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Minimally invasive lobectomy versus stereotactic ablative radiotherapy for stage I non-small cell lung cancer

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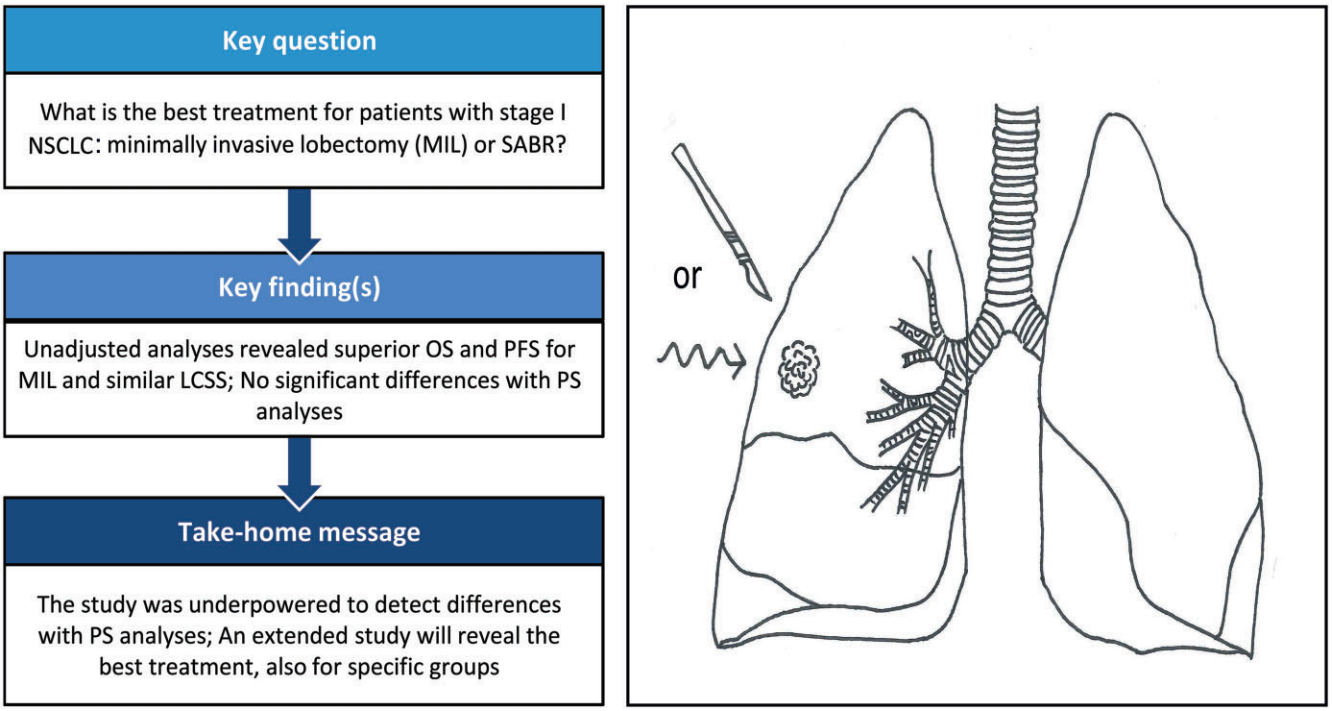

Abstract

OBJECTIVES: A minimally invasive lobectomy (MIL) is the standard treatment for stage I non-small cell lung cancer (NSCLC) in medically operable patients. Stereotactic ablative radiotherapy (SABR) is recommended for inoperable patients and has been proposed as a potential alternative for operable patients as well. Here, we present the results of a feasibility study in preparation for a nationwide retrospective cohort study, comparing outcomes between both treatment modalities.

[†]Members of the ESLUNG group are listed in the Acknowledgements section.
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METHODS: In this retrospective cohort study, data from patients with clinical stage I NSCLC treated with MIL or SABR in 2014–2015 were retrieved from databases from 12 Dutch hospitals. Progression-free survival (PFS), overall survival (OS) and lung cancer-specific survival (LCSS) were compared between MIL and SABR.

RESULTS: A total of 597 patients with clinical stage I NSCLC treated with MIL ($n = 356$) or SABR ($n = 241$) were included. In total, 106 (30%) patients had died in the MIL group and 142 (59%) in the SABR group. After MIL and SABR, unadjusted 5-year PFS was 63% and 30%, OS was 72% and 38% and LCSS was 81% and 76%, respectively. Propensity score-weighted analyses did not show significant differences between MIL and SABR in OS [hazard ratios (HR) 0.74 (95% confidence interval (CI) 0.43–1.29)], PFS [HR 0.74 (95% CI 0.42–1.32)] or LCSS [HR 0.81 (95% CI 0.42–1.59)].

