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The role of surgery for stage I non-small cell lung cancer in octogenarians in the era of stereotactic body radiotherapy in the Netherlands

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ABSTRACT

Objectives: Resection is the standard treatment for stage I non-small cell lung cancer (NSCLC) in operable patients. Stereotactic body radiotherapy (SBRT) is recommended for inoperable patients. A shift from surgery to SBRT is expected in elderly patients due to increased frailty and competing risks. We assessed the current influence of age on treatment decision-making and overall survival (OS).
Materials and methods: We performed a retrospective cohort study using data from patients with clinical stage I NSCLC diagnosed in 2012–2016 and treated with lobectomy, segmentectomy, wedge resection, or SBRT, retrieved from the Netherlands Cancer Registry. Patient characteristics and OS were compared between SBRT and (sub)lobar resection for patients aged 18 − 79 and ≥ 80 years.
Results and Conclusion: 8764 patients treated with lobectomy (n = 4648), segmentectomy (n = 122), wedge resection (n = 272), or SBRT (n = 3722) were included. In 2012–2016, SBRT was increasingly used for octogenarians and younger patients from 75.3% to 83.7% and from 30.8% to 43.2%, respectively. Five-year OS in the whole population was 70% after surgery versus 39% after SBRT and 50% versus 27% in octogenarians. After correction for age, gender, year of diagnosis, and clinical T-stage, OS was equal after lobectomy and SBRT in the first 2 years after diagnosis. However, after > 2 years, OS was better after lobectomy than after SBRT.

SBRT is the prevailing treatment in octogenarians with stage I NSCLC. While surgery is associated with better OS than SBRT, factors other than treatment modality (e.g. comorbidity) may have had a significant impact on survival. The wider application of SBRT in octogenarians likely reflects the frailty of this group. Registries and trials are required to identify key determinants of frailty in this specific population to improve patient selection for surgery or SBRT.

1. Introduction

Anatomical surgical resection is considered the standard treatment for stage I non-small cell lung cancer (NSCLC) in medically operable patients [1,2]. Historically, patients received conventional radiotherapy if considered inoperable, frequently being elderly patients with comorbidities or impaired pulmonary function. However, radiotherapy for these patients was associated with only a modest survival benefit compared to best supportive care due to a high local recurrence rate [3,4]. Due to the moderate survival rates and the side effects of conventional radiotherapy, 32% of elderly patients (≥ 75 years) with early-stage NSCLC did not receive treatment with curative intent in 2001 in the Netherlands [5]. After the introduction of stereotactic body radiotherapy (SBRT) as a potential curative treatment of NSCLC in 2003, the proportion of Dutch elderly patients undergoing non-curative treatment decreased to 19% around 2013 [6]. The recent phase 3 CHISEL trial confirmed the effectiveness and superiority of SBRT over conventional radiotherapy in inoperable early-stage NSCLC [7]. Also in the

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population aged ≥80 years, the effectiveness and safety of SBRT were demonstrated [8]. Since surgery is associated with a risk of postoperative complications up to 30% and increasing procedure-related mortality in the elderly population [9–11], we hypothesized that treatment for stage I NSCLC has shifted from surgery to SBRT in this patient group. Since the proportion of patients aged ≥80 years and diagnosed with stage I NSCLC has currently increased to 12% in the Netherlands [12], effort is needed to understand the influence of old age on treatment decision-making and survival. For this purpose, we reviewed data from the Netherlands Cancer Registry (NCR) in the period 2012-2016 and compared treatment decisions and survival among the octogenarian population with stage I NSCLC with those among the population aged 18−79 years.

2. Materials and methods

2.1. The Netherlands Cancer Registry

The NCR collects data on all cancer patients diagnosed in the Netherlands. It is notified of newly diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Data on demographics, diagnosis, staging, and treatment is extracted from medical records by NCR personnel. Survival status is updated annually via a computerized link with the national civil registry. This study was approved by the NCR Privacy Review Board. In accordance with the regulations of the Central Committee on Research involving Human Subjects, this type of study did not require approval from an ethics committee in the Netherlands.

