

Sublobar Resection, Radiofrequency Ablation or Radiotherapy in Stage I Non-Small Cell Lung Cancer

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Key Words

Lung cancer surgery · Radiation therapy · Ablation

Abstract

Background: The best therapy for patients with stage I non-small cell lung cancer (NSCLC) who are medically unfit for lobectomy or prefer not to undergo surgery has not yet been demonstrated. **Objectives:** We analyzed data from our prospective database to evaluate the recurrence and survival rates and assess the extent to which the type of treatment explains outcome differences. **Methods:** This study included 116 patients with histologically proven clinical stage I NSCLC who were treated with sublobar resection (SLR; n = 42), radiofrequency ablation (RFA; n = 25) or radiotherapy (RT; n = 49) between 2009 and 2013. The primary end point was the time to primary tumor recurrence (PR). Kaplan-Meier curves and Cox regression were used to compare the recurrence patterns and survivals after adjustments for potential confounders. **Results:** The SLR patients were younger and exhibited better performance status. The RT patients had larger

tumors. After adjusting for age and tumor size, there were differences between the different treatments in terms of the PR rate, but no differences were observed in overall (OS) or disease-free survival. The hazard ratio for PR comparing SLR versus RT adjusted for age and tumor size was 2.73 (95% confidence interval, CI, 0.72–10.27) and that for SLR versus RFA was 7.57 (95% CI 1.94–29.47). **Conclusions:** Our study suggests that SLR was associated with a higher primary tumor control rate compared to RFA or RT, although the OSs were not different. These results should be confirmed in prospective trials.

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Introduction

According to current guidelines, radical lobectomy remains the standard of care for patients with clinical stage I non-small cell lung cancer (NSCLC). However, up to 25% of patients with clinical stage I NSCLC cannot tolerate lobectomy secondary to their comorbid conditions

[1]. Less invasive modalities are being considered for these patients. Sublobar resection (SLR), also referred to as limited resection, is reserved for patients who are unable to tolerate lobectomy specifically to preserve pulmonary function [2]. SLR can be performed by nonanatomical wedge resection or anatomical segmentectomy, which has been shown to be superior to wedge resection in terms of primary tumor control. Thoracic radiotherapy (RT) and radiofrequency ablation (RFA) are reasonable nonsurgical options for high-risk stage I NSCLC patients. RT can be performed as conventionally fractionated radiotherapy (CFRT) or as stereotactic ablative body radiation (SABR), which was formerly referred to as stereotactic body radiation therapy. SABR enables highly focal treatment of cancer with single or few fractions of high-dose radiation and is preferred to CFRT [3]. RFA is a minimally invasive method that involves image-guided percutaneous placement of an electrode into a tumor and generation of heat to cause complete tumor destruction.

For those who are not candidates for lobectomy, SLR is recommended over nonsurgical therapy. Because untreated patients with clinical stage I NSCLC have a poor median survival of only 14–18 months, nonsurgical ablative treatment is preferred over no therapy for those who cannot tolerate SLR [1]. However, the superiority of SLR over nonsurgical ablative treatment is controversial. Currently, results from randomized controlled trials comparing surgery with nonsurgical ablative treatment are not available.

In this study, we analyzed the survival, recurrence patterns and treatment-related morbidity of high-risk operable patients with potentially curable clinical stage I NSCLC after SLR, RT and RFA.

Materials and Methods

Our institutional database query for patients with histologically proven clinical stage I NSCLC (American Joint Committee on Cancer, 7th edition) who were treated with SLR, RFA or RT at Heidelberg University Hospital between January 2009 and December 2013 identified 174 cases. Patients with metachronous or presumed synchronous double lung tumors, nonbiopsied tumors or missing follow-up data were excluded. A total of 116 patients remained eligible and were analyzed with institutional review board approval (study No.: 080/2006).