CONCLUSIONS: Unadjusted analyses revealed superior OS and PFS for MIL and similar LCSS, but this feasibility study was not sufficiently powered to demonstrate significant differences using propensity score methodology. Therefore, this study is currently being extended to include more than half of Dutch hospitals in order to enlarge the population to ≥1880 patients, not only to determine the best treatment for patients with stage I NSCLC overall, but also to assess the preferred treatment for patient groups with specific characteristics.

Keywords: Lobectomy • Non-small cell lung cancer • Outcome • Stage I • Stereotactic ablative radiotherapy • Video-assisted thoracoscopic surgery

ABBREVIATIONS

CCI	Charlson Comorbidity Index
CI	Confidence interval
cT	Clinical tumour stage
CT	Computed tomography
DLCO	Diffusion capacity for carbon monoxide
FEV1	Forced expiratory volume in 1 second
HR	Hazard ratio
LCSS	Lung cancer-specific survival
MIL	Minimally invasive lobectomy
NSCLC	Non-small cell lung cancer
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PS	Propensity score
RCT	Randomized controlled trial
SABR	Stereotactic ablative radiotherapy
VATS	Video-assisted thoracoscopic surgery
WHO	World Health Organization

INTRODUCTION

Lung cancer has been the leading cause of cancer-related deaths worldwide in the last few decades [1], with non-small cell lung cancer (NSCLC) being the predominant type of lung cancer [2]. In the Netherlands, 16% of patients are diagnosed with stage I NSCLC [3]. Uncertainty exists regarding the optimal treatment for stage I NSCLC. According to national and international guidelines, a minimally invasive lobectomy (MIL) is recommended for operable patients [4, 5]. Video-assisted thoracoscopic surgery (VATS) has increasingly replaced thoracotomy, leading to shorter hospital stay and fewer complications compared to thoracotomy and similar oncologic outcome [6, 7]. However, many patients are considered unfit to undergo surgery due to comorbidities or impaired pulmonary function.

Stereotactic ablative radiotherapy (SABR) has proven to be a suitable option for inoperable patients with stage I NSCLC due to high local control and low toxicity [8]. Whereas SABR was initially reserved for inoperable patients, SABR is now increasingly used in operable patients as well, including patients who are not willing to accept the operative risks [9–11]. Whether an increased use of SABR in operable patients is appropriate has been discussed over the past years. Unfortunately, treatment results cannot readily be compared in observational studies due to confounding by indication. Fit patients are selected for surgery, while frail patients are more likely to be treated with SABR. Two meta-analyses of retrospective studies reported an overall survival rate favouring surgery, with both lobectomy and sublobar resection being superior to SABR [12, 13]. Several randomized controlled trials (RCTs) (ROSEL, STARS and ACOSOG Z4099) have been initiated to compare outcomes in patients with operable early-stage NSCLC, but all three studies individually failed to complete accrual. Pooled data from the STARS and ROSEL trials showed, in contrast with the previously mentioned retrospective studies, better 3-year overall survival after SABR versus surgery and equal 3-year progression-free survival [14]. However, because of the small sample size and selection criteria in these RCTs, it is still controversial which treatment is optimal for patients with stage I NSCLC.

Results from three other RCTs (STABLE-MATES, POSTILV and VALOR) are expected to be presented in 2024, 2026 and 2027, respectively. At the moment, these trials are recruiting patients, but it is questionable whether recruitment targets will be met. For instance, the SABRTOOTH study (NCT02629458), a study comparing SABR and surgery in high-risk patients with early-stage NSCLC, was closed due to difficulties in accrual owing to patient preferences for one treatment over the other.

Awaiting the results from ongoing RCTs, dedicated clinical registries are suitable to establish the optimal treatment for patients with stage I NSCLC. In a nationwide cohort study, involving more than half of Dutch hospitals performing lung surgery and/or SABR, we will retrospectively compare outcomes between MIL and SABR. Ahead of this nationwide project, we performed a study with a similar study design in 12 hospitals to assess the feasibility of performing detailed data collection on a large scale.

METHODS

Ethics statement

This study was approved by the Institutional Review Boards of the participating centres. Data were collected anonymously and informed consent was not obtained.

Patient population

Data from patients, who underwent MIL or SABR for clinical stage I NSCLC between 1 January 2014 and 31 December 2015, were collected from databases from 12 Dutch hospitals. MIL comprised VATS and robotic-assisted thoracoscopic surgery. Conversions to thoracotomy were included; however, information on the exact number of conversions was not available. Clinical staging was performed according to the 7th edition of the International Union Against Cancer Tumour Node Metastasis classification [15]. Patients with prior NSCLC or with multiple primary NSCLCs were excluded, as well as patients with a potential lung metastasis without pathological confirmation of NSCLC. Segmentectomies were not included since its exact role in stage I NSCLC remains a matter of debate [16], still awaiting the results of the CALGB/Alliance 140503 trial and the JCOG0802/WJOG4607L trial, and since its use was limited (2% of all lung resections for stage I NSCLC) in the study period in the Netherlands [17].

