

Stage I Nonsmall Cell Lung Cancer in Patients Aged ≥ 75 Years

Outcomes After Stereotactic Radiotherapy

Cornelis J. A. Haasbeek, MD; Frank J. Lagerwaard, MD, PhD; Marilisa E. Antonisse; Ben J. Slotman, MD, PhD; and Suresh Senan, MRCP, PhD

BACKGROUND: The number of patients aged ≥ 75 years who present with a stage I nonsmall cell lung cancer (NSCLC) is increasing. Elderly patients often have significant comorbidity and may be unfit for surgery. Furthermore, surgery in the elderly is associated with increased mortality and morbidity. In this study, the authors evaluated the outcomes of stereotactic radiotherapy (SRT) in elderly patients. **METHODS:** Since 2003, 203 tumors in 193 patients aged ≥ 75 years were treated using SRT (118 T1 tumors, 85 T2 tumors). The median patient age was 79 years, 80% of patients were considered medically inoperable, and 20% of patients declined surgery. The median Charlson comorbidity score was 4, and severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease Class III or greater) was present in 25% of patients. Risk-adapted SRT schemes were used with the same total dose of 60 grays in 3 fractions (33%), 5 fractions (50%), or 8 fractions (17% of patients), depending on the patient's risk for toxicity. **RESULTS:** SRT was well tolerated, and all but 1 patient completed treatment. Survival rates at 1 year and 3 years were 86% and 45%, respectively. Survival was correlated with performance score ($P = .001$) and pre-SRT lung function ($P = .04$). The actuarial local control rate at 3 years was 89%. Acute toxicity was uncommon, and late Radiation Therapy Oncology Group grade ≥ 3 toxicity was observed in $<10\%$ of patients. **CONCLUSIONS:** SRT achieved high local control rates with minimal toxicity in patients aged ≥ 75 years despite their significant medical comorbidities. These results indicated that more active diagnostic and therapeutic approaches are justified in elderly patients and that SRT should be considered and discussed as a curative treatment alternative. *Cancer* 2010;116:406-14. © 2010 American Cancer Society.

KEYWORDS: lung cancer, elderly patients, stereotactic radiotherapy, comorbidities, toxicity.

Curative treatment of elderly patients with stage I nonsmall cell lung cancer (NSCLC) remains a challenge. Although the number of elderly patients with cancer is increasing, older patients consistently receive less screening, less aggressive surgery, less systemic therapy, and less participation in clinical trials.¹ Octogenarians who undergo guideline-recommended lung resection have a substantially higher operative mortality than younger patients (6.9% vs 3.7%).^{2,3} Survival among octogenarians after lung surgery is correlated with the presence of multiple comorbidities, and 5-year survival is generally low.² The increased surgical morbidity and mortality in the elderly and the high additional costs because of the need for prolonged postoperative care warrant the evaluation of less toxic treatment alternatives.

In recent years, stereotactic radiotherapy (SRT) has emerged as a curative treatment alternative in patients with stage I NSCLC who are medically inoperable.⁴ SRT is a form of high-precision, image-guided, high-dose radiotherapy and generally uses only 3 to 8 treatments on an outpatient basis. Different investigators have reported high local control rates with little morbidity using SRT. The high local control rates, low toxicity, and convenience for patients has led to SRT increasingly being considered the treatment of choice for patients who are unfit to undergo surgery.⁴ However, the tolerance and outcomes of SRT in patients aged ≥ 75 years with high comorbidity rates is less well characterized, and we analyzed outcomes in such patients who have been referred to our department for SRT since 2003.

Corresponding author: Cornelis J. A. Haasbeek, MD, Department of Radiation Oncology, VU University Medical Center (VUMC), de Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands; Fax: (011) 31-20-4440410; cja.haasbeek@vumc.nl

Department of Radiation Oncology, VU University Medical Center, Amsterdam, the Netherlands

