Clinical Outcomes in Early-stage NSCLC Treated with Stereotactic Body Radiotherapy *Versus* Surgical Resection

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Abstract. *Background: Surgical resection is the treatment of first choice for patients with stage I-II non-small cell lung cancer (NSCLC). However, stereotactic body radiotherapy (SBRT) has been shown to be a good alternative treatment. Patients and Methods: Overall survival (OS), progression-free survival (PFS) and recurrence rates were compared between patients with stage I-II NSCLC treated with SBRT (n=53) and those treated with surgical resection (n=175). The propensity score method was used to correct for confounding by indication. Results: Before correction, the OS and PFS rates at 1 and 3 years were significantly different between SBRT and surgery, in favor of surgery. After correction, the OS and PFS after SBRT were not significantly different compared to surgery. The recurrence rates for the two treatments were also similar both before and after correction. Conclusion: This retrospective study showed that clinical outcomes after SBRT are equal to those after surgery in patients with stage I-II NSCLC.*

Lung cancer remains the most common cause of cancer-specific mortality worldwide accounting for almost 20% of all cancer deaths per year. Most such cancer are non-small cell lung cancer (NSCLC), out of which 30-35% are diagnosed as stage I or II disease (1). The increased use of low-dose computed tomographic (CT) scan for the screening of lung cancer might increase the incidence of stage I and II NSCLC.

For patients with stage I and II NSCLC, anatomical surgical resection is the standard treatment (2, 3). However, due to comorbidities and poor pulmonary function, stereotactic body radiotherapy (SBRT) has emerged as an alternative treatment. The toxicity of SBRT is favorable because fewer than 10% of patients experience important side-effects (4). In addition, the pulmonary function does not deteriorate after SBRT, even in patients with poor baseline lung function (5). Several prospective studies with SBRT have shown a 2-year overall survival (OS) of 65-70%, with a 2-year local tumor control rate of more than 90% (2, 6). Even in specific patient groups, such as older patients or in patients with at least chronic obstructive pulmonary disease (COPD) GOLD III, the median OS and local control were comparable to outcomes of similar patients who underwent surgery (7, 8).

Multiple attempts were made to compare clinical outcomes after surgery and SBRT in patients with stage I or II NSCLC in a randomized prospective study, but none has been completed, in particular due to poor recruitment of patients. Zheng *et al*. compared treatment outcomes of SBRT with those of surgery in patients with operable stage I NSCLC. They concluded that after adjustment for age and operability, OS and disease-free survival were not significantly different between the two groups (9). More recent cohort studies that compared SBRT and surgery directly, mostly in stage I NSCLC, showed recurrence and survival rates that were comparable with the results of Zheng *et al*. (10-14). These results together make it fair to state that the outcomes after SBRT are comparable to those after surgical resection. However, confounding by indication might have influenced the results of these studies and the meta-analysis because the selection of patients for SBRT or surgical treatment is influenced by different patient characteristics, such as age, pulmonary function and performance score. As a result, the baseline characteristics of the two treatment groups might differ significantly. In the present study, we address this research question by taking into account this potential bias using the propensity score method. In our study, the propensity score was added as a covariate to the analysis to compare both treatment groups for the outcomes adjusted for patient characteristics (15).

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We compared OS, progression-free survival (PFS) and recurrence rates in patients with early-stage NSCLC treated with surgery or SBRT. In contrast to other studies we included both stage I and II NSCLC, all ages, patients with COPD GOLD I-IV and both kinds of surgery [thoracotomy as well as video-assisted thoracoscopic surgery (VATS)].

Patients and Methods

In this retrospective study, we included all patients diagnosed with stage I or II NSCLC between 2008 and 2011 in the Saint Antonius Hospital, Nieuwegein, the Netherlands, and were treated either with surgical resection or SBRT. Patients were excluded if they had recurrence of earlier diagnosed lung cancer, if they had received induction chemotherapy or radiotherapy, or if they had a double tumor prior to this study.

Data of the patients were collected by reviewing the patients' electronic medical records. The database of the Dutch Cancer Registry was also consulted to verify if all patients who received SBRT in the above-mentioned period were included in the database (16).