Studied variables

The study variables and follow-up data were collected from the electronic patient files by surgeons or radiation oncologists from the treating hospitals. Pretreatment variables included: age, gender, Charlson Comorbidity Index (CCI), World Health Organization (WHO) performance status, forced expiratory volume in 1 second (FEV1), diffusion capacity for carbon monoxide (DLCO), tumour location, clinical tumour stage (cT) and histological subtype (adenocarcinoma, squamous cell carcinoma or large cell carcinoma/other). Tumour location comprised both the affected lung lobe and whether the tumour was located centrally—within a range of 2 cm from the proximal bronchial tree—or peripherally [18]. Furthermore, it was registered whether a computed tomography (CT) and/or positron emission tomography (PET) scan was performed and whether diagnostic histology or cytology was obtained before start of the treatment. For SABR patients, the fractionation schedule was registered. For all patients, the following information was collected: date of last tumour evaluation, date of last follow-up alive or date and cause of death. Cause of death was determined based on the available information in the (electronic) patient records. In patients with unknown cause of death and with progression of NSCLC, death was considered lung cancer related. In patients with unknown cause of death and without reported tumour progression in the last 6 months (during years 1 and 2 of follow-up) or the past 1 year (during years 3–5 of follow-up) preceding death, death was considered to be due to another cause. If a patient developed recurrence (suspected based on (PET–)CT or pathologically confirmed) on multiple levels (i.e. local, regional and/or distant), all levels of recurrence were registered. Local recurrence was defined as a lesion at the ipsilateral lung staple line(s) or thoracic wall (port metastasis) for MIL patients and as a lesion in the same lobe (infield or outfield) as the primary tumour for SABR patients. Regional recurrence was defined as tumour progression within the ipsilateral hilum or mediastinum and distant recurrence as failure outside of the thorax or in the contralateral lung or contralateral mediastinal lymph nodes. Complications were registered if these were classified as grade 2 or higher according to the CTCAE version 5.0 [19] for the SABR group and according to the Clavien–Dindo classification [20] for the MIL group.

Outcomes were defined as progression-free survival (PFS), overall survival (OS), lung cancer-specific survival (LCSS), recurrence (local, regional or distant) and complication rate. Patients without progression were followed for at least 5 years.

Statistical analysis

Patients were stratified by MIL or SABR. To study differences in patient characteristics between the two treatment groups, independent two sample *T*-tests were used for the continuous variables age, CCI, FEV1 and DLCO and Fisher's exact tests for the categorical variables gender, WHO performance status, lobe, central/peripheral location, cT and histological subtype.

Recurrence rates at 1, 3 and 5 years were calculated with Kaplan–Meier, both total and specific, i.e. local, regional and distant. PFS was calculated from start of the treatment to first date of recurrence or death, whichever came first. Patients alive with no recorded progression were censored for PFS at the date of last tumour evaluation. OS was calculated from start of the treatment to death from any cause. LCSS was calculated from start of the treatment to death from NSCLC (event) or death from another cause (competing risk). For both OS and LCSS, patients being still alive were censored at the date of last follow-up alive. Supplementary Material, Fig. S1 shows how patients with an unknown cause of death were analysed. PFS and OS were calculated with the Kaplan–Meier method and compared between groups using propensity score (PS)-weighted Cox models (see below for more information on the weighting). LCSS was calculated with the Aalen–Johansen method and compared between groups with PS-weighted Fine–Gray models.

Differences between treatment groups were tested for significance using two-sided log-rank tests, both unadjusted and adjusted for relevant patient characteristics by PS weighting. Patients in this retrospective cohort are not randomly assigned to one of the two treatment groups, but rather at the discretion of the physician. To compensate for this and to recreate the setting of an RCT as much as possible, we used inverse probability weighting [21]: in the Cox models (for PFS and OS) and Fine–Gray models (for LCSS) comparing outcomes between groups, we weighted every patient with the inverse of the probability (based on patient characteristics) of that patient receiving the treatment (SABR or lobectomy) that he/she received. This has the net effect that in the weighted population every 'virtual patient' has equal probability of ending up in either treatment group, just as would be the case in an RCT. The mentioned probabilities of receiving either treatment (PS) are produced by a model fitted on the study data.

Concretely, a binary logistic regression model with type of treatment (MIL or SABR) as the dependent variable was constructed to estimate the corresponding scores from the following independent covariates: gender, age, CCI ($\geq$5 vs $\leq$4), WHO performance status (0 vs 1 vs 2–3), FEV1, DLCO, cT and tumour location (upper/middle versus lower lobe) [22]. Initially, all variables mentioned at the beginning of this paragraph were considered for inclusion in the regression model. Cut-off points for CCI and WHO performance status were determined by backward elimination from a larger model containing '$\leq x$ vs $>x$' indicator variables for all possible WHO and CCI values 'x'. Multiple imputation was used for missing values using non-missing predictors. Variable selection took place based on Akaike's information criterion [23]. With these PS-weighted analyses, we assessed the influence of

treatment group on PFS, OS and LCSS. The prognostic impact is represented by hazard ratios (HR) with 95% confidence intervals (CI). *P*-values <0.05 were considered statistically significant. All analyses were performed in R.