2.2. Patient population

Data from 11,802 patients diagnosed with clinical stage I NSCLC from 1 January 2012 to 31 December 2016 were retrospectively retrieved from the NCR. The study population consisted of patients who were treated either with SBRT or (sub)lobar resection with curative intent for stage I NSCLC based on the 7th edition of the Union for International Cancer Control TNM classification [13]. Diagnosis of stage I NSCLC was generally based on positron emission tomography (PET) and/or computed tomography (CT) findings, preferably confirmed by histology or cytology. The following patients were excluded: age < 18 years (n = 4); synchronous (n = 738) or metachronous tumours (n = 552); patients treated with best supportive care (n = 805), chemotherapy or chemoradiotherapy (n = 119), neoadjuvant treatment before surgery (n = 26), conventionally fractionated radiotherapy (n = 314), bi-lobectomy or pneumonectomy (n = 442), or other surgical/bronchoscopic intervention (e.g. endoluminal laser therapy, cryotherapy, etc.) (n = 38). After exclusion, 8764 patients were eligible for analysis.

2.3. Statistical analysis

Study size was determined by a convenience sample, anticipating more than 200 octogenarians who were operated. Patients were stratified by age (18−59, 60−69, 70−79, ≥80 years), gender, TNM clinical T-stage (cT; 1A, 1B, 2A), and year of diagnosis. Parameters predictive of treatment choice were assessed by tabulations and tested for significance with chi-square testing. Patients undergoing resection were subdivided in age groups 18−79 years and ≥80 years to investigate the influence of age ≥80 years on surgical extent, surgical approach, delivery of systemic adjuvant therapy, and postoperative 90-day mortality.

Overall survival (OS) was calculated from day of diagnosis until day of death or 1 February 2019 using Kaplan-Meier analysis. Differences in survival between patients treated by SBRT or surgery were plotted, stratified by age group.

Multivariable survival analysis was performed using proportional hazards regression analysis, to compare lobectomy versus SBRT, segmentectomy, and wedge resection. Covariates included in the regression model were age, gender, cT, and year of diagnosis. One additional model was constructed to compare video-assisted thoracoscopic surgery (VATS) and open resections, with conversions designated as VATS. A second additional model was developed to compare tumours with and without pathological confirmation of malignancy in patients treated with SBRT. Prognostic impact is represented by hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was tested with log-log plots and appeared to be violated for the variable treatment as the hazard ratio between SBRT and surgery varied considerably over time since diagnosis. This issue was resolved by applying stratified models to assess the prognostic impact of treatment in the first two years versus later years. P-values < 0.05 were considered statistically significant. All analyses were performed in Stata V14 (College Station, TX, USA).

3. Results

3.1. Patient characteristics

A total of 8764 patients were included. Patient characteristics are shown in Table 1. The median age was 74 years for patients treated with SBRT and 66 years for patients receiving a resection. Patients with larger tumours underwent a lobectomy more frequently, whereas sublobar resections were mainly performed for T1a tumours. Of the 3722 SBRT patients, 1800 (48%) were pathologically confirmed (data not shown). Among all patients who had either a (sub)lobar resection or SBRT for stage I NSCLC, the proportion of patients receiving SBRT increased from 36.1% in 2012 to 48.5% in 2016. In the age groups 18−79 years and ≥80 years, the proportion of patients receiving SBRT in this period increased from 30.8% to 43.2% and from 75.3% to 83.7%, respectively (data not shown separately).