Patients were staged with bone scans, computed tomography (CT) scans of the chest and upper abdomen and CT scans or magnetic resonance imaging of the brain. Mediastinoscopy or bronchoscopy with endobronchial ultrasound was performed at the discretion of the tumor board if the CT or positron emission tomography results were suggestive of mediastinal or hilar lymph node metastases. These cases were excluded if histological or cytological

mediastinal assessment was lacking. Uncertain proof of malignancy in the intraoperative frozen section prevented lobectomy in 7 cases. These patients refused completion lobectomy within a second operation. Ninety-four percent of the RT patients and 92% of the RFA patients were deemed medically inoperable for lobectomy. Six percent of the RT patients and 8% of the RFA patients refused surgery. Histology was attained in all cases (table 1).

Treatment

The type of treatment indicated was based on the consensus of a multidisciplinary team discussion. An SLR was termed an anatomical segmentectomy only if individual dissection and ligation of the segmental vessels and bronchus to an anatomically defined lung segment were performed; otherwise, we used the term atypical or wedge resection. When identifying a nodule or stapling lung parenchyma seemed difficult due to target location or characteristics, a limited anterolateral thoracotomy was necessary. We performed lymph node dissection or lymph node sampling only on an individual basis due to concerns about longer operative time and greater total chest tube drainage. Depending on tumor depth and location, 15 patients (36%) underwent video-assisted thoracoscopic surgery (VATS), and 27 patients (64%) underwent limited anterolateral thoracotomy. Six patients (14%) underwent anatomical segmentectomy, and 36 patients (86%) underwent wedge resections. Twelve SLR patients (29%) underwent lymph node dissection and 4 SLR patients (9.5%) lymph node sampling. All RT patients underwent a 4-dimensional planning CT scan [4]. Twenty-eight patients (57%) underwent SABR with a median total dose of 45 Gy, a median of 3 fractions and a median dose of 18 Gy/fraction. Twenty-one patients (43%) underwent CFRT with a median total dose of 66 Gy, a median of 31 fractions and a median dose of 2 Gy/fraction. We performed bipolar RFA under general anesthesia as previously described [5].

Follow-Up

According to national guidelines, the follow-ups for all patients consisted of chest CT scans every 3 months for the first year, every 6 months in the second year, and on an individual basis thereafter. Restaging was performed for clinically symptomatic patients. Radiological evidence of recurrence was confirmed by biopsy. Primary tumor recurrence (PR) was defined as tumor recurrence in the former resection line or at the ablation site. The diagnosis of PR was based on biopsy (histology or cytology). Cases without definitive diagnoses were excluded from the PR analysis. Locoregional recurrence was defined as PR or tumor recurrence in the same lobe, ipsilateral hilar or ipsilateral mediastinal lymph nodes. Any other tumor recurrence was defined as a distant recurrence. The primary end point was freedom from PR.

Statistical Analyses

To compare the patient demographics and tumor characteristics between the groups, 1-way analysis of variance (ANOVA) and χ^2 tests were used. For only the results that exhibited statistically significant differences, we performed independent sample t tests, and we report the p values from the pairwise comparisons. The time to recurrence was calculated from the time of the intervention. To account for the competing risks while analyzing the progression-free survival, we performed a time-to-first event analysis in which death or any type of tumor recurrence was counted as an event [6]. The differences in overall survival (OS), progression-free survival and time to recurrence were compared using pairwise log

