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SBRT of lung cancer

Treatment of stage I NSCLC in elderly patients: A population-based matched-pair comparison of stereotactic radiotherapy versus surgery ☆

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ABSTRACT

Background: Elderly patients with stage I NSCLC who undergo surgical resection are at high risk of treatment-related toxicity. Stereotactic body radiation therapy (SBRT) may provide an alternative treatment with a favorable toxicity profile.

Methods: A population-based registry in North-Holland was used to conduct a matched-pair analysis of overall survival (OS) after surgery versus SBRT for elderly patients (age $\geqslant$75) who were diagnosed between 2005 and 2007. Patients were matched by age, stage, gender, and treatment year; co-morbidity data was not available. SBRT was delivered at two centers; 17 centers provided surgery.

Results: A total of 120 patients could be matched (60 surgery, 60 SBRT). Median age was 79 years, 67% were male, and 64% had T1 disease. Median follow-up was 43 months. Thirty-day mortality was 8.3% after surgery and 1.7% after SBRT. OS at one- and three-years was 75% and 60% after surgery, and 87% and 42% after SBRT, respectively (log-rank $p = 0.22$). Limiting the analysis to SBRT patients with pathological confirmation of disease and their matches revealed no significant difference between groups.

Conclusion: Similar OS outcomes are achieved with surgery or SBRT for stage I NSCLC in elderly patients. Comorbidity data and outcomes from centralized surgical programs are needed for more robust conclusions.

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The treatment of elderly patients with stage I non-small cell lung cancer (NSCLC) presents a therapeutic challenge to patients and clinicians. Although stage I NSCLC is localized and, therefore, theoretically curable, treatment can be hampered by medical co-morbidity, frailty, lack of access to care, or unwillingness to pursue treatment on the part of the patient or physician [1,2]. As a result, some patients do not receive curative-intent treatment [3] and these untreated patients can have poor survival outcomes [4]. Unfortunately, this clinical scenario is increasingly common: lung cancer is already a disease of the elderly (with one-third of patients older than 75), and changing population demographics in many countries are expected to further increase the number of cases in elderly patients [1,5].

The introduction of stereotactic body radiation therapy (SBRT; also known as stereotactic ablative radiotherapy) for stage I NSCLC has led to an improvement in local control rates, with low incidence of high-grade toxicity [6], even in patients with substantial comorbidities [7]. Both the low toxicity and preservation of quality of life in the elderly [8,9] indicate that SBRT could have major advantages in elderly patients [10]. SBRT is particularly appealing as 30-day surgical mortality rates of >7% have been reported in patients aged 75 and older [3]. In contrast, mortality rates after SBRT are very low and local control rates generally exceed 90% when sufficiently high radiation doses are delivered [10–12]. The introduction of SBRT, delivered in the outpatient setting, has been associated with increased access to care in elderly patients with stage I NSCLC, a decrease in the proportion of patients going untreated, and an improvement in survival at population level [13].

Radiotherapy has traditionally been considered a second-choice treatment for lung cancer, indicated in patients who are unfit for surgery or refuse to undergo an operation, with surgery reserved for the fittest subgroup of elderly patients [14]. However, the encouraging outcomes reported after SBRT have prompted randomized comparisons of surgery versus SBRT as first line treatment for patients with an operable stage I NSCLC [15,16]. A single-institution matched analysis found no significant differences between surgery and SBRT in local recurrence, disease-specific survival, or overall survival outcomes [17]. In the present analysis, we used a population-based matched-pair study design in order to compare overall survival after SBRT versus surgery for elderly patients with stage I NSCLC.

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Methods

The Amsterdam Cancer Registry is a population-based registry [18,19] capturing data on all residents of the provinces of North-Holland and Flevoland (population ~3 million people, representing 18% of the Netherlands population). Data are collected on all cancer patients, including demographics, stage, and treatment, directly from patient records; however, staging investigations, comorbidities, and performance status, are not captured. Type of surgery is recorded, but specific details of radiotherapy are not available in the database and were obtained for this study, along with co-morbidities for SBRT patients, by linking with databases from the two radiotherapy centers in the region providing SBRT; seventeen surgical centers performed resections on the cohort of patients included in this study. The registry is linked to municipal death registries. Any deaths occurring before February 1, 2010 were captured in the database. Cause of death is not available.