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METHODS AND MATERIALS

Patient Characteristics

Between 2003 and 2008, 428 patients with stage IA/IB NSCLC underwent SRT at the VU University Medical Center in Amsterdam. The current analysis focuses on 193 patients who were aged ≥ 75 years at the time of SRT. Details of our selection criteria and treatment were described in a previous report on the first 206 patients who underwent SRT.⁵ Similar eligibility criteria were used for elderly patients who had to have a stage I lung tumor that measured ≤ 8 cm in greatest dimension and the absence of metastases on an ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) scan. In the absence of a cytohistologic confirmation of malignancy, patients who had a new or growing lesion with an appearance on a diagnostic computed tomography (CT) scan that was consistent with malignancy, in conjunction with local uptake on the ¹⁸FDG-PET scan, also were accepted for treatment.⁶ A cytohistologic confirmation of malignancy was available in 39% of patients. We retrospectively calculated the probability of malignancy in patients using criteria published by Swensen et al⁷ and by using a method that was based on the Swensen et al criteria but that also included information on ¹⁸FDG-PET uptake that was validated in a Dutch population by Herder et al.⁶ Staging was performed according to the American Joint Committee on Cancer/International Union Against Cancer TNM classification and was based on measurement of the maximum tumor dimension on the pretreatment planning CT scan.

Patients with stage I lung cancer were accepted for SRT if they were considered medically inoperable or if they had refused surgery. All patients were discussed by a multidisciplinary team before they were accepted for SRT. The most common reasons for medically inoperability were poor pulmonary function, cardiovascular comorbidity, advanced age in combination with poor general condition, or a synchronous second malignancy. The performance status and general health status of patients were assessed using the World Health Organization (WHO) performance score and the Charlson comorbidity index, respectively. In the Charlson comorbidity index, comorbid conditions are weighted and scored, and additional points are added for age. For the age-adjusted Charlson score, an extra point is added to the comorbidity score for each decade over age 40 years.^{8,9} Overall WHO performance was scored prospectively in all patients by the treating radiation oncologist.

Treatment Details

SRT was delivered using 3 fractionation schemes that were applied consistently as described previously^{5,10-13}; 3 fractions of 20 grays (Gy) (for T1 tumors), 5 fractions of 12 Gy (for T1 tumors with broad contact with the chest wall and for T2 tumors), or 8 fractions of 7.5 Gy (for tumors adjacent to the heart, large blood vessels, hilus, brachial plexus, or mediastinum). Planning target volumes (PTVs) for SRT were derived from an individualized incorporation of tumor mobility based on data from 4-dimensional CT (4DCT) scans plus an extra margin of 3 mm.¹² 4DCT scans or respiration-correlated CT scans were obtained during uncoached, quiet respiration using the Real-Time Position Management system (RPM; Varian Medical Systems, Palo Alto, Calif) and a 16-slice CT scanner (Lightspeed 16; GE Medical Systems, Waukesha, Wis). All dose schemes were prescribed to the 80% PTV-encompassing isodose using 8 to 12 noncoplanar beams. SRT was delivered using a Novalis linear accelerator (BrainLAB, Feldkirchen, Germany) in 3 fractions per week. Treatment plans were calculated using Brainscan version 5.31 (BrainLAB, Feldkirchen, Germany) software. Treatment duration for each fraction was from 30 to 45 minutes, including image-guided patient setup using the ExacT rac system (BrainLAB).

Follow-Up

Patients were followed routinely at 3 months, 6 months, 1 year, and annually thereafter. Quality of life was scored prospectively using validated European Organization for Research and Treatment of Cancer (EORTC) instruments,¹⁴ and follow-up CT scans were obtained at each visit. The percentage of available CT scans at 12 months post-treatment was used to assess the completeness of follow-up. ¹⁸FDG-PET scans were obtained only when there was suspicion of disease recurrence in patients who were fit to undergo salvage treatment. For patients who were unable or unwilling to attend follow-up at our center, the general practitioner or referring lung physician was contacted for follow-up details.

Statistics

Treatment outcomes in terms of overall and disease-free survival, and actuarial local, regional, and distant failure rates were calculated using the Kaplan-Meier method.¹⁵ Comparisons between groups were made using log-rank tests. Results were considered significant at a *P* value $< .05$. *P* values were derived from univariate analysis unless stated otherwise. SPSS version 15.0 (SPSS Inc.,

Chicago, Ill) was used for statistical analysis. The toxicity of SRT was evaluated using the Radiation Therapy Oncology Group (RTOG) definitions for acute reactions and the RTOG/EORTC classification for late reactions. A comparison also was made between our elderly patient group and a cohort of 235 younger patients who underwent SRT at our center.