Table 2 shows characteristics for surgically treated patients when stratified based on age (18−79 years versus ≥80 years). There was no significant difference in the proportion of sublobar resections (10.2% versus 7.7%), nor in the proportion of resections performed with VATS (83.7% versus 77.8%) for octogenarians versus younger patients. The percentages of postsurgical pathological upstaging to stage II or higher were similar in the octogenarian and younger population (20.9% versus 20.7%). Upstaging after sublobar resections is less common than after lobectomies (10.4% versus 21.6%). After postsurgical pathological examination, 12.5% of patients aged 18-79 years and 3.3% of patients aged ≥80 years received adjuvant chemotherapy or radiotherapy combined with chemotherapy. 90-day mortality after surgery was

Table 1
Patient characteristics.

		SBRT		Sublobar resection		Lobectomy		
		n	%	n	%	n	%	P-value
Age	18−59	317	20.2	92	5.8	1164	74.0	< 0.001
	60−69	962	32.5	148	5.0	1848	62.5	
	70−79	1548	49.6	132	4.2	1443	46.2	
	≥80	895	80.6	22	2.0	193	17.4	
Gender	Men	2110	44.8	167	3.5	2429	51.6	< 0.001
	Women	1612	39.7	227	5.6	2219	54.7	
cT	1A	1860	47.3	289	7.3	1784	45.4	< 0.001
	1B	1012	43.4	65	2.8	1253	53.8	
	2A	850	34.0	40	1.6	1611	64.4	
Year	2012	540	36.1	70	4.7	885	59.2	< 0.001
	2013	630	38.2	72	4.4	946	57.4	
	2014	705	41.6	79	4.7	912	53.8	
	2015	884	45.5	77	4.0	980	50.5	
	2016	963	48.5	96	4.8	925	46.6	
Total		3722		394		4648		

Abbreviations: cT, clinical T-stage; SBRT, stereotactic body radiotherapy.

Table 2
Characteristics of patients undergoing (sub)lobar resection, stratified by age groups 18-79 years and ≥80 years.

		Age 18−79				Age ≥80			
		Sublobar resection		Lobectomy		Sublobar resection		Lobectomy	
		n	%	n	%	n	%	n	%
Surgical approach	VATS	269	72.3	3486	81.9	21	95.5	159	82.4
	Open	103	27.7	969	18.1	1	4.5	34	17.6
Surgical extent (sublobar resections)	Wedge resection	257	69.1	–	–	15	68.2	–	–
	Segmentectomy	115	30.9	–	–	7	31.8	–	–
p-stage	I	333	89.5	3495	78.5	20	90.9	150	77.7
	≥II	39	10.5	960	21.5	2	9.1	43	22.3
Systemic adjuvant therapy		19	5.1	586	13.2	1	4.5	6	3.1
Mortality	POM90	3	0.8	74	1.7	2	9.1	11	5.7
Total		372		4455		22		193	

Abbreviations: POM90, 90-day postoperative mortality; p-stage, pathological stage; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracoscopic surgery.

0.6%, 1.8%, 2.2% and 6.1% for age groups 18-59, 60-79, 70-79 and ≥80 years old, respectively.

3.2. Overall survival by treatment

In total, 3357 of 8764 (38%) patients had died and median follow-up for censored patients was 48 months. Five-year OS was 70% for surgery (i.e. lobectomy and sublobar resection) versus 39% for SBRT. Fig. 1a-d shows survival curves for both treatments, stratified by age group. In all age categories, five-year OS was significantly better for surgery compared to SBRT: 80% versus 56%, 73% versus 46%, 62% versus 39%, and 50% versus 27% for age groups 18-59, 60-79, 70-79 and ≥80 years, respectively. Median survival was 46 months for all SBRT patients. Median survival was not reached among all operated patients (70% survived longer than 60 months). For octogenarians, median survival was 58 months after surgery and 37 months after SBRT. Fig. 1d shows an initial higher mortality rate after a (sub)lobar resection among octogenarians. However, after 14 months, survival is better after a (sub)lobar resection in this age group.