Table 1. Patient demographics and tumor characteristics

	SLR (n = 42)	RT (n = 49)	RFA (n = 25)	p
Age, years	69.6±7.1	73.5±7.2	71.2±6.4	0.01 ^a
Range	53–84	57–89	55–80	
Male	27 (64%)	34 (69%)	18 (72%)	0.78 ^b
FEV ₁ , %	69.4±23.7	62.5±27.0	67.1±29.5	0.50 ^a
Range	25–118	23–142	23–132	
DLCO, %	58.4±16.4	48.3±19.6	50.3±19.4	0.21 ^a
Range	29–79	22–91	26–90	
Charlson Comorbidity Index (age-adjusted)	5.9±2.3	6.6±2.4	6.2±2.2	0.55 ^a
Range	2–13	3–11	2–11	
ECOG performance status				<0.01 ^b
0	18 (43%)	10 (20%)	4 (16%)	
1	24 (57%)	32 (66%)	21 (84%)	
2	0	7 (14%)	0	
3	0	0	0	
Prior cancer	12 (29%)	12 (24%)	7 (28%)	0.92 ^b
Tumor size, mm	18.5±9.5	28.4±9.8	21.9±7.3	<0.01 ^a
Range	2–45	10–50	10–35	
Clinical stage ^c				0.05 ^b
T1N0M0	28 (67%)	27 (55%)	21 (84%)	
T2N0M0	14 (33%)	22 (45%)	4 (16%)	
Histology				0.25 ^b
Adenocarcinoma	30 (71%)	27 (55%)	17 (68%)	
Squamous cell carcinoma	11 (26%)	19 (39%)	6 (24%)	
NSCLC not otherwise specified	0	3 (6%)	1 (4%)	
Other NSCLC histology	1 (2%)	0	1 (4%)	
Histology not attained	0	0	0	
Criteria for ineligibility for anatomical lobectomy				
Mental disease or status after stroke	3 (7%)	6 (12%)	2 (8%)	
Alcohol abuse or liver cirrhosis	2 (5%)	3 (6%)	0	
Age >84 years	1 (2%)	6 (12%)	0	
Severe renal insufficiency	5 (12%)	5 (10%)	0	
Pulmonary insufficiency	18 (43%)	30 (61%)	19 (76%)	
Cardiac insufficiency	7 (17%)	19 (39%)	10 (40%)	
Previous RT to lung	0	0	2 (8%)	
Previous lung surgery	0	0	5 (2%)	
Potentially operable	–	3 (6%)	2 (8%)	

The data are presented as the absolute and relative frequencies in parentheses or means ± standard deviations. ^a χ^2 test. ^b ANOVA test. ^c Pathological stage in case of SLR.

rank tests with Kaplan-Meier plots for illustration. Due to the high number of comparisons, the resulting p values could not be adjusted for multiple comparisons and are therefore of a purely descriptive nature. All variables were assessed for potential confounding effects in univariate and multivariable Cox regression models. Changes in the regression coefficients of more than 5% were regarded as indicative of confounding variables. The results of the Cox model are described as the means of the hazard ratios (HRs) together with the 95% confidence intervals (CIs), and the p values were based on the Wald test [7]. The analyses were performed with SPSS Statistics version 22 (IBM, Armonk, N.Y., USA) and were 2-sided.

Results

Patient Characteristics

The SLR patients were significantly younger (SLR vs. RT: p = 0.012; SLR vs. RFA: p = 0.37) and exhibited better ECOG performance statuses (SLR vs. RT: p = 0.07; SLR vs. RFA: p = 0.024; RT vs. RFA: p = 0.10). The RT patients had larger tumors (SLR vs. RT: p = 0.001; SLR vs. RFA: p = 0.13; RT vs. RFA: p = 0.05) and were in advanced clinical stages (SLR vs. RT: p = 0.26; SLR vs. RFA: p = 0.12;

Table 2. Times (months) to tumor recurrence after SLR, RT and RFA

	SLR (n = 42)	RT (n = 49)	RFA (n = 25)
Mean time to primary tumor recurrence	20.0 (18.7)	6.8 (3.3)	8.8 (7.5)
Range	2–47	1–46	1–27
Mean time to locoregional recurrence	13.9 (6.7)	8.7 (7.0)	10.1 (8.1)
Range	2–47	1–46	1–47
Mean time to distant recurrence	10.3 (8.5)	6.7 (6.7)	11.4 (7.3)
Range	2–23	1–22	3–21
Mean time to any recurrence	11.8 (8.0)	6.0 (3.0)	11.9 (8.1)
Range	2–46	1–46	1–24

The data are presented as the absolute frequencies for ranges and means and standard deviations in parentheses.

RT vs. RFA: $p = 0.01$). No significant differences were observed between the groups in terms of the pulmonary function parameters, gender, comorbidity index, prior history of cancer or lung cancer histology (table 1).