The diagnosis of NSCLC stage was evaluated as described by the regularly updated guideline Non-Small Cell Lung Cancer of the National Comprehensive Cancer network (http://www.nccn.org), and included a contrast enhancement on CT scan and an ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) scan. Staging of disease was performed according to the current international system for staging of lung cancer (seventh edition of TNM classification), which was revised in 2010 (17). Patients treated before 2010 were re-staged according to the current system. Patients with suspected nodal disease underwent a minimally invasive endoscopic biopsy. In the case of negative results, a mediastinoscopy was performed.

All patients were seen by a pulmonary physician and their cases were discussed weekly by the Multidisciplinary Pulmonary Oncology Panel comprising a pulmonary physician, thoracic surgeon, radiation oncologist and radiologist. Whether the patients underwent surgery or SBRT depends on their pulmonary function and Eastern Cooperative Oncology Group (ECOG) performance status. If patients eligible for radiotherapy were accepted for radiotherapy, they were referred for treatment to the University Medical Centre of Utrecht.

For most patients (70%) who received SBRT, a pathological diagnosis could not be made due to poor pulmonary function and the risk for complications when performing a biopsy. Therefore, the single pulmonary nodule (SPN) calculator was used to generate a percentage probability of malignancy. This SPN calculator can be found at http://www.chestx-ray.com. It is a convenient and reliable calculator which takes into account the likelihood ratios from a list of clinical and radiological factors (18).

Lung function, diffusing capacity for carbon monoxide (DLCO) and forced expiratory volume in one second (FEV_1), were determined according to the guidelines of the American Thoracic Society and the European Respiratory Society (19, 20).

Radiotherapy was delivered in an outpatient setting at the University Medical Centre of Utrecht. Different stereotactic regimens were used depending on tumor size and location: three fractions of 18 Gy, five fractions of 12 Gy, or eight fractions of 7.5 Gy. Patients were treated three times a week.

During surgery, nodal dissection was routinely carried out in accordance with the guidelines of the European Society of Thoracic Surgeons (21). The type of resection and type of incision were at the discretion of the treating surgeon. Most patients underwent thoracotomy but during the inclusion period, the number of VATS increased due to increasing experience of the surgeons. The surgical technique used for VATS was described earlier (22).

The follow-up schedule comprised clinical visits every 3 months during the first 2 years, and every 3-6 months thereafter for both patient groups. The usual follow-up procedures includes a physical examination, chest radiography and an evaluation of the serum tumor markers. A thoracoabdominal CT scan was mostly performed annually, in cases of changes on the chest radiography or suspected clinical symptoms. ^{18}F-FDG-PET scans were only performed when recurrence of disease was suspected.

The OS was defined as the time between the first date of treatment and the date of death from any cause or the end of follow-up with or without disease. The median follow-up was defined as the time from the start of treatment until death or end of follow-up. PFS was defined as the time from the start of treatment until tumor recurrence or death. Patients who were lost to follow-up were censored at the last date of follow-up. In December 2014, the last update was performed to complete 3 years' follow-up. Progression of disease was defined as locoregional recurrence (LRR) or distant recurrence (DR). For the patients who received SBRT, LRR was defined as recurrence in or adjacent to the planning target volume or in the ipsilateral hilum or mediastinum. For the patients who underwent surgery, LRR was defined as recurrence that arose at or adjacent to the surgical resection margins or in the ipsilateral hilum or mediastinum. Recurrence that could not be defined as LRR was considered as DR. Recurrence in patients who underwent surgery was confirmed either by biopsy or by ^{18}F-FDG-PET scan. Recurrence in the SBRT-treated patients was determined by biopsy, by ^{18}F-FDG-PET scan or determined as clinically based on imaging. The date of recurrence was the date of the first observation of the new lesion.

Statistical analysis. Continuous data are presented as the mean±standard deviation and differences per treatment group were tested by Student's *t*-test. Frequencies and percentages were used for categorical data and we used Pearson's chi-square test for statistical testing of differences between the treatment arms. Crude survival and recurrence rates for both treatment groups were evaluated and compared by Kaplan–Meier survival and Cox proportional hazard analyses.