Table 3 shows a major difference in hazard ratios between the univariable and the two multivariable analyses. In the first period, 0−2 years after diagnosis, survival after lobectomy does not differ from SBRT (HR 0.99, 95% CI 0.89-1.11). Prognosis after wedge resection is significantly worse compared to lobectomy (HR 1.96, 95% CI 1.08-3.58), whereas results of segmentectomy are similar (HR 1.29, 95% CI 0.93-1.79). In the second period, > 2 years after diagnosis, survival is

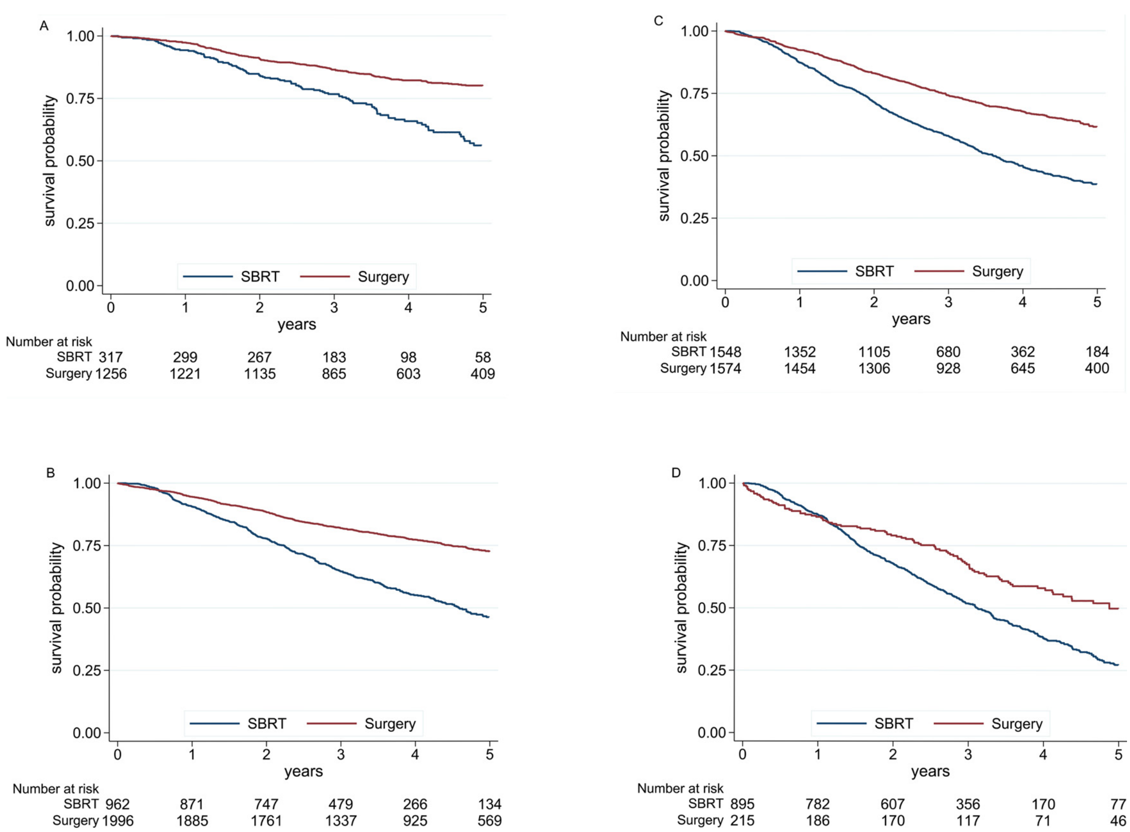

Fig. 1. a-d. Overall survival by treatment, stratified by age group.
a) 18−59; b) 60−69; c) 70−79; d) ≥80 years.
Abbreviations: SBRT, stereotactic body radiotherapy.

Table 3
Multivariable survival analysis, stratified by time since diagnosis.

