissection than is performed during a traditional lobectomy. One of the great advantages of performing a lobectomy is the gain of knowledge of the lymph node status. Therefore, one can argue these are the best-staged patients.

Other less invasive modalities are now being considered for patients with early-stage lung cancers whose medical conditions preclude them from being treated according to the standard of care. Among them are ablative therapies, which are excellent methods of local control. RFA induces heat denaturation of cellular proteins resulting in cell death. Cryoablation destroys tumor cells by intracellular and extracellular ice crystal formation, which results in membrane rupture and cell dehydration.[7,8] Both of these methods accomplish gross destruction of radiologically evident disease. As such, they are used to provide palliation for patients with inoperable lung tumors.[9,10]

Ablations present some definitive advantages over surgical resections. The majority of patients undergoing radiofrequency or cryoablation in our study were able to go home within 24 hours of the procedure. Complications, although frequent, were relatively minor and never had any long-term importance for patients. Also, ablations did not result in any loss of pulmonary function tests in our study at 6 months follow-up. Ablative therapies have the advantage of being able to be repeated if a patient has a recurrence or a new malignancy develops.

In our study, overall and cancer-specific survival were almost identical between SLR and the ablation groups at 3 years (Figs. 1 and 2). We did notice a tendency toward lower disease-free survival in the ablation group (Fig. 3). We also noted a trend toward higher recurrence in the RFA group and longer cancer-free intervals in the SLR group (Table 3). This suggests a superiority of SLR to ablative options, RFA in particular, in terms of local control. A post-hoc power calculation with a power of 0.95 and an α error of 0.01 estimated a sample size of 196 patients necessary to show a statistically significant advantage for time to recurrence by SLR. In addition, in a power calculation, time to detect a difference in survival with an odds ratio of 0.85 was estimated to be 76 months, with a power of 0.95 favoring SLR.

All data available on RFA come from small observational studies. The study from Pittsburgh reported a 50% survival for a group of 46 patients with primary lung cancer (all stages).[11] The study that came out of Massachusetts General Hospital in 2009 analyzed a sample of 31 patients with stage I NSCLC who were deemed medically inoperable.[12] All of them underwent RFA, and 23 of 31 patients (74%) were alive at medium follow-up of 17 months. Of 8 patients who died, only 3 died of disseminated lung cancer. Simon and colleagues looked at 153 patients with primary metastatic lung cancer treated with RFA.[13] They reported overall 3-year survival of 36% for stage I NSCLC patients. We have observed 87% 3-year survival for our RFA group. This might be attributable to more careful patient selection, but a small sample size is a substantial limitation in our study. Data in the literature on cryoablation for NSCLC is very limited. Based on our data, cryoablation is an excellent alternative for inoperable patients. We did observe results superior to RFA in terms of local control, although the difference was not statistically significant ($p > 0.05$). Cryoablation does not result in substantial collagen damage, which is associated with RFA, and appears to be a better option for patients with extensive emphysema.

We conclude that all 3 options that we discussed (SLR, RFA, and PCT) are reasonable alternatives to lobectomy for patients who are poor candidates for major surgery. Because none of these options have been known to be clearly superior to another, selection of therapy should be made on a case by case basis. Our study has obvious limitations. It is a small retrospective, nonrandomized review. When assigning patients to different treatment groups, we were trying to pick the best option for each particular patient based on the characteristics of their lesion and their medical condition. This is obviously fraught with selection bias. In addition, ablative and less invasive surgical options inherently suffer from what some would call inadequate staging without systematic pathological assessment of lymph nodes. However, based on our experience with lymph node sampling for the SLR group, the likelihood of understaging lung tumors with PET/CT and now endobronchial ultrasonography is low. Larger prospective studies with longer follow-up are necessary to better define the role of ablative therapies in the treatment of early-stage lung cancer. Finally, it has to be noted that stereotactic body radiotherapy was not included in the comparison.

Author Contributions

Study conception and design: Zemlyak, Moore, Bilfinger
Acquisition of data: Zemlyak, Moore, Bilfinger
Analysis and interpretation of data: Zemlyak, Moore, Bilfinger
Drafting of manuscript: Zemlyak, Bilfinger
Critical revision: Zemlyak, Moore, Bilfinger

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