The history of SBRT introduction in the region has been previously described [13]. In brief, SBRT was first introduced in 2003, whereas after 2005 it was considered widely available, offered at two radiotherapy (RT) centers that treated more than 80% of all stage I RT patients in the period between 2005 and 2007. These two centers accepted referrals from hospitals not providing SBRT. Criteria for management of lung cancer patients were in accordance with Dutch practice guidelines, developed by multidisciplinary teams and available online (www.oncoline.nl). SBRT patients were discussed at a multi-disciplinary thoracic oncology tumor board before final treatment decisions were made in order to facilitate a consensus opinion regarding operability. Specific physiological data (e.g. predicted post-operative forced expiratory volume in 1 s) were not recorded in the databases.

Patients were included in this study if diagnosed with clinical stage I NSCLC (UICC 5th and 6th editions) between 2005 and 2007, and were aged 75 or older at diagnosis. Patients were excluded if there was a previous history of lung cancer. All patients studied had clinical stage I (cT1 or cT2) disease. Patients who had cT1 or cT2 disease based on pre-operative investigations, but were subsequently pathologically up-staged at surgery, were also included in this analysis, to ensure an equal comparison with the clinically staged SBRT patients.

Matched-pair analysis is a method to reduce bias in observational studies by creating two comparable groups with similar baseline factors, thus reducing confounding [20,21]. From the population of patients receiving SBRT and surgery, patients were matched 1:1 based on the following factors: age (within 3 years), stage (T1 or T2), gender, and treatment year. If a match could not be found, the patient was excluded. Matching was done using a semi-automated method with Microsoft Access (Microsoft Corporation, Redmond, Washington, USA). The dataset used in the matching process had encrypted unique patient identifiers and outcomes variables were removed, to ensure that the matching was done in a blinded fashion.

Kaplan–Meier estimates of overall survival (OS) from date of diagnosis were created and differences compared using the log-rank test. A separate pre-specified subgroup analysis was done to compare OS among SBRT patients with pathological confirmation of disease and their corresponding surgical matches. All statistical tests were two-sided, with a threshold of $p \leqslant 0.05$ for statistical significance, and were done using STATA (version 10, StataCorp LP, College Station, Texas, USA).

Results

A total of 346 elderly patients were diagnosed with stage I NSCLC in the provinces of North-Holland and Flevoland between 2005 and 2007, and treatment of these patients was as follows: 109 (32%) received surgery, 81 (23%) received SBRT, 65 (19%) received standard conventional conformal RT, and 91 (26%) underwent neither surgery nor RT. Of the 190 patients treated with surgery or SBRT, a total of 120 patients (60 SBRT and 60 surgery) were matched, according to the criteria above. Not all patients could be matched, as there were insufficient numbers of octogenarian surgery patients to match the older SBRT cohort. Baseline patient characteristics by treatment modality for matched and unmatched patients are shown in Table 1.

Median follow-up was 43 months. For patients undergoing surgery, 49 (82%) underwent lobectomy (including two sleeve lobectomies), two (3%) underwent pneumonectomy and nine (15%) underwent sublobar excision. Thirty-six percent of the cT1-tumors were upstaged after surgery, and 43% of cT2-tumors were upstaged. Two surgical patients (3%) received adjuvant chemotherapy.

SBRT doses were as follows: 51 patients received 60 Gy (either in three fractions [$n = 15$ patients], five fractions [$n = 29$] or eight fractions [$n = 7$]; at one center this was based on a risk-adapted scheme [22]); eight patients received 54 Gy in three fractions; one received 32 Gy in two fractions. Eighty-two percent of SBRT patients (49/60) were considered medically unfit for surgery, whereas the rest (18%, 11/60) were considered medically operable, but had refused surgery. Reasons for inoperability included COPD (22 cases), cardiovascular diseases (eight cases), combination of COPD and cardiovascular diseases (seven cases), other cancers (four cases) and poor general condition (eight cases).

A total of 61 deaths were recorded in the cohort: 26 in the surgical group and 35 in the SBRT group. The 30-day mortality calculated from the start date of treatment was 8.3% for surgery (five deaths) and 1.7% for SBRT (one death). Thirty-day mortality for the surgical group was 2.6% (one death) for patients below age

Table 1
Baseline characteristics of 120 matched elderly patients and 70 unmatched patients with stage I NSCLC treated with surgery or stereotactic radiotherapy. SBRT: stereotactic body radiation therapy; IQR: interquartile range.

