Chapter 5

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

D. Palma[1], O. Visser[2], F.J. Lagerwaard[1], J. Belderbos[3], B. Slotman[1], S. Senan[1]

[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam, Netherlands

[2]Comprehensive Cancer Centre Amsterdam, Netherlands

[3]Netherlands Cancer Institute, Amsterdam, Netherlands

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Abstract

Background

Elderly patients with stage I NSCLC are at high risk of treatment-related toxicity after surgical resection. Stereotactic body radiation therapy (SBRT) is an effective treatment with a low toxicity profile, but randomized data comparing surgery and SBRT for elderly patients is lacking.

Methods

A comprehensive 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 ≥75) who were diagnosed between 2005-2007. Treatment decisions were based on Dutch national guidelines. Details of surgery were recorded in the registry; radiotherapy details were obtained through patient databases from the two regional centres providing SBRT. Patients were matched by age, stage, gender, and treatment year; controlling for co-morbidity was not possible.

Results

A total of 120 patients from the registry could be matched (60 surgery, 60 SBRT). Median follow-up was 43 months. Median age was 79 years, 67% were male, and 64% had T1 disease. The majority of SBRT patients (82%) were medically unfit for surgery. Thirty-day mortality was 8.3% after surgery and 1.7% after SBRT. OS at 1- and 3-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 also revealed no significant difference between treatment groups.

Conclusion

No difference in OS for elderly stage I NSCLC patients was observed between surgery and SBRT, despite the fact that a large majority of SBRT patients were unfit for surgery.

Introduction

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 an unwillingness to pursue treatment on the part of the patient or physician.[1-3] As a result, many elderly patients go without curative treatment,[4] and these untreated patients can have poor survival outcomes.[5] 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 the expansion of the elderly demographic in many countries is expected to further increase the number of cases in elderly patients.[1, 6, 7]

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.[8] Both the low toxicity and preservation of quality of life in the elderly[9, 10] indicates that SBRT could have major advantages in elderly patients.[11] SBRT is particularly appealing as 30-day surgical mortality rates of >7% have been reported in patients aged 75 and older.[4] In contrast, mortality rates after SBRT are very low and local control rates generally exceed 90% when sufficiently high radiation doses are delivered.[8, 11, 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 a 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 a randomized comparison of surgery versus SBRT as first line treatment for stage I NSCLC.[15] Computer simulation models suggest that SBRT becomes the preferred treatment as operative mortality risk increases,[16] a scenario that applies to elderly patients.[6, 17] The goal of the current study was to compare outcomes after SBRT vs. surgery for elderly patients with stage I NSCLC, using a population-based match pair study design.

Methods

Data Sources

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 is 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. The registry is linked to municipal death registries. Any deaths occurring before February 1, 2010 were captured in the database.

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 2005-2007. These two centres 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).

Patients were included in this study if diagnosed with clinical stage I NSCLC (UICC 5th and 6th editions) between 2005-2007 and were age 75 or greater 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.

Matching and Statistical Analysis

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 $p \leq 0.05$ for statistical significance, and were done using STATA (version 10, StataCorp LP, College Station, Texas, USA.)

Results

Demographics and Treatment

A total of 346 elderly patients were diagnosed with stage I NSCLC in the provinces of North Holland and Flevoland between 2005-2007, and treatment of these patients was a 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 2 sleeve lobectomies), 2 (3%) underwent pneumonectomy and 9 (15%) underwent sublobar excision. Thirty-six percent of the cT1-tumours were upstaged after surgery, and 43% of cT2-tumours were upstaged. Two surgical patients (3%) received adjuvant chemotherapy.

SBRT doses were as follows: 51 patients received 60 Gy (either in 3 fractions [n=15 patients], 5 fractions [n=29] or 8 fractions [n=7]; at one center this was based on a risk-adapted scheme[20]); 8 patients received 54 Gy in 3 fractions; 1 received 32 Gy in 2 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. Inoperability was due to COPD in 22 cases, cardiovascular diseases in 8 cases, combination of COPD and cardiovascular diseases in 7 cases, other cancers in 4 cases and poor general condition in 8 cases.