Univariate Cox Regression

The median follow-ups for the SLR, RT and RFA patients were 18, 10 and 13 months, respectively. The probabilities of 1- and 2-year OS were 94 and 85% for the SLR patients, 86 and 74% for RFA patients and 93 and 69% for the RT patients, respectively. Table 2 summarizes the mean times to primary tumor and to locoregional, distant and any recurrence. The lungs were the most frequent initial site of distant recurrence in all three groups. An unadjusted comparison of recurrence using an univariate Cox model revealed better primary tumor control after SLR than after RT or RFA (SLR vs. RT: $p = 0.03$; SLR vs. RFA: $p = 0.02$; RT vs. RFA: $p = 0.36$). No statistically significant differences were identified in distant metastasis (SLR vs. RT: $p = 0.93$; SLR vs. RFA: $p = 0.84$; RT vs. RFA: $p = 0.48$), freedom from any failure (fig. 1c) or OS (fig. 1d). The Kaplan-Meier curves for primary tumor control, locoregional control, progression-free survival and OS are shown in figure 1.

Effects of the Surgical Procedures and the Radiotherapy Types

To determine whether the type of surgical procedure affected the PR or OS, the surgical cases were divided into the following pairs of groups: (a) lymph node dissection (LND; $n = 12$) versus no LND ($n = 30$), (b) anatomical segmentectomy ($n = 6$) versus wedge resection ($n = 36$) and (c) open thoracotomy ($n = 27$) versus VATS ($n = 15$). No statistically significant differences were found in PR (LND vs. no LND: $p = 0.64$; segmentectomy vs. wedge:

$p = 0.47$; open vs. VATS: $p = 0.82$) or OS (LND vs. no LND: $p = 0.84$; segmentectomy vs. wedge: $p = 0.75$; open vs. VATS: $p = 0.70$). To investigate the effect of RT type on the PR and OS, we separated the RT group into SABR ($n = 27$) and CFRT ($n = 20$) groups. No statistically significant differences in PR ($p = 0.92$) or OS ($p = 0.56$) were identified between the SABR and conventionally ablated cases (fig. 2).

Multivariable Cox Regression

Pairwise comparisons between the three groups revealed significant differences in age, tumor size, ECOG performance status and clinical stage. Thus, we utilized multivariable Cox regression models to evaluate the differences in recurrence and survival while controlling for these potential confounders. Because the total number of events was limited in this data set, all possible confounders were not analyzed in a single multivariable model to avoid overfitting. Therefore, we calculated several multivariable models that each included only a subset of the potential confounders and compared the results. ECOG performance status and clinical stage exhibited no influence on the HRs. The results of the final Cox regression model that adjusted for the variables of age and tumor size are summarized in table 3. The RFA patients exhibited significantly increased risks for PR and locoregional tumor recurrence compared to the surgical patients. The HRs of 2.73 (95% CI = 0.72–10.27; $p = 0.137$) for RT and 7.57 (95% CI = 1.94–29.47; $p = 0.004$) for RFA indicate that the risk of PR after nonsurgical treatment was greater than that after SLR (table 3).

Procedural Complications

One SLR patient was readmitted for ipsilateral pleural effusion. One SLR patient was reoperated on for postop-