Parameter	Matched patients		Patients who were not matched	
	Surgery $n = 60$	SBRT $n = 60$	Surgery $n = 49$	SBRT $n = 21$
Age (median, IQR)	79 (76–80)	79 (76–81)	76 (75–79)	83 (82–86)
Sex				
Male	40 (67%)	40 (67%)	35 (71%)	15 (71%)
Female	20 (33%)	20 (33%)	14 (29%)	6 (29%)
cT-stage				
cT1	39 (65%)	39 (65%)	19 (39%)	19 (90%)
cT2	21 (35%)	21 (35%)	30 (61%)	2 (10%)
Pathological confirmation				
Yes	All	28 (47%)	All	5 (24%)
No		32 (53%)		16 (76%)

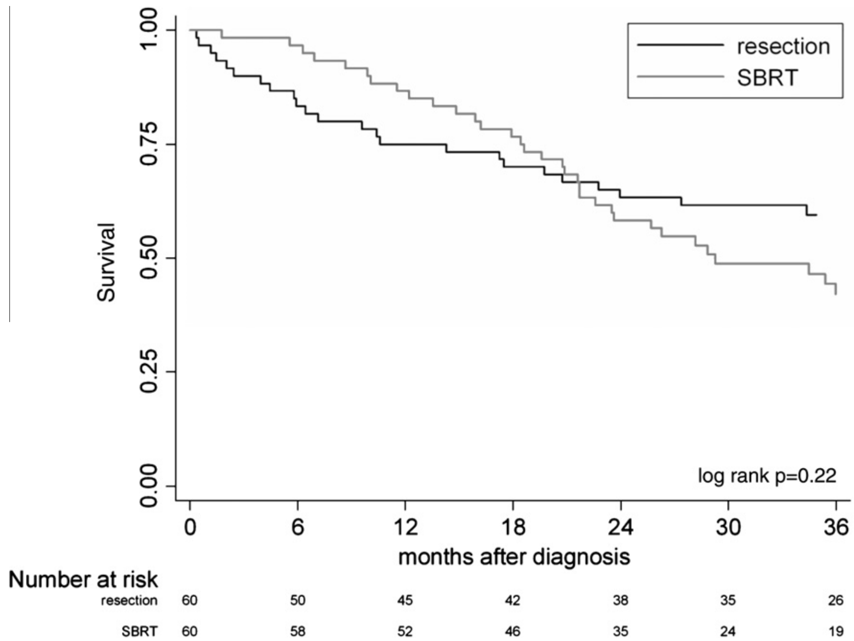

Fig. 1. Overall survival (OS) for 120 elderly patients (age ⩾75) with stage I NSCLC by treatment. There was no difference in OS between surgery and SBRT (log-rank test $p = 0.22$).

80, and 18.2% (four deaths) for patients 80 years or older. For SBRT the respective 30-mortality rates were 0% and 4.4%.

OS at 1 year was 75% after surgery and 87% after SBRT. At 3 years, OS was 60% after surgery and 42% after SBRT. There was no significant difference between surgery and SBRT (Fig. 1; log-rank $p = 0.22$).

The subgroup analysis comparing SBRT patients with pathological confirmation of disease (47%) and their matched pairs is shown in Fig. 2. Results were similar to the whole group analysis: OS at 1 year was 78% after surgery and 82% after SBRT; at 3 years, OS was 61% after surgery and 47% after SBRT, with no significant difference between the two groups (log-rank $p = 0.36$).

Discussion

This current matched-pair analysis of surgery versus SBRT for stage I NSCLC using population-based data found no difference in mortality between the two treatments. The survival patterns shown here are compelling for a number of reasons. Firstly, more than 80% of patients undergoing SBRT were considered unfit for surgery due to medical co-morbidity, which in itself is associated with a high risk of intercurrent death and a survival detriment of 10–20% at 5 years, when compared to patients who were operable [23]. This suggests that SBRT OS outcomes would have been better in a more fit patient group. Secondly, SBRT, a non-invasive, out-patient treatment, has a low rate of 30-day mortality (<2% in this study), despite the high-risk patient population treated. This finding is of particular importance for patient decision making, as patients are averse to taking risks that involve the possibility of short-term death [24].