		Univariable		Multivariable 0 – 2 years		Multivariable > 2 years	
		HR	95% CI	HR	95% CI	HR	95% CI
Age	18 – 59	1		1		1	
	60 – 69	1.64	1.45 – 1.85	1.24	1.04 – 1.49	1.57	1.32 – 1.86
	70 – 79	2.52	2.24 – 2.84	1.23	1.03 – 1.46	2.01	1.69 – 2.38
	≥ 80	3.86	3.38 – 4.40	1.33	1.09 – 1.64	2.58	2.12 – 3.15
Gender	Men	1		1		1	
	Women	0.67	0.62 – 0.71	0.95	0.86 – 1.05	0.83	0.75 – 0.91
Year		0.98	0.95 – 1.01	0.98	0.95 – 1.01	0.96	0.92 – 1.00
cT	1A	1		1		1	
	1B	1.18	1.08 – 1.28	1.03	0.91 – 1.17	1.11	0.99 – 1.25
	2A	1.51	1.40 – 1.64	1.11	0.99 – 1.25	1.43	1.28 – 1.61
Treatment	Lobectomy	1		1		1	
	Segmentectomy	0.82	0.56 – 1.20	1.29	0.93 – 1.79	1.05	0.64 – 1.72
	Wedge resection	1.10	0.88 – 1.38	1.96	1.08 – 3.58	1.11	0.80 – 1.54
	SBRT	2.48	2.31 – 2.66	0.99	0.89 – 1.11	2.43	2.19 – 2.71

Abbreviations: HR, hazard ratio; CI, confidence interval; cT, clinical T-stage; SBRT, stereotactic body radiotherapy.

clearly worse after SBRT (HR 2.43, 95% CI 2.19-2.71). The poorer survival in octogenarians was more pronounced in the second period: HR 1.33 (95% CI 1.09-1.64) in period 1 versus HR 2.58 (95% CI 2.12-3.15) in period 2. Additional analyses (data not shown) revealed similar survival after thoracoscopic versus open surgery (HR 0.98, 95% CI 0.87-1.11) and poorer survival in SBRT cases with pathological confirmation of lung cancer compared to SBRT cases without pathological confirmation (HR 1.22, 95% CI 1.11-1.33).

4. Discussion

4.1. Main outcomes

Our study shows that age is an important determinant for treatment choice for patients with stage I NSCLC. Surgery is clearly preferred in younger patients, while SBRT is the most common treatment among octogenarians. However, our results show that even among octogenarians, survival is considerably better after surgery. Unfortunately, treatment results cannot readily be compared in observational studies due to confounding by indication. Fit patients will be selected for surgery, while frail patients are more likely to be treated with SBRT. The major limitation of our analyses is that we could not control for variation in comorbidity, pulmonary function, and performance status. However, even if this information was available, disparity between treatment groups cannot fully be resolved by propensity score methodology [14].

In contrast, survival outcomes after SBRT may be overrated due to two factors. First, SBRT was mainly performed for cT1a tumours, whereas cT2a tumours were more often treated with a lobectomy. Secondly, only 48% of patients treated with SBRT had pathological confirmation of malignancy, against 100% for the surgical series. With the possible inclusion of benign lesions, survival after SBRT might be biased and overestimated. Our data showed that among patients treated with SBRT, there was a survival deficit for patients with pathology-verified malignancy, which is concordant with a recent meta-analysis by IJsseldijk et al. [15]. The high proportion of SBRT-treated patients without pathological confirmation might be explained by the ESMO guideline stating that treatment is warranted when the risk of malignancy is over 85% based on PET-CT findings [1,16,17].

4.2. Surgical strategies for octogenarians

Old age (≥80 years) was not associated with increases in sublobar resections and resections performed with VATS compared to younger patients. When a (sub)lobar resection was performed, lobectomy was the preferred type of resection (89.8% of operated patients aged ≥80 years). Sublobar resections were mainly performed for cT1a tumours. VATS was the preferred technique if a surgical procedure was performed (83.7% of procedures in patients aged ≥80 years).