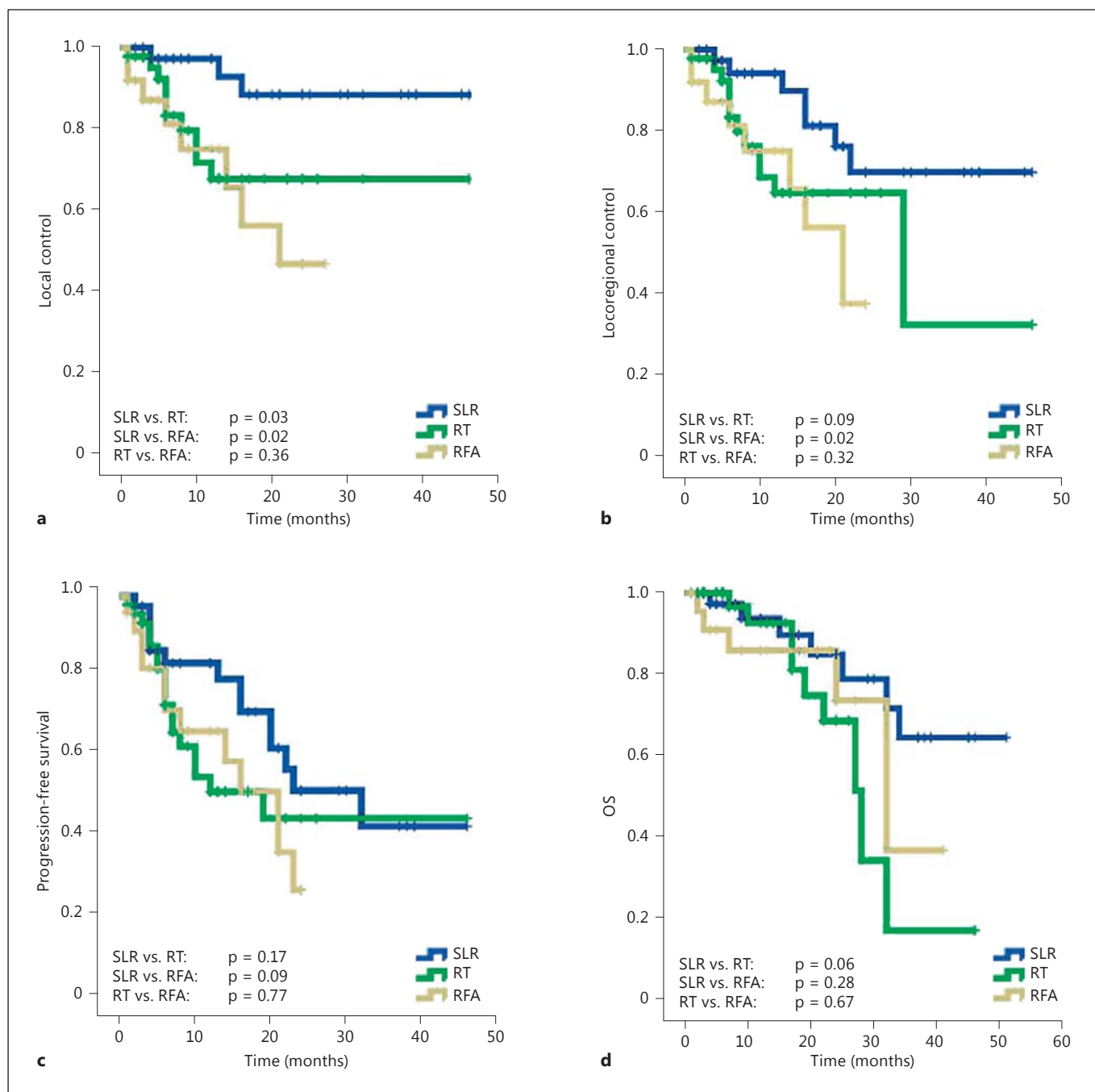


Fig. 1. Outcomes following SLR (n = 42), RT (n = 49) and RFA (n = 25) for stage I NSCLC. SLR, RT and RFA in terms of freedom from primary tumor failure (a), freedom from locoregional failure (b), progression-free survival (c) and OS (d).

erative hemothorax. Three SLR patients developed new-onset postoperative atrial fibrillation. One SABR patient was readmitted for acute exacerbation of pain. One CFRT patient was readmitted 15 months after completing CFRT

with grade 3 pneumonitis. One SABR patient developed grade 1 pneumonitis 2 months after the ablation. One CFRT patient was readmitted for grade 3 pneumonitis 3 months after the ablation. One RFA patient was operated