Importantly, the results of this study do not change if the cohort is restricted to SBRT patients with pathological confirmation of disease and their surgical matches. Although pathological confirmation of disease should be sought wherever possible, in many cases pulmonary function, frailty, or small lesion size precludes trans-thoracic biopsy (or repeated biopsy if the first is indeterminate) [22,25]. In such cases, validated algorithms can be used to calculate malignancy risk based on history and findings on CT and PET in that population [26]. In the North-Holland region, use of clinical, PET and CT information achieves a low rate of benign diagnosis at thoracotomy, [26–28] but selection of patients using this approach could be inferior in geographic areas with higher rates of benign infectious disease which may lead to false positive PET scans. Furthermore, patients who do not undergo biopsy in the North-Holland region have inferior survival compared to those with a pathological diagnosis [13], a finding that is likely to be due to intercurrent death from the underlying co-morbid conditions that increased the risk of biopsy at the time of diagnosis, confirming that inclusion of patients without pathological confirmation of disease does not bias toward improved survival results.

SBRT has several inherent advantages that may be appealing in an elderly population: treatment times are short (3–8 fractions), the side effect profile is favorable, (with <10% of elderly patients experiencing grade 3 or higher toxicity [10]) it is performed in an outpatient setting, and hospitalization is rare. In contrast, surgical intervention is associated with prolonged hospitalization and loss of independence: nearly 25% of patients aged 80 and above are not able to be discharged home after a lung resection [29].

This study is consistent with others that have been published previously [17,30–32], and is a useful addition to the available literature. Comparisons between surgery and SBRT have been hampered by their retrospective nature and difficulty in controlling for confounding variables; however, SBRT outcomes appear to be similar to surgery if operable patients are studied [30,31], if propensity score analysis is used to attempt control for such confounders [17]. Comparable results for SBRT have also been demonstrated in patients with severe COPD, another group at high risk of surgical complications [33]. In comparison to wedge resection, SBRT may achieve superior disease control, based on retrospective data [32].

The relative effectiveness of surgery versus SBRT likely depends on several features of the study population and the intervention. A Markov-model based comparison of surgery versus SBRT for patients aged 65 or 70 predicts that surgery confers an overall

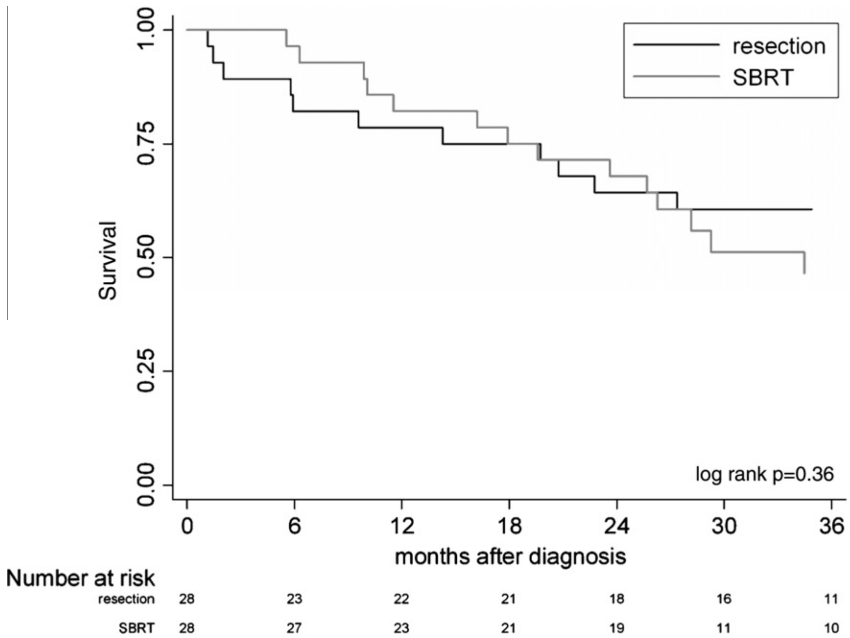

Fig. 2. Overall survival (OS) for the subset of elderly SBRT patients (age ⩾75) with pathological confirmation of disease versus the corresponding matched patients who underwent surgery. There was no difference in OS between surgery and SBRT (log-rank test $p = 0.36$).

survival benefit of 2–3% at 5 years over SBRT. However, once operative mortality increases above 4%, the survival advantage of surgery is negated and SBRT is preferred [34].