RESULTS

Patient characteristics are summarized in Table 1. The median follow-up was 12.6 months (range, 3-52 months). The series consisted of 131 men and 62 women, and the median age was 79 years at the time of treatment. Included were 155 patients who were considered medically inoperable and 38 patients who refused surgery. All patients underwent a pretreatment, staging, whole-body ^{18}F FDG-PET scan, and none of the patients had evidence of regional or distant metastases. The mean likelihood of malignancy calculated using the method described by Swensen et al⁷ in all 193 patients was 0.87 ± 0.13 (1 standard deviation), and there was no significant difference between patients with and without pathologic verification of malignancy (0.91 ± 0.10 vs 0.85 ± 0.14 , respectively). The mean probability of malignancy, as calculated using the method described by Herder et al⁶ (which also includes ^{18}F FDG-PET information), was 0.95 ± 0.04 , and there was no significant difference between patients with and without pathologic verification of malignancy (0.96 ± 0.02 vs 0.94 ± 0.05 , respectively).

No patient received planned concurrent or sequential chemotherapy. Only 1 patient received 3 courses of carboplatin/vinorelbine preceding SRT, before it was realized that the option of curative SRT was feasible. No additional toxicity was observed in this patient, although the patient was oxygen-dependent before SRT.

The majority of patients had a history of chronic obstructive pulmonary disease (COPD), and 25% of all patients were classified with severe COPD, ie, Class III or greater, using the Global Initiative for Chronic Obstructive Lung Disease scoring system (available at: <http://goldcopd.com>; accessed March 3, 2009). Baseline spirometry data were available for 172 patients (89%), and the median forced expiratory volume in 1 second (FEV₁) was 71% of the predicted volume (range, 20%-130%). The median Charlson comorbidity score was 4 (range, 2-9), and the median age-adjusted Charlson score was 7 (range, 5-12). Thirty-eight patients were considered medically operable but had refused surgery. In this subgroup of

Table 1. Patient and Tumor Characteristics

Characteristic	No. of Patients (%)
Sex	
Men	131 (68)
Women	62 (32)
Age, y	
Median [range]	79 (75-91)
75-80	120
81-85	56
85-90	15
91	2
WHO performance score	
0	23
I	104
II	57
III	9
Tumor classification, n=203	
T1	118 (58)
T2	85 (42)
Maximum tumor dimension, cm	
3-5	61
5.1-8	24
Reason for referral	
Medically inoperable	155 (80)
Refusing surgery	38 (20)
Pathologic confirmation	
No	118 (61)
Yes	75 (39)
Histology, n=75	
Adenocarcinoma	23
Squamous cell carcinoma	18
Undifferentiated NSCLC	34
Fractionation scheme: Total, 60 Gy^a	
20 Gy×3 fractions	69 (34)
12 Gy×5 fractions	101 (50)
7.5 Gy×8 fractions	33 (16)
Severity of COPD: GOLD score	
No COPD	53 (28)
Class I	32 (16)
Class II	61 (31)
Class III	38 (20)
Class IV	9 (5)

WHO indicates World Health Organization; NSCLC, nonsmall cell lung cancer; Gy, grays; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

^aThe dose prescribed to the encompassing 80% isodose.

favorable patients, the nonage-adjusted Charlson score was 4 (range, 2-7), which was identical to the whole group of patients.

At 12 months of follow-up, at least 3 CT scans (at 3 months, 6 months, and 1 year of follow-up) were available in 88% of patients who were still alive and disease free. In

the remaining patients, clinical data were available with or without information on chest x-ray results. No difference in the completeness of follow-up CT scans was observed between the elderly patients and the younger patients (88% vs 90% after 12 months, respectively).

In total, 203 primary lung tumors were treated in 193 patients (10 patients were treated for 2 synchronous tumors). Most tumors were located in the upper lobes (60%), followed by the lower lobes (34%), and the middle lobe (6%). One hundred eighteen tumors (58%) were classified as T1, 85 tumors (42%) were classified as T2, and the mean PTV was 40 cm³ (range, 4-208 cm³). The proportions of patients who received the 3-fraction, 5-fraction, and 8-fraction schemes were 33%, 50%, and 17%, respectively.