To correct for potential bias in the selection of SBRT *versus* surgery (confounding by indication), the propensity score method was used (15). The propensity score was added as a covariate to the Cox proportional hazard analyses to compare both groups for outcomes adjusted for patient characteristics. For every patient, propensity scores were estimated by a logistic regression model that included the treatment group as dependent variable and age, gender, ECOG performance status, FEV_1, DLCO, clinical nodule diameter and clinical TNM classification as independent variables. Histology was not included in the propensity score because histology was not known for the majority of patients treated with SBRT. DLCO values were not available for four SBRT-treated and five surgical patients. These missing values were imputed by single imputation (23).

All statistical analyses were two-sided and values of $p<0.05$ were considered statistically significant. Statistical analyses were

performed with the SPSS statistical software program package version 22.0 (SPSS Inc., Chicago, IL, USA). Graphs were made by using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Results

Patients' characteristics. During the study period, 228 patients were included. Fifty-three patients were treated with SBRT. A surgical resection was performed in 175 patients, 104 of which by thoracotomy and 71 by VATS. The baseline characteristics of the two cohorts are listed in Table I. The surgical patients were more often male, significantly younger and had a significantly better performance score and pulmonary function than patients treated with SBRT. The patients who were treated with SBRT had significantly smaller tumors but the clinical TNM classification was not significantly different.

The median follow-up time for the entire cohort was 39.6 months (interquartile range (IQR)=23.0-54.9 months). The median follow-up time for the SBRT-treated patients was 31.8 months (IQR=19.0-48.0 months) and for the surgical patients was 41.5 months (IQR=27.5-57.2 months).

In the SBRT cohort, 15 patients received three fractions of 18 Gy, 25 five fractions of 12 Gy and 12 received eight fractions of 7.5 Gy. One patient had an adjusted schedule because of the central location of the tumor; he started with one fraction of 12 Gy followed by six fractions of 7.5 Gy.

In the surgical cohort, the median number of dissected lymph node zones was two (range=0-7). In 70 patients (40%) three or more lymph node zones were dissected. The median dissected number of lymph nodes per zone was one (range=0-17). In 34 patients, N1 nodal disease was detected, five of which were expected. N2 nodal disease was detected in 14 patients, four of which were expected to have N1 disease. The number of cases of N1 and N2 nodal disease was not significantly different between VATS and thoracotomy (p=0.11).

Disease in 26 patients (15%) was up-staged due to size of the tumor. Out of 19 patients diagnosed with stage 1A, 15 were up-staged to 1B, one to 2A, and three to 2B. Of six patients diagnosed with stage 1B, three were up-staged to 2A, two to 2B and one to 3A. One patient with stage 2A disease was up-staged to 2B.

Adjuvant treatment was given to 42 patients, 32 patients received chemotherapy, six patients received chemotherapy and radiotherapy and four patients received only radiotherapy. For 106 patients, no indication for adjuvant treatment was present. For another 27 patients, there was an indication for adjuvant chemotherapy with/without radiotherapy but 16 patients did not receive any adjuvant treatment due to poor performance and the remaining 11 patients refused adjuvant treatment.

Table I. *Baseline characteristics of the stereotactic body radiotherapy (SBRT) and surgical cohorts. Data are the mean (standard deviation) or number (%).*