Our study uses prospectively collected, population-based data with outcomes that are always ascertainable through municipal death records. Nevertheless, a number of limitations inherent to a retrospective analysis must be kept in mind. A potential major limitation of this comparison is the large number of institutions performing resections (seventeen) in comparison to the number of institutions performing SBRT (two). At the time these patients were treated, surgical care was not yet centralized in the Netherlands. In general, hospitals performing the largest numbers of resections carry out more thorough pre-operative staging [35], and have significantly lower post-operative mortality and better 5-year survival, compared to the lowest-volume hospitals [36]. It is possible that after centralization of lung cancer surgery in the Netherlands, post-operative survival will improve. In centralized surgical centers, post-lobectomy mortality may be as low as 1–2%, depending on the ages and baseline characteristics of the patients [37]. It remains to be determined whether similar SBRT results can be achieved at smaller centers, and this is the subject of ongoing research.

Like many population-based databases, data were not available on all baseline characteristics of interest (such as co-morbidities for surgical patients, detailed reasons for inoperability for SBRT patients, weight loss at presentation, performance status, and pulmonary function tests) or all outcomes (such as cause of death, cause-specific survival, local recurrence, or quality of life). Co-morbidity has been shown to be a strong predictor of overall survival in patients treated with SBRT [38]. In the current study, matching allowed for the comparison of two groups that were equal in all measured baseline factors, however, some of the unmeasured variables may be confounders that could affect the results of the study, and cannot be controlled for retrospectively. The lack of baseline co-morbidity data is likely to bias the results against SBRT, since the SBRT group is negatively selected by virtue of their high comorbidity rates.

The rates of surgical upstaging in this series is consistent with the published literature: one study of patients with stage IA disease based on CT and PET staging reported upstaging at surgery in 35% of patients; in patients with PET-positive tumors more than 2 cm in size, the upstaging rate was 55% at surgery [39]. Finally, surgical mortality rates may be lower in specialized, higher volume institutions that report single institution results; the surgical mortality reported here is consistent with other population-based studies [4].

Due to the differences in the populations of patients undergoing SBRT or surgery, not all patients could be matched: there were insufficient old surgical patients to match some SBRT patients; conversely, there were insufficient young SBRT patients to match some surgical patients. This resulted in a modest sample size, similar to other comparisons of SBRT versus surgery [32]. Even if all patients could have been matched, this study would be underpowered to prove equivalence, a goal which would require nearly 1000 patients [40]. The comparison of SBRT versus surgery for elderly patients can only be definitively answered in the context of a randomized trial. However, one such trial has already closed due to lack of accrual, and results from others are at least several years, if accrual is successful. In the absence of such data from controlled clinical trials, population-based data provide the next highest level of evidence [41].

Although a lack of comorbidity data may bias the results against SBRT, there are competing factors that may bias the results against surgery, including the distributed nature of surgical care in the province, and the potential for under-staging of surgical patients at smaller centers. Furthermore, we cannot exclude a potential benefit for surgery in the long term, based on Figs. 1 and 2. In general, the tails of Kaplan–Meier survival curves should not be used to draw firm conclusions, since the numbers at risk are low at those time points. Nonetheless, the data presented herein could be consistent with better long-term survival after surgery than after SBRT. If this is the case, there could be several potential explanations, including differences in recurrence patterns, late toxicities, or intercurrent deaths due to baseline co-morbid conditions; this study cannot differentiate among these potential causes. Long term outcomes after SBRT, including data on cause of deaths, require future study as results mature.

In summary, this study suggests that in patients aged ⩾75 years, there is clinical equipoise as to the optimal first-line treatment for stage I NSCLC; however, these conclusions would be strengthened by further studies incorporating comorbidity data, and outcomes from centralized surgical programs. The choice of SBRT versus surgery might be best made at the individual patient level, taking into account life expectancy, co-morbidity, operative mortality risk, and quality of life. All patients should be informed about the advantages and disadvantages of surgery and SBRT prior to treatment.

Conflict of interest statement

The VU University Medical Center has a master research agreement with Varian Medical Systems, Inc.

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