A history of prior malignancy was present in 39% of patients, including 28 patients (15%) who had a prior lung cancer diagnosed at a median of 5 years before SRT. Treatment for this prior lung cancer consisted of pneumonectomy (n = 6), bilobectomy (n = 2), lobectomy (n = 14), SRT (n = 3), conventional radiotherapy (n = 1), wedge resection (n = 1), and concurrent chemotherapy and radiotherapy for a small cell lung cancer (n = 1).

Survival

The median overall survival was 32.5 months (Fig. 1), with actuarial survival at 1 year and 3 years of 85.7% and 45.1%, respectively (Table 2). The importance of performance score was reflected in survival: The median actuarial survival for patients with a WHO performance score of 0 or 1 (40 months) was significantly superior compared with the survival for patients with performance score of 2 or 3 (median, 16 months; $P < .005$). Performance score was not related to disease-free survival ($P = .4$). Multivariate analysis for prognostic factors indicated that overall survival was correlated significantly with both WHO performance score (0-1 vs 2-3; $P = .001$) and pre-SRT pulmonary function ($FEV_1 > 50\%$ vs $\leq 50\%$ of predicted; $P = .04$). All other factors that we investigated, including Charlson score, sex, T classification, prior malignancy, histologic confirmation of malignancy, were not correlated independently with survival.

Disease-free survival rates at 1 year and at 3 years were 89.2% and 72.6%, respectively, and multivariate analysis for prognostic factors indicated that none of the investigated variables differed significantly. The only factor that had borderline significance was T classification ($P = .06$), with a trend toward worse disease-free survival

for patients with T2 tumors because of an increase in regional and distant metastasis.

Patterns of Failure

The actuarial local failure rate 3 years post-SRT was 10.7% (Fig. 1). None of the investigated factors were correlated significantly with local failure (pathologic confirmation of malignancy, $P = .44$; fraction dose, $P = .19$; stage, $P = .97$; prior malignancy, $P = .26$), which is not surprising, because the number of local failures was very low (n = 6). Regional and distant failure rates at 3 years were 8.4% and 20.7%, respectively.

Comparison Between Patients Aged <75 Years and Aged >75 Years

A comparison between patients aged ≥ 75 years (n = 193) and a younger cohort of patients (n = 235) with stage I NSCLC who underwent SRT at the VU University Medical Center was performed. Overall survival for the older patient group did not differ significantly from overall survival for the younger patient cohort ($P = .18$); however, disease-free survival was slightly better for the older patients ($P = .04$). Although local control ($P = .77$) and regional control ($P = .06$) after SRT did not differ significantly between younger patients and older patients, distant control indicated a better outcome for patients aged ≥ 75 years ($P = .02$). Actuarial regional and distant failure rates at 3 years for the younger patient group were 17.7% and 34.4%, respectively, versus 7.7% and 20.1%, respectively, for the older patient group.

Toxicity

Despite their advanced age and high comorbidity rates, SRT was well tolerated, and all but 1 of our patients completed the course of SRT as planned. The 1 exception was a patient who developed a nontreatment-related cerebrovascular accident during his course of treatment. One hundred sixteen patients (60%) reported no early side effects. Commonly reported general side effects in the first 3 months after SRT were fatigue (32.6%) and nausea (4.1%). Respiratory symptoms were increased cough (5.7%) and dyspnea (5.2%). Local chest wall pain was reported in 3.1% of patients, and grade 1 chest wall erythema was reported in 3 patients (1.6%).

Severe late toxicity also was uncommon, with grade ≥ 3 radiation pneumonitis requiring treatment with steroids in 4 patients (2.1%). In 3 patients, rib fractures without signs of local recurrence developed 2 years after SRT within the high-dose area on the chest wall (1.6%).