	SBRT n=53	Surgery n=175	*p*-Value
Gender			
Male	19 (36%)	109 (62%)	0.001
Female	34 (64%)	66 (38%)	
Age (years)	71.6 (10.2)	66.5 (9.1)	0.001
Smoking status			
Non-smoker	0 (0%)	15 (9%)	0.0004
Smoker (<30 PY)	24 (45%)	70 (40%)	
Smoker (30-39 PY)	7 (13%)	30 (17%)	
Smoker (>40 PY)	15 (29%)	58 (33%)	
Unknown	7 (13%)	2 (1%)	
Location of the tumour			
Left upper lobe	13 (25%)	45 (26%)	0.98
Left lower lobe	9 (17%)	32 (18%)	
Right upper lobe and middle lobe	21 (40%)	65 (37%)	
Right lower lobe	10 (18%)	33 (19%)	
ECOG performance score			
0	20 (38%)	151 (86%)	<0.0001
1	30 (57%)	23 (13%)	
2	3 (5%)	1 (1%)	
Pulmonary function			
FEV1 (percentage of predicted)	56.6 (22.3)	87.1 (20.0)	<0.0001
DLCO (percentage of predicted)	50.8 (17.9)	73.5 (17.0)	<0.0001
SPN value	96.8 (10.9)	n.a.	
Morphology			<0.0001
Carcinoma NOS	37 (70%)	0 (0%)	
Large cell carcinoma	2 (4%)	10 (6%)	
Non small cell carcinoma	4 (8%)	3 (2%)	
Squamous cell carcinoma	5 (9%)	58 (33%)	
Adenocarcinoma	5 (9%)	104 (59%)	
Surgery	n.a.		n.a.
VATS		71 (41%)	
Thoracotomy		104 (59%)	
Lobectomy		140 (80%)	
Bilobectomy		9 (5%)	
Pneumonectomy		18 (10%)	
Wegde resection		5 (3%)	
Sleeve resection		3 (2%)	
Time to treatment (months)	2.3 (1.1)	1.8 (1.0)	0.003
cTNM			
1A	38 (72%)	93 (53%)	0.12
1B	7 (14%)	37 (21%)	
2A	4 (7%)	24 (14%)	
2B	4 (7%)	21 (12%)	
pTNM			
1A	n.a.	65 (37%)	n.a.
1B		36 (21%)	
2A		29 (17%)	
2B		26 (15%)	
3A		19 (10%)	
Clinical tumor diameter (cm)	2.3 (1.3)	3.1 (1.8)	0.007
Pathological tumor diameter (cm)	n.a.	3.3 (2.2)	n.a.

DLCO, Diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; n.a., not applicable; PY: pack years; SBRT, stereotactic body radiotherapy; SPN, single pulmonary nodule.