RESULTS

In total, 597 patients with clinical stage I NSCLC treated with MIL ($n = 356$) or SABR ($n = 241$) were included. Patient characteristics are shown in Table 1. Patients receiving SABR were significantly older and had more comorbidities, poorer performance status and poorer lung function. A total of 61.0% of patients treated with SABR had pathological confirmation of NSCLC. In patients with known histological subtype, adenocarcinomas were more prevalent among operated patients than among patients treated with SABR, 68.9% vs 52.4%, respectively. Among SABR patients, 127 (52.7%) received 3 fractions, 70 (29.0%) 5 fractions, 38 (15.8%) 8 fractions, 5 (2.1%) 12 fractions and 1 (0.4%) patient received 24 fractions.

In the lobectomy group, postsurgical pathological upstaging occurred in 62 patients (17.4%): cT1–2a became pT2b–4 in 18 patients (5.1%) and cN0 became pN1–2 in 48 patients (13.5%) (4 patients had both tumour and nodal upstaging). After surgery, 36 patients (10.1%) received adjuvant chemotherapy, 2 (0.6%) adjuvant radiotherapy and 9 (2.5%) adjuvant chemoradiotherapy.

The median follow-up was 63.0 months (95% CI 61.6–64.7) after surgery and 59.6 months (95% CI 57.6–61.3) after SABR. Actuarial recurrence rates are shown in Table 2. In the MIL group, 68 patients had a recurrence and in 32 patients (47%) this was pathologically confirmed. In the SABR group, recurrence occurred in 58 patients and this was pathologically confirmed in 30 (52%) patients. Differences in recurrence rates between patients treated with MIL and SABR were not statistically significant.

Complications (grade ≥2) occurred in 32.3% of operated patients and in 19.1% of SABR patients (Table 3).

Progression-free, overall and lung cancer-specific survival

In the lobectomy group, 106 patients (30%) died. Among these deceased patients, 72 (68%) died from NSCLC, 29 (27%) from other causes and 6 (6%) from an unknown cause. In the SABR group, 142 patients (59%) died, of whom 52 (37%) died from NSCLC, 69 (49%) from other causes and 21 (15%) from an unknown cause.

Figures 1–3 show Kaplan–Meier survival estimates after lobectomy versus SABR. Unadjusted 5-year PFS and OS were better after lobectomy compared to SABR [PFS 63% (95% CI 58–68%) vs 30% (95% CI 24–37%), $P < 0.001$, and OS 72% (95% CI 67–77%) vs 38% (95% CI 32–64%), $P < 0.001$, respectively]. LCSS at 5 years was 81% (95% CI 77–86%) in the lobectomy group vs 76% (95% CI 70–82%) in the SABR group ($P = 0.28$).

Table 1: Patient characteristics

	MIL		SABR		*P*-Value
	N (%)	Missing (%)	*N* (%)	Missing (%)	
Total	356		241		
Gender		0		0	0.400
Men	182 (51.1)		132 (54.8)		
Women	174 (48.9)		109 (45.2)		
Age (years), median [IQR]	67 [60–71]	0	74 [67–80]	0	<0.001
CCI, median [IQR]	3 [2–4]	0	5 [4–6]	0	<0.001
WHO performance status		93 (26.1)		5 (2.1)	<0.001
0	193 (54.2)		53 (22.0)		
1	60 (16.9)		123 (51.0)		
2	9 (2.5)		53 (22.0)		
3	1 (0.3)		7 (2.9)		
FEV1 (% predicted), median [IQR]	80 [67–95]	38 (10.7)	59 [47–71]	64 (26.6)	<0.001
DLCO (% predicted), median [IQR]	88 [76–100]	6 (1.7)	65 [47–84]	25 (10.4)	<0.001
Lobe		0		0	0.049
Right upper lobe	125 (35.1)		79 (32.8)		
Middle lobe	22 (6.2)		7 (2.9)		
Right lower lobe	71 (19.9)		45 (18.7)		
Left upper lobe	87 (24.4)		83 (34.4)		
Left lower lobe	51 (14.3)		27 (11.2)		
Tumour location		10 (2.8)		12 (5.0)	0.430
Peripheral	301 (84.6)		205 (85.1)		
Central	45 (12.6)		24 (1.0)		
Clinical T stage		3 (0.8)		0	0.530
1A (≤2 cm)	149 (41.9)		113 (46.9)		
1B (>2–3 cm)	114 (32.0)		70 (29.0)		
2A (>3–5 cm)	90 (25.3)		58 (24.1)		
Histological subtype		28 (7.9)		94 (39.0)	0.001
Adenocarcinoma	226 (63.5)		77 (32.0)		
Squamous cell carcinoma	78 (21.9)		59 (24.5)		
Large cell carcinoma/other	24 (6.7)		11 (4.6)		

CCI: Charlson Comorbidity Index; DLCO: diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; IQR: interquartile range; MIL: minimally invasive lobectomy; SABR: stereotactic ablative radiotherapy; WHO: World Health Organization.