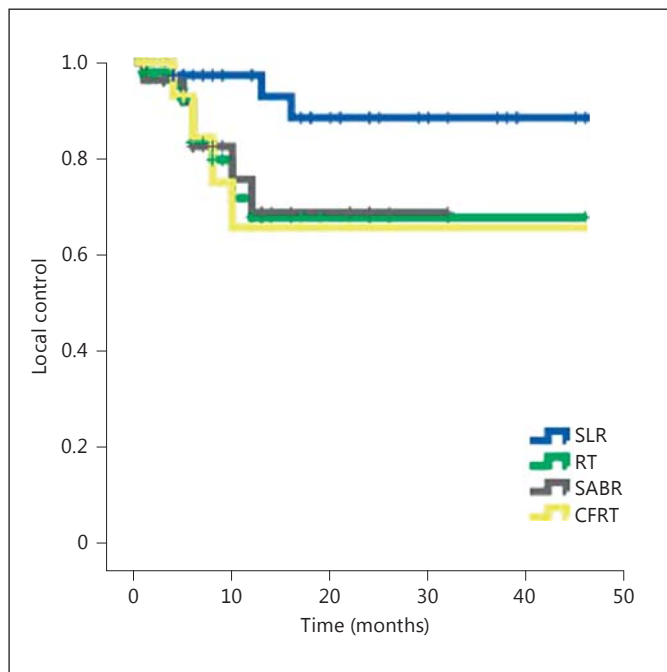


Fig. 2. Primary tumor control after lung SLR (n = 42) versus RT (n = 49) in general ablative body radiation and SABR (n = 27), and CFRT (n = 20).

on day 1 after RFA for a hemothorax. Three patients were readmitted after RFA for a contralateral pleural effusion, an ipsilateral pneumothorax on day 20 and a late-occurring ipsilateral pneumothorax on day 41. Three RFA patients required pleurocentesis for pleural effusion early after RFA. In 7 RFA patients, chest tube insertions were performed for iatrogenic pneumothorax during or soon after RFA. No postoperative or postinterventional in-hospital deaths occurred.

Discussion

The purpose of this study was to compare the outcomes following alternative treatment options for 116 stage I NSCLC patients who were medically unfit for lobectomy or preferred not to undergo surgery. The alternative treatment modalities seemed to be associated with reduced procedural morbidity and mortality, although the increased risk for PR compared to anatomical lobectomy was a concern. We observed no mortalities and acceptable procedural morbidities following SLR, RT and RFA.

The identification of so-called ‘high-risk’ patients remains a clinical decision. A multidisciplinary team indi-

cated the procedure that best met each patient’s situation. Pulmonary function was the primary indication for alternative tumor therapy. The majority of patients could have been operated on according to the FEV₁ and DLCO values; however, combinations with other comorbidities were the primary reasons for foregoing standard lobectomies.

Unadjusted primary tumor recurrence analysis revealed a significantly lower risk after SLR than after RFA or RT (table 2; fig. 1). However, the patients who underwent SLR were younger and had better ECOG performance statuses than did the RT and RFA patients (table 1). We found larger tumors in the RT patients, which might be attributable to the limitation of bipolar RFA to tumors >3 cm in diameter and the consequent exclusion of patients from surgery when centrally located malignancies technically required lobectomy.

To address the differences, we performed multivariable Cox regression. Only age and tumor size influenced the HRs. Multivariable analyses with adjustments for age and tumor size resulted in HRs that were indicative of a greater risk of PR in the nonsurgical groups. The HR for PR after RT was not statistically significant, which is primarily attributable to the small sample size. Our results are in line with some retrospective analyses and data from nonrandomized prospective studies that suggest higher primary tumor control rates after RT and surgery compared with RFA. The level of evidence regarding RFA and primary tumor control is low. The reported 2- and 3-year PR rates after RFA range from 12 to 43% and 8 to 37%, respectively.

In our series, we observed lower PR rates after SLR than after SABR (9.5 vs. 20%). Retrospective and prospective studies that have evaluated SABR for clinical stage I NSCLCs have reported 2- and 3-year primary tumor control rates ranging from 78 to 98% [8]. Results from RT studies need to be interpreted with caution because patients who are not candidates for resection are staged clinically. Primary tumor histologies are attained in all surgical cases, whereas the diagnoses rely on positron emission tomography/CT morphological criteria in a significant number of RT patients. The sensitivity of positron emission tomography/CT ranges between 68 and 100%, but it only has a moderate positive predictive value [9].