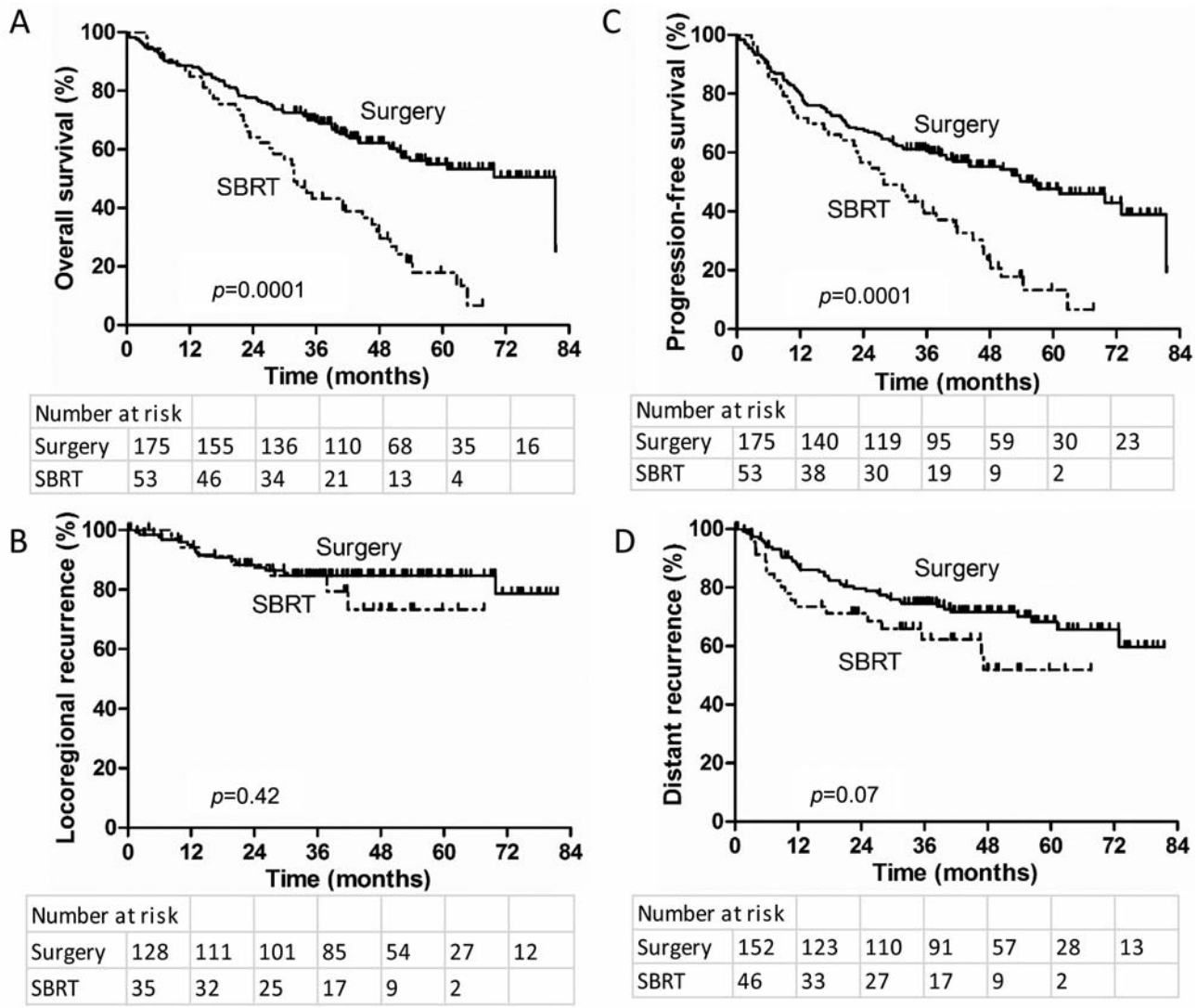

Figure 1. *Clinical outcomes (Kaplan–Meier analyses) for the unadjusted cohorts. Overall survival (A), progression-free survival (B), locoregional recurrence (C) and distant recurrence (D) after stereotactic body radiotherapy (SBRT) and surgery for early-stage non-small cell lung cancer. Time is months from the start of treatment. p-Values were derived from log-rank tests.*

Survival. There was no 30-day mortality and no 90-day mortality in the SBRT-treated patients. In the surgical patients, the 30-day mortality was 1.7% and the 90-day mortality 4%.

Before adjustment by propensity score, the OS rates at 1 and 3 years after SBRT were 87% and 43% and after surgery 89% and 70% (Hazard Ratio (HR)=2.42, 95% Confidence Interval (CI)=1.65-3.56; p=0.0001; Figure 1A, Table II). The PFS at 1 and 3 years was 72% and 39% after SBRT and 80% and 60% after surgery (HR=2.07, 95% CI=1.43-2.99; p=0.0001; Figure 1B). After adjustment with the propensity score method, the OS and PFS after SBRT were not significantly different compared to surgery (HR=1.71, 95% CI=0.87-3.35; p=0.12 and HR=1.56; 95% CI=0.83-2.93; p=0.17, respectively).

Recurrence. Recurrence of disease was detected in 25 (47%) SBRT-treated patients, compared to 62 (35%) surgical patients (p=0.19). In the SBRT-treated patients, 40% of recurrences were diagnosed by biopsy compared to 61% in the surgical group (p=0.02). The median time-to-recurrence in the SBRT cohort was 10.7 months and 16.3 months in the surgical cohort. Out of the 25 SBRT-treated patients who had recurrence of disease, seven (28%) developed LRR and 18 (72%) DR. Out of the 62 surgical patients who had recurrence of disease, 19 (31%) developed LRR and the other 43 (69%) DR. After VATS, 23 (33%) of the patients had recurrence of disease compared to 39 (37%) after thoracotomy (p=0.44). Five patients had LRR after VATS and 14 after thoracotomy

Table II. *Effect of treatment with surgery or stereotactic body radiotherapy (SBRT) on outcome in patients with stage I or II non-small cell lung cancer: Cox proportional hazard analyses, with crude values and values adjusted by the propensity score. Hazard ratio is surgery versus SBRT.*