PS-weighted analyses showed a difference between MIL and SABR in PFS [HR 0.74 (95% CI 0.42–1.32)], OS [HR 0.74 (95% CI 0.43–1.29)] and LCSS [HR 0.81 (95% CI 0.42–1.59)] in favour of surgery, although the differences were not statistically significant.

DISCUSSION

Over the past decade, the role of SABR in operable patients has been subject of debate. Retrospective analyses comparing surgery and SABR are hampered by imbalances in patient characteristics between the treatment groups. Therefore, we planned a nationwide study, in which detailed patient data are collected to make a proper comparison of PFS, OS and LCSS between SABR and MIL. Ahead of this nationwide project, we performed a study in 12 hospitals to assess the feasibility of performing detailed data collection on a large scale. Since 597 patients, treated in 2014–2015, were included in this feasibility study by 12 hospitals, we considered it feasible to extend this study to enlarge the population to ≥1880 patients, treated in 2014–2016. Based on data from previous studies [17, 24], we estimated that this sample size is needed to be able to detect a clinically relevant OS advantage (HR ≤0.7) of MIL over SABR in a two-sided test at the 95% confidence interval with 80% power.

The imbalances in baseline prognostic factors between the two treatment groups were evident in our study population: patients treated with SABR were older, had a higher comorbidity index, a poorer performance status and poorer pulmonary function. These imbalances could, at least partly, explain the large differences in unadjusted PFS and OS between MIL and SABR.

Hence, we adjusted for these potentially confounding factors in PS-weighted analyses to enable a proper comparison of PFS, OS and LCSS between surgery and SABR. PS-weighted analyses control for confounding but were underpowered to detect significant variation in outcomes. For the main study, a more than threefold sample will be required to assess relevant differences.

Several other studies comparing these treatment modalities for stage I NSCLC have been performed using PS methodology and showed varying outcomes. In a recently published meta-analysis of PS studies [25], two studies found better OS for surgery compared to SABR and seven studies found equal OS. Furthermore, two studies favoured surgery regarding PFS, one favoured SABR and three showed equal outcome. Compared to most of these studies, we included more patients, had larger information regarding pretreatment variables and longer follow-up and studied multiple outcomes (PFS, OS, LCSS and recurrences).

In theory, the risk of recurrence may be higher after SABR since these patients may harbour occult lymph node metastases that remain undetected by initial CT and PET staging, which is in contrast to surgical treatment, in which draining lymph node stations are

Table 2: Actuarial recurrence rates

Total (*N*)	MIL % 356	SABR % 241	*P*-Value
Any recurrence			0.34
1 year	8.4	13.5	
3 years	20.6	23.5	
5 years	24.9	27.8	
Local recurrence			0.74
1 year	2.3	2.1	
3 years	5.9	5.3	
5 years	7.2	6.3	
Regional recurrence			0.74
1 year	2.9	5.1	
3 years	7.7	9.6	
5 years	10.0	10.2	
Distant recurrence			0.32
1 year	6.1	9.5	
3 years	15.1	17.4	
5 years	18.6	22.5	

MIL: minimally invasive lobectomy; SABR: stereotactic ablative radiotherapy.

Table 3: Complications after minimally invasive lobectomy or stereotactic ablative radiotherapy (grade 2 or higher)

MIL Total	*N* (%) 356	SABR Total	*N* (%) 241
Any complication	115 (32.3)	Any complication	46 (19.1)
(Broncho)pneumonia	31 (8.7)	Radiation pneumonitis	16 (6.6)
Air leak >5 days	24 (6.7)	Rib fracture	6 (2.5)
Atrial fibrillation	19 (5.3)	Dyspnoea	4 (1.7)
Atelectasis	11 (3.1)	Dysphagia	3 (1.2)
Subcutaneous emphysema	9 (2.5)	Chest wall pain	2 (0.8)
Haemorrhage	7 (2.0)	Dermatitis	2 (0.8)
Wound infection	6 (1.7)	Pleural effusion	2 (0.8)
Delirium	4 (1.1)	Pulmonary fibrosis	2 (0.8)
Empyema	4 (1.1)	Radiation osteonecrosis	2 (0.8)
COPD exacerbation	3 (0.8)	Fatigue	1 (0.4)
Damage recurrent laryngeal nerve	3 (0.8)	Other	7 (2.9)
Thrombotic event	3 (0.8)		
Airway obstruction	2 (0.6)		
Myocardial infarction	1 (0.3)		
Respiratory failure	1 (0.3)		
Other	41 (11.5)		

COPD: chronic obstructive pulmonary disease; MIL: minimally invasive lobectomy; SABR: stereotactic ablative radiotherapy.