Although a sublobar resection leads to more remaining lung parenchyma, more lung function preservation, and better perioperative outcomes compared to a lobectomy [18,19], octogenarians did not have sublobar resections more often than younger patients. Sublobar resections, in particular wedge resections, might be inferior to lobectomies as a result of inadequate intrapulmonary lymph node dissection, leading to higher cancer-specific mortality [20,21]. However, in patients with cT1a tumours, the intrapulmonary lymph node dissection might have a smaller impact because of the relatively small risk of nodal upstaging in these tumours [22].

In contrast, in this study we observed equal survival after sublobar resections (wedge resection and segmentectomy) and lobectomies on the long term (after > 2 years of follow-up). The worse survival seen in the first 2 years after wedge resection might be explained by confounding by indication, because more patients with a poor baseline prognosis might have been selected for this type of resection. This assumption is supported by a meta-analysis comparing lobectomy and sublobar resection, which concluded that survival after a sublobar resection was worse in the whole patient population, but that comparable survival rates were achieved in patients who could have tolerated either operation [23]. The favourable long-term results suggest that a sublobar resection (preferably an anatomical segmentectomy) should be considered in patients who are unfit to undergo a lobectomy. Hence, it seems remarkable that sublobar resections, especially segmentectomies, were not increasingly performed in elderly patients with more comorbidity compared to younger patients. It is likely that due to the introduction of SBRT, patients who are unfit for a lobectomy were referred for SBRT instead of a sublobar resection. Whether this policy is commendable remains to be elucidated. Retrospective studies showed considerably better outcomes after sublobar resection compared to SBRT [24,25], however, results from randomized trials are needed for treatment guidance in patients who cannot tolerate a lobectomy.

VATS resection was not more common among octogenarians. This might be explained by the fact that surgical approach is mainly determined by the location of the lesion [26]. VATS was not associated with improved survival compared to open procedures, which is in accordance with results from a propensity score analysis by Yang et al. [27]. Yet, literature suggests that VATS should be preferred over a thoracotomy because of a shorter hospital stay, less postoperative pain, and a better quality of life in the first year after operation among patients undergoing VATS [27,28]. Currently, the effectiveness, cost-effectiveness, and acceptability of VATS lobectomy versus open surgery are being studied in the VIOLET trial [NCT03521375], which is expected to be completed in September 2020.

In case of postsurgical pathological upstaging to a stage II or higher, guidelines advise systemic adjuvant therapy to increase cancer-specific survival probability [29]. However, systemic adjuvant treatment was considerably less frequently used among octogenarians compared to the younger population, probably due to worse tolerance in case of severe comorbidity, a poor performance score, or by refusal of the patient, which is more frequently encountered in the elderly population [30]. Therefore, the impact of a systematic lymph node examination is smaller with regard to the use of adjuvant chemotherapy in the elderly population compared to younger patients. However, it may improve local control.

4.3. Survival

We compared absolute survival between surgical resection and SBRT and found a considerable survival difference between the two modalities, which was similar in all age groups. Among octogenarians, five-year OS was 50% after surgery. Studies performed in Japan [31] and Italy [32] reported higher survival rates of 57.5% and 60%, respectively. In contrast, a nationwide study in the USA reported a five-year OS of 40% after surgery [33]. The variation in survival rates may be explained by differences in patient selection for surgical resection. Stringent selection criteria for surgery will yield better survival in the surgery subgroup but may reduce survival in the overall series of patients with stage I NSCLC.

Octogenarians had a worse survival and were less often treated with surgery when compared to younger age groups, which likely reflects the frailty of this population with competing risks. The fact that the survival difference between surgical resection and SBRT remained constant with increasing age, suggests that the selection of elderly patients for surgical resection was performed properly in the Netherlands. However, patient selection for either surgical resection or SBRT could possibly be improved with future research investigating key determinants of frailty in the octogenarian population.