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**		**Unmatched Patients**	
	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%)

Survival Outcomes

There were a total of 61 deaths 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 (5 deaths) and 1.7% for SBRT (1 death). 30-day mortality for the surgical group was 2.6% (1 death) for patients below age 80, and 18.2% (4 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 (Figure 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 Figure 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).

Figure 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)

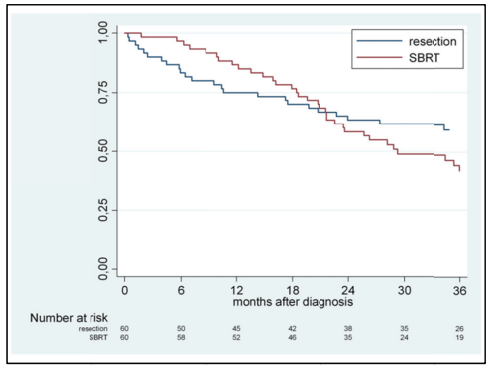
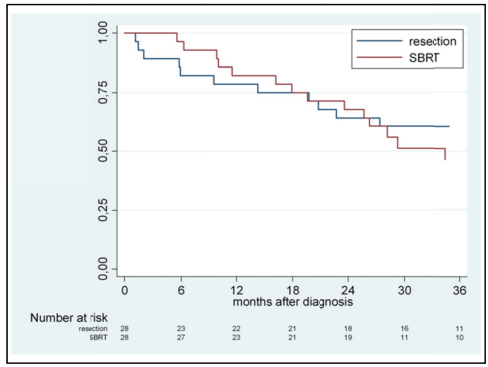


Figure 2. Overall survival (OS) for the subset of elderly SBRT patients (age ≥ 75) with pathological confirmation of disease vs. the corresponding matched patients who underwent surgery. There was no difference in OS between surgery and SBRT (log- rank test p=0.36).



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, compared to operable patients.[21] This suggests that SBRT OS outcomes would have been better in a more fit patient group. Secondly, SBRT, a non-invasive 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.[22]

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).[20, 23] In such cases, validated algorithms can be used to calculate malignancy risk based on history and findings on CT and PET in that population.[24-26] Patients who do not undergo biopsy in the North Holland region have inferior survival compared to those with a pathological diagnosis,[13] likely due to intercurrent death from the underlying co-morbid conditions, such as COPD, that precluded biopsy at the time of diagnosis.

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,[11] 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.[27]

This study is consistent with others that have been published previously,[28, 29 30] and adds to the literature in several important ways. 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,[28, 29] or if propensity score analysis is used to attempt control for such confounders.[30] Comparable results for SBRT have also been demonstrated in patients with severe COPD, another group at high risk of surgical complications.[31]

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 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.[16]

The results of this study must be considered in the context of its strengths and limitations. This study uses population-based data that was prospectively collected, with an outcome that is virtually always ascertainable through municipal death records. However, this study also has limitations inherent to a retrospective analysis. Like many population-based databases, data was not available on all baseline characteristics of interest (such as co-morbidities for surgical patients, weight loss at presentation, performance status, and pulmonary function tests) or all outcomes (such as cause-specific survival, local recurrence, or quality of life). 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. Another potential confounding factor is that surgical rates can vary across geographic regions, as they have been shown to be low and variable in different European countries.[32] However, this is not the case in the Netherlands, where 23% of all NSCLC patients, and 60% of patients with early stage NSCLC, are operated upon.[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.[33] Even if all patients could have been matched, this study would be underpowered to prove equivalence (which would require nearly 1000 patients[34]). The comparison of SBRT vs. surgery for elderly patients can only be

definitively answered in the context of a randomized trial. However, while awaiting the results of such trials (which are several years away), population-based data provides the next highest level of evidence.

In summary, this study suggests that in elderly patients (age ≥ 75) there is clinical equipoise as to the optimal first-line treatment for stage I NSCLC. The choice of SBRT vs. 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.

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Chapter 6

Curative treatment of stage I non-small cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review

D. Palma[1], F.J. Lagerwaard[1], G. Rodrigues[2], C. Haasbeek[1], S. Senan[1]

[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam, Netherlands

[2]London Regional Cancer Program, London, Canada

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