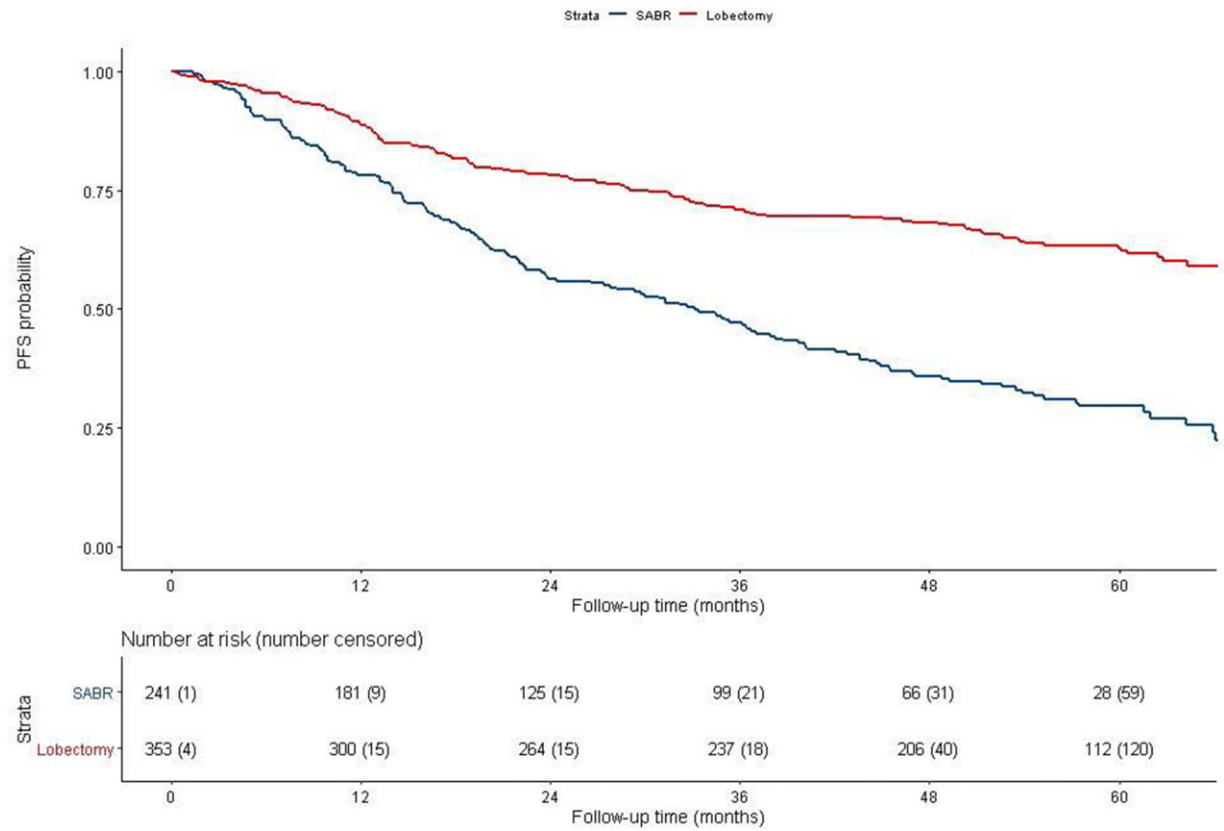

Figure 1: Progression-free survival (unadjusted) in patients treated with minimally invasive lobectomy or stereotactic ablative radiotherapy.

resected simultaneously with the lobectomy. In our study, upstaging occurred in 17.4% of operated patients, which leads to more frequent use of adjuvant systemic therapies, confirming previous studies [26, 27]. Since upstaging does not occur after SABR, these patients might be refrained from adjuvant therapy. Van den Berg *et al.* [28] reported a significantly higher locoregional recurrence rate after SABR as a result of more nodal failures. In contrast, a systematic review [29] suggested that the combination of CT, PET and endoscopic or endobronchial ultrasound results in a nodal failure rate of 10% only. In our study, we did not detect differences in recurrence rates and/or adjusted PFS and LCSS between SABR-treated patients and operated patients; however, this might be due to insufficient sample size.

As expected and reported before [13, 24, 30], death from other causes than NSCLC was more common among SABR patients. This finding challenges the use of OS in comparative studies, especially when the differences remain after statistical methods to reduce confounding by indication.