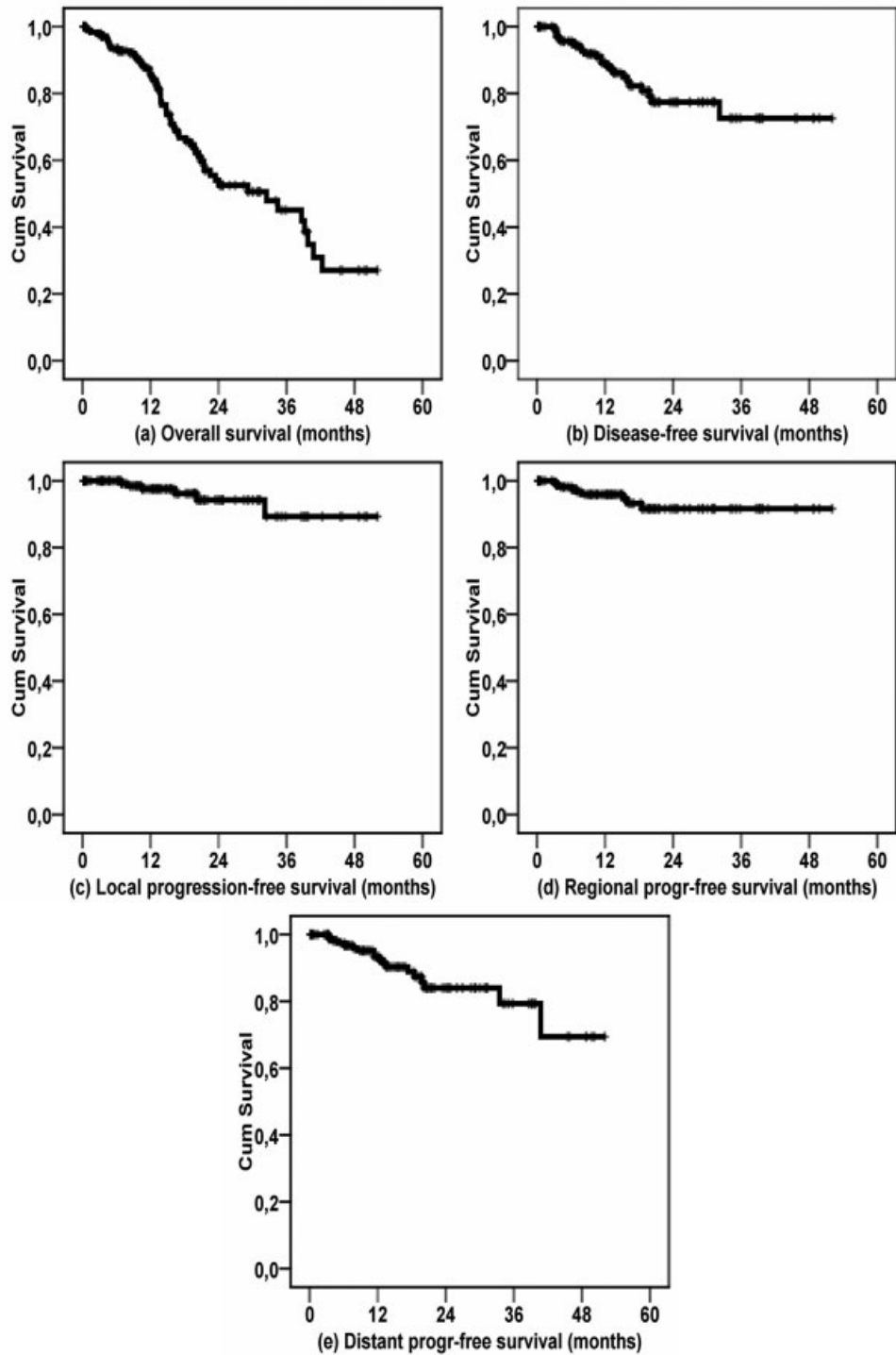


Figure 1. These charts illustrate cumulative (Cum) (a) actuarial overall survival, (b) actuarial disease-free survival, (c) actuarial local progression-free survival, (d) actuarial regional progression-free survival, and (e) distant progression-free survival for patients aged ≥ 75 years who underwent stereotactic radiotherapy ($n = 193$)

Table 2. Actuarial Survival and Failure Rates at 1 Year, 2 Years, and 3 Years After Stereotactic Radiotherapy

Variable	Rate, %		
	1 Year	2 Years	3 Years
Overall survival	85.7	54	45.1
Disease-free survival	89.2	77.4	72.6
Local failure	2.4	5.7	10.7
Regional failure	4.1	8.4	8.4
Distant failure	6.6	16	20.7

Chronic chest wall pain syndromes were observed in another 5 patients (2.6%), and nonmalignant pleural effusion was observed in 3 patients (1.6%).