Factor	Hazard ratio	95% Confidence interval	*p*-Value
Overall survival			
Crude	2.42	1.65-3.56	0.0001
Adjusted	1.71	0.87-3.35	0.12
Progression-free survival			
Crude	2.07	1.43-2.99	0.0001
Adjusted	1.56	0.83-2.93	0.17
Locoregional recurrence			
Crude	1.43	0.60-3.43	0.42
Adjusted	2.11	0.56-7.75	0.26
Distant recurrence			
Crude	1.67	0.96-3.92	0.07
Adjusted	1.24	0.48-3.20	0.65

(p=0.41). Four surgical patients were lost to follow-up and recurrence of disease was not known.

Before adjustment by the propensity score, the locoregional recurrence-free rates at 1 year after SBRT and surgery were 94% and 95%, respectively, and at 3 years 85% for both treatment groups (HR=1.43, 95% CI=0.60-3.43; p=0.42; Figure 1C). The distant recurrence-free rates at 1 and 3 years after SBRT were 73% and 62% and after surgery 88% and 74% (HR=1.67, 95% CI=0.96-3.92; p=0.07, Figure 1D). After adjustment with the propensity score method, the locoregional and distant recurrence-free rates between the two treatments were also not significantly different (HR=2.11, 95% CI=0.56-7.75; p=0.26 and HR=1.24, 95% CI=0.48-3.20; p=0.65, respectively).

Discussion

This retrospective study showed that after the use of the propensity score method to correct for confounding by indication, OS, PFS and recurrence rates of patients with early-stage lung cancer who were treated with SBRT are equal to surgical results. This suggests that despite the fact that surgical resection is still the standard treatment of early-stage NSCLC because of the lack of randomized controlled trials, SBRT might be considered a good alternative for such patients. SBRT is a treatment with a mild toxicity profile compared to surgery, and treatment-related deaths were not observed. Another important consideration for patients fit enough for surgery but who choose to have SBRT is that salvage surgery might be feasible when local recurrence develops (24).

Although different studies have already analyzed recurrence rates and survival after surgery and SBRT in patients with early-stage lung cancer, as far as we are aware of, this is the first study to compare treatment outcomes of both stage I and II NSCLC after surgical resection, thoracotomy as well as VATS, and SBRT. Furthermore, the inclusion of patients was not restricted to a specific patient group, *i.e.* only elderly or patients with COPD GOLD I or II.

The ability to accurately stage nodal disease has been deemed an advantage of surgery because surgery will show that up to 20% of patients with clinical stage I NSCLC have occult nodal metastases (25). It is known that tumors detected by screening have a lower incidence of unexpected nodal disease (26), but during the treatment period of this study (2008-2011), screening of high-risk patients was not common in daily practice. In this cohort, 22% of patients had unexpected nodal disease. This suggests that a proportion of patients who received SBRT also have undiagnosed nodal disease and receive no adjuvant treatment. Nevertheless, these patients did not have a shorter OS or higher recurrence rate compared to surgical patients. This might be due to several reasons. Firstly, SBRT for early-stage lung cancer results in a significant radiotherapy dose to draining lymph nodes. This dose may be sufficient to eliminate subclinical microscopic disease (27). Another reasonable explanation for the low recurrence rate after SBRT can be found in the interaction between the radiotherapy dose and the immune system. SBRT induces expression of tumor necrosis factor-α and other cytokines and stimulates the $CD4^+$ and $CD8^+$ T-cell-mediated immunity, which leads to the eradication of occult regional micrometastases (28). In contrast to SBRT, surgical procedures are associated with transient postoperative decrease in cell-mediated immunity (29). Finally, an explanation for low nodal recurrence after SBRT despite the lack of nodal staging can be found in the selection of patients. Many SBRT-treated patients are medically inoperable due to poor pulmonary function and may undergo frequent chest imaging, which might lead to early tumor detection. This is supported by our results, which show significantly smaller tumors in SBRT-treated patients compared to surgical patients. In addition, many patients with poor pulmonary function also suffer from other comorbidities that may contribute to death from other causes before nodal recurrence is detected.