Strengths and limitations

The main strength of this study is that it contains detailed clinical data from a real-world series with modern staging, qualified treatment and long-term follow-up. By using clinical knowledge and previously published literature on this subject, we registered and adjusted for established confounders to make a proper comparison between both treatments. Moreover, through our dedicated data collection, we were able to report on different survival outcomes (PFS, OS and LCSS) and recurrences, which enables us to study underlying mechanisms in case of survival differences. However, residual (unknown) confounding might still remain (e.g. by expert knowledge or the 'gut feeling' of the doctors), which cannot be adjusted for in PS analyses. This is a limitation in observational studies and can only be avoided by performing an RCT. Since no RCT has been completed so far, an observational study with dedicated data collection and PS analyses is currently the best option to investigate the optimal treatment for stage I NSCLC.

Another limitation is the difficulty in determining if a death was due to NSCLC or due to another cause. In 30.2% of deceased patients, the cause of death was unknown. Rules with clinical substantiation were implemented to attribute these deaths to either NSCLC or another cause (Supplementary Material, Fig. S1). These limitations concerning cause of death must be considered when interpreting the LCSS.

Moreover, we did not record information about treatment of recurrences. Variation in recurrence management may lead to differences in OS and LCSS. However, before the introduction of immunotherapy with nivolumab in 2016 [31], the existing recurrence treatments were not likely to cause large differences in outcome.

Although this study is one of the largest PS studies published so far [24], the major limitation was that we still had insufficient statistical power to compare outcomes by PS analysis. An increased sample size is necessary to make a more precise estimate of survival outcomes for both treatment modalities.

Therefore, we are extending our study, including more than half of Dutch hospitals performing lung surgery or radiotherapy, aiming to include at least 1880 patients. This large cohort will also give us the opportunity to further reduce prognostic baseline differences by adjusting for more covariates (e.g. smoking status,

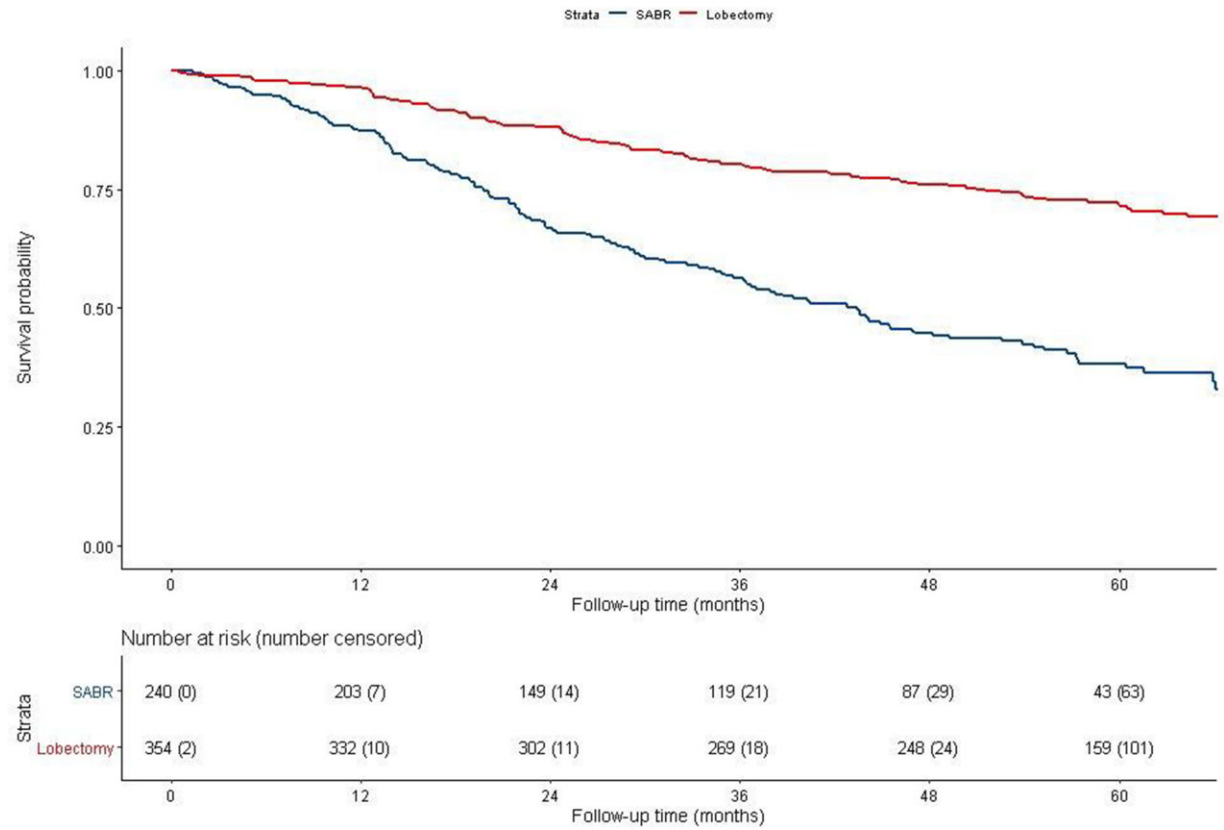

Figure 2: Overall survival (unadjusted) in patients treated with minimally invasive lobectomy or stereotactic ablative radiotherapy.