So far, no studies have been published comparing surgical resection and SBRT in the octogenarian population. In a population with a mean age of 75 years, Shirvani et al. found similar results, showing that SBRT was associated with a better OS in the first six months after diagnosis, but with worse survival thereafter [34]. Detillon et al. also reported results supporting better long-term outcome after surgery in patients aged ≥65 years [35]. The initial higher mortality in octogenarians undergoing surgical resection is concordant with an earlier reported association between age and postoperative mortality [9]. The excess mortality might be explained by the increased prevalence of cardiopulmonary comorbidity in elderly patients, putting them at higher risk of death from complications [9,36]. Therefore, the risk of complications should be carefully weighed against the possible benefit of surgery on the long term, based on the condition and preferences of the patient.

Several phase III randomized trials have been initiated in order to make a proper comparison between surgery and SBRT in patients with operable early-stage NSCLC: the ROSEL trial [NCT00687986], the STARS trial [NCT00840749], and the ACOSOG Z4099 trial [NCT01336894] compared outcomes between the two treatment modalities for patients with resectable and operable early-stage NSCLC, but all three studies failed to complete accrual. Results from three prospective randomized trials (STABLE-MATES, POSTILV, and VALOR) are expected in 2024, 2026 and 2027, respectively. However, it is not clear whether these randomized studies will have sufficient patient inclusion for results to be published over at least 4–7 years. For instance, the SABRTOOTH study [NCT02629458], a study comparing SABR and surgery in high risk patients with stage I NSCLC, had difficulties in accrual due to patient preferences. Patients preferred one treatment over the other, making it not feasible to conduct a large randomized controlled trial in the United Kingdom. Moreover, only the VALOR trial includes solely anatomical resections (lobectomies and segmentectomies; no wedge resections). Finally, to enable a valid comparison between these two treatment options among specific patient subgroups (e.g. octogenarians), registration and analysis of detailed prospective observational data is necessary, using modern methodology such as propensity matching.

4.4. Strengths and weaknesses

The main strength of this study is that it is population-based, including 8764 patients among which 215 surgically treated octogenarians. These real world data give a good reflection of Dutch clinical practice. Nonetheless, comparison of absolute survival rates might be confounded by differences in baseline prognosis between patients treated with a resection or SBRT. Fit patients are selected for surgery, while patients receiving SBRT are often inoperable due to comorbidities, poor pulmonary function, and a poor performance score, factors that are associated with an inferior prognosis [37]. After correction for age, gender, incidence year, and clinical T-stage, the difference in survival rates between surgery and SBRT decreased, confirming the existence of prognostic disparity between the two groups regardless of the treatment given and probably reflecting the transition of operable patients with minor comorbidity to the SBRT group in time. However, further adjustment for prognostic factors was not possible, since information on comorbidity, performance status and complications is not registered in the NCR database. Consequently, proper comparison of survival outcome after surgery and SBRT was not feasible. Moreover, progression-free survival could not be estimated, since no data on recurrences were available from the NCR database. Finally, information from the Dutch Central Bureau of Statistics on cause of death was not available due to privacy restrictions, making it impossible to differentiate between cancer-specific death and death from other causes. Therefore, we were unable to study the differences in (non-)cancer-related mortality between the surgery and SBRT group.

5. Conclusions

In conclusion, SBRT has become the prevailing treatment for octogenarians with stage I NSCLC. While surgical resection is associated with better survival than SBRT, factors other than the treatment modality, such as comorbidity, pulmonary function, and performance score, may have had significant impact on survival. The wider application of SBRT in octogenarians likely reflects the frailty of this age group with competing risks. Dedicated clinical registries and prospective trials are required to identify key determinants of frailty in this specific population in order to improve patient selection for SBRT or surgery.

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CRediT authorship contribution statement

Julianne C de Ruiter: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Project administration. **David J Heineman:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Johannes MA Daniels:** Investigation, Writing - review & editing. **Judi NA van Diessen:** Investigation, Writing - review & editing. **Ronald AM Damhuis:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Visualization. **Koen J Hartemink:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.04.005.

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