Recent literature showed that lobectomy by VATS was associated with a reduced disruption of the innate immune response compared with conventional thoracotomy, which might also lead to better survival (30). Two other trials showed a similar OS and disease-free survival and even better local control after VATS compared with thoracotomy (31, 32). We performed a sub-group analysis which showed no difference in OS, PFS and recurrence rates after VATS compared to thoracotomy.

In our SBRT cohort, 30% of diagnoses were biopsy-proven. This might lead to inclusion of patients with benign lesions with better clinical outcomes. For patients without a tissue-based diagnosis who are treated with SBRT, an 85% likelihood of malignancy has been suggested (33). We determined the percentage probability of malignancy in the SBRT cohort using the SPN calculator (http://www.chestx-ray.com). The mean value was 96.8%, which suggests that for most patients without a pathological diagnosis, treatment with SBRT was based on the correct assumption.

Our study has several limitations. Firstly, this study has a retrospective design. Secondly, compared to several other studies, we did not perform propensity score matching prior to the analysis (11, 13, 14). However, in the process of analyzing our data, we did perform propensity score matching with a caliper width of 0.2 without replacement. This matching process based on the propensity score resulted in 23 SBRT-treated patients and 23 surgical patients of which in the surgical cohort no patients were diagnosed with distant recurrence. In conclusion, these 46 patients were not representative of the total cohort of 228 patients and, therefore, were not suitable for further analysis. Therefore, we chose to perform an adjustment using the propensity score (15). This propensity score method prevents patients being excluded because no suitable match was found. Not all differences between treatment groups might be captured with propensity score matching, as matching can be done with only a limited number of variables. Furthermore, inclusion of some important variables, such as staging procedure, would limit the number of patients for matching as described by Mokhles *et al*. (11). Thirdly, lobectomy via VATS was introduced at the Saint Antonius Hospital in 2009. Before 2009, only non-anatomical resections were carried out by VATS. Poorer outcome in the early period after introduction of VATS might exist due to the learning curve necessary for achieving optimal performance of resections (34). Furthermore, the VATS technique used in this study is different from that described in other studies, which makes a direct comparison with other studies difficult (22, 34). Fourthly, compared with other studies, we did not perform CT scans on a regular basis, only on indication as described above. This could lead to a delay in the diagnosis of recurrence. However, the median time to recurrence in our study was 10.7 and 16.3 months for SBRT-treated and surgical groups, respectively, which was not longer compared with others who reported times of 10 to 11.3 months for SBRT and 8.2 to 10 months for surgery (11, 14). Finally, in cases of recurrence of disease after SBRT, a confirmatory biopsy was not available for the majority (60%) of the patients. For these patients, recurrence of disease was diagnosed based on imaging, which could have led to overestimation of the recurrence rate after SBRT.

Nowadays, the choice of treatment, surgical resection or SBRT, for early-stage NCSLC is made based on several variables such as patient characteristics, tumor characteristics and local practice (35). Personalized predictive models to assess the risk of mortality for a patient based on their characteristics and tumor characteristics are not yet available. Mokhles *et al*. suggested that long-term survival of patients with NSCLC might be optimized by focusing on patient- and tumor-specific factors in addition to the TNM classification (35). The development of a personalized treatment model to determine the best treatment for a patient with early-stage NSCLC based on several such characteristics might be the next step in the treatment of these patients.

Our study showed that the OS, PFS and recurrence rates in patients with stage I or II NSCLC after SBRT are not inferior compared with those after surgical resection. However, randomized controlled trials are needed to support these findings. Due to the lack of these trials, a thorough discussion of individual patient's merits and drawbacks of surgical resection and SBRT should be the cornerstone of the treatment of early-stage NSCLC. These merits and drawbacks not only include outcome, but also aspects such as quality of life, treatment toxicity, and cost-effectiveness. The final decision for the optimal treatment of a patient with early-stage NSCLC can be substantiated by a personalized treatment model which includes patient and tumor characteristics.

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