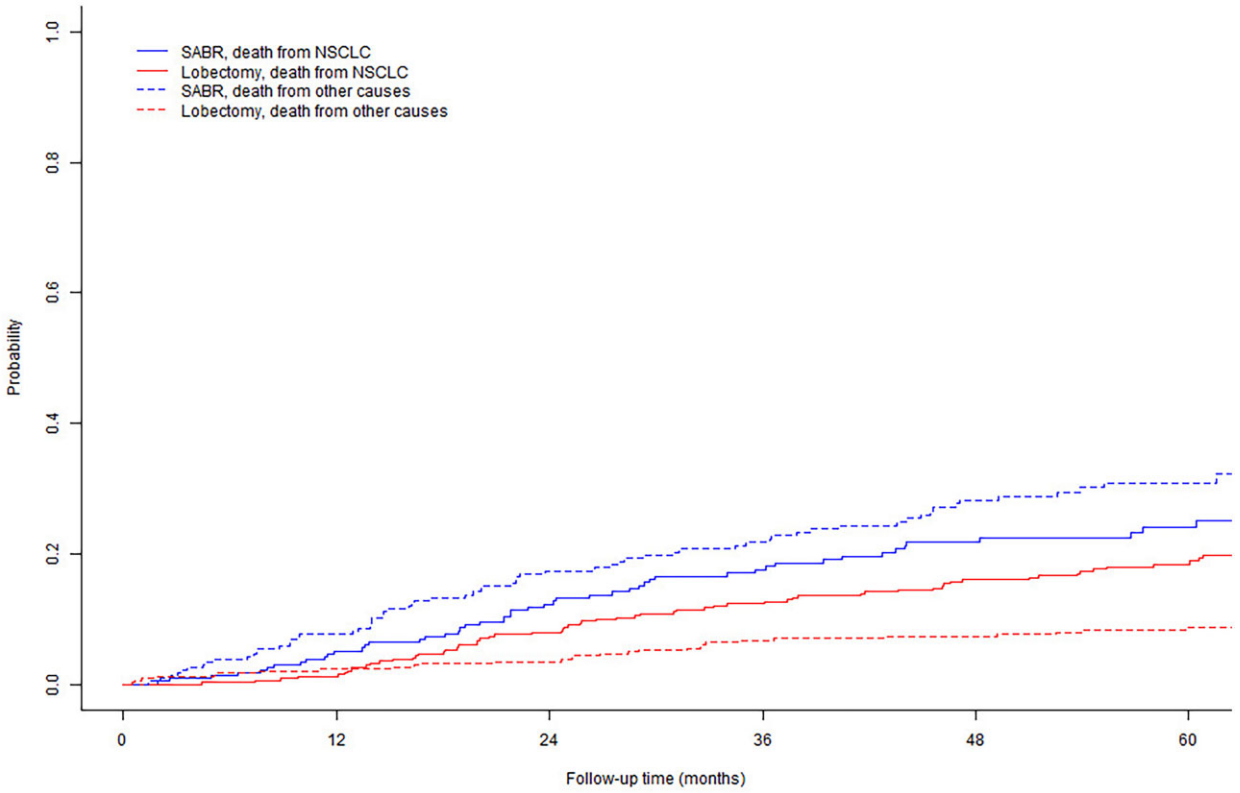

Figure 3: Lung cancer-specific mortality (unadjusted) in patients treated with minimally invasive lobectomy or stereotactic ablative radiotherapy.

history of interstitial lung disease and prior malignancies). We hypothesize that there is not one treatment modality that suits every stage I NSCLC patient best. Aim of our extended study is the identification of specific patient groups who are more eligible for either surgery or SABR, by performing comparative subgroup analyses, for example for different tumour sizes, histological subtypes, age groups, lung function values and patients with cardiopulmonary comorbidity. By analysing outcomes of the different treatment options for stage I NSCLC, we aim to offer patients the optimal treatment with curative intent, less recurrences and improved survival, taking into account individual patient and disease characteristics.

CONCLUSION

Unadjusted analyses comparing MIL and SABR revealed superior PFS and OS for MIL and similar LCSS. However, this feasibility study was not sufficiently powered to demonstrate significant differences using PS methodology. Therefore, the study is currently being extended to include more than half of Dutch hospitals to enlarge the population to ≥1880 patients, not only to determine the best treatment for patients with stage I NSCLC overall, but also to assess the preferred treatment for patient groups with specific characteristics.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

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