In a retrospective study that investigated tumor recurrence after SABR in 676 early stage NSCLC patients, the 2-year rate of PR was 4.9% [10]. Malignancy was proven in only 235 cases (35%). The majority of this population (n = 441; 65%) underwent SABR without previous proof

Table 3. Uni- and multivariable Cox models adjusted for age and tumor size

Variable	Unadjusted HR	95% CI	p	HR adjusted for age and tumor size	95% CI	p
Overall survival						
SLR versus RT	2.52	0.89–7.11	0.081	2.46	0.80–7.59	0.116
SLR versus RFA	2.05	0.63–6.65	0.234	2.72	0.77–9.59	0.121
Progression-free survival						
SLR versus RT	1.66	0.81–0.85	0.170	1.39	0.64–2.97	0.403
SLR versus RFA	1.85	0.85–4.03	0.123	1.79	0.82–3.92	0.143
Primary tumor recurrence						
SLR versus RT	3.89	1.07–14.18	0.040	2.73	0.72–10.27	0.137
SLR versus RFA	5.94	1.57–22.43	0.009	7.57	1.94–29.47	0.004
Locoregional recurrence						
SLR versus RT	2.23	0.87–5.75	0.096	1.70	0.64–4.54	0.292
SLR versus RFA	3.26	1.19–8.94	0.022	3.62	1.29–10.2	0.015
Regional recurrence						
SLR versus RT	2.05	0.56–7.50	0.278	1.65	0.41–6.60	0.480
SLR versus RFA	1.67	0.37–7.67	0.507	1.73	0.37–8.11	0.489
Distant recurrence						
SLR versus RT	1.71	0.63–4.64	0.294	1.29	0.46–3.66	0.629
SLR versus RFA	1.17	0.33–3.82	0.861	1.11	0.32–3.80	0.875

of malignancy. In other studies in which histology was confirmed by biopsy in up to 100% of the cases before SABR was conducted for clinical stage I NSCLC, the 2-year rates of PR have been reported to range from 7 to 21% [8].

We observed no difference in primary tumor control between CFRT and SABR. In contrast to our data, non-randomized evidence suggests superior disease-specific survival and OS in stage I NSCLC following SABR compared to CFRT. The same can be stated regarding wedge and anatomical segmentectomy cases because there is evidence in the literature that, in contrast to our data, these types of surgery result in different disease-free survivals. The difference observed in our results might have resulted from the low sample size, which is a limitation of this study. Although some prospective clinical trials have reported acceptable primary tumor control rates with SLR, RT and RFA, no direct comparative data from randomized controlled trials are available for this subset of operable patients. These patients have been referred to as ‘borderline surgical candidates’, ‘high-risk operable’ or ‘medically inoperable’ patients. The imprecise definition has resulted in numerous biases that confound interpretation. Therefore, the numbers of comparisons reported here with respect to RT and RFA, which are worse than those reported elsewhere in the literature [11], necessitate

caution in the interpretation of these results. In addition there was an inherent selection bias related to the general and primary tumor operabilities being defined by surgery, which resulted in a decision algorithm that permitted RT or RFA primarily only after surgery had been excluded. This bias not only allows, but also requires that it should be borne in mind that some primary tumor therapy should occur even in cases in which the general patient status or tumor localization is unfavorable. In contrast, it is therefore conceivable that, based on the localization in the lung, a number of suitable tumors that would have been better accessed and treated with RT or RFA went into the surgery arm. This patient selection bias was well reflected.

Prospective trials that randomize medically inoperable patients to either surgery or ablative therapy are needed. Unfortunately, poor patient recruitment led to the premature closure of a randomized trial (NCT00687986) that intended to randomize patients with stage IA NSCLC to either surgery or SABR. Another randomized trial (NCT00840749) of lobectomy or pneumonectomy versus SABR also closed secondary to low accrual. The ACOSOG/RTOG trial Z4099/1021 (NCT01336894) is comparing high-risk patients with stage I NSCLC treated with either SLR with or without brachytherapy to those treated with SABR. The estimated completion date is August 2019. In-

deed, if completed, the results of this trial will not be available for some time. Therefore, we believe that retrospective studies such as ours, despite their limitations, might be helpful in guiding decisions for the individual treatment of high-risk patients.

Financial Disclosure and Conflicts of Interest

C.P.H. and M.B. have received honoraria as declared in the conditions for publication form. For the remaining authors none were declared.

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