DISCUSSION

Surgery in elderly patients who present with stage I NSCLC is associated with higher morbidity and mortality than for younger patients, even when minimally invasive surgical techniques are used.¹⁶ Nearly 70% of elderly patients with NSCLC in the National Cancer Institute's Surveillance, Epidemiology, and End Results database were not treated according to guidelines,¹⁷ and concerns about increased surgical morbidity and mortality were a common reason for deferring from guideline-recommended therapy, although older patients tend to present with earlier stage lung cancer.¹⁸⁻²⁰ Despite this, surgery still is the recommended therapy for the elderly, because realistic nonsurgical treatment options were lacking until the emergence of SRT in recent years.

Historically, the only curative treatment alternative for surgery was conventional radiotherapy, which resulted in relatively low local control rates compared with surgery and, as a consequence, a low 5-year cancer-specific survival rate of 13% to 39%.²¹ However, a problem comparing published surgical and nonsurgical series is that surgical series emphasize strict patient selection, and patients with poor performance status were referred for conventional radiotherapy.^{22,23} Although the prognosis of untreated patients is poor,¹⁹ the mortality and morbidity of surgery, combined with the poor results from conventional radiotherapy, led to the widespread perception among patients and physicians that advanced age combined with the presence of comorbidities is a reason to defer from curative treatment.^{24,25}

Recent publications have reported local control rates for SRT that are in the range reported with surgery; and,

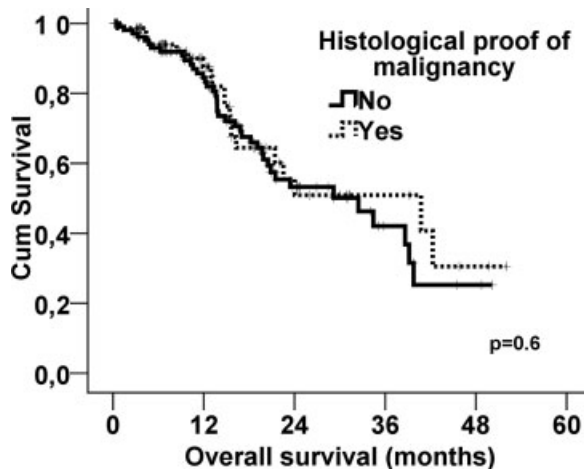
notably for a patient cohort with considerable comorbidities, SRT is associated with a low incidence of grade ≥ 3 toxicity (Table 3).^{5,26,27} Our results in 193 patients aged ≥ 75 years indicate that SRT is well tolerated even in patients with significant comorbidity. The median Charlson comorbidity score was 4 (range, 2-9), underscoring the presence of multiple comorbidities in the patients in this series with an expected 5-year noncancer-related mortality of at least 50%.⁸ In our cohort, 80% of patients were judged by a multidisciplinary tumor board to be unfit for surgery; however, with SRT, the local failure rate was only 10% at 3 years. Comparison of the outcomes of these elderly patients with a cohort of 235 patients with stage I NSCLC aged <75 years did not reveal differences in toxicity or tumor control (data not shown). Our previous analysis of quality of life after SRT revealed little deterioration, in marked contrast to the reported negative impact of quality of life postsurgery.^{28,29}

In our study, cytohistologic confirmation of malignancy was available only in 39% of patients, and this low percentage is not uncommon in trials that evaluate the management of suspected early NSCLC.³⁰ Similar findings were observed by Sawada et al in 1039 patients who underwent surgical resection for a diagnosis of lung cancer or suspected lung cancer and in whom routine investigations confirmed a histologic diagnosis of lung cancer in only 523 patients.³¹ Because the elderly have a high prevalence of COPD, pulmonologists were reluctant to perform invasive staging procedures. The likelihood of inadvertently treating benign disease can be reduced by applying the criteria described by Swenson et al (age, smoking history, previous cancer, greatest tumor dimension, spiculation, and tumor location⁷) combined with the results of FDG-PET⁶ to estimate the probability of malignancy. Although the use of FDG-PET reduces the likelihood of benign disease to $<5\%$,³² we continue to recommend a cytologic or histologic diagnosis when possible, particularly because a preoperative transthoracic biopsy has not been associated with an increased risk of death.³³ In our patients, identical outcomes were observed between patients with and without histologic proof of malignancy (Fig. 2).

Nearly 40% of patients in our study had undergone treatment for a prior malignancy. Although FDG-PET did not reveal any tumor activity at distant sites, it is possible that some patients were not treated for an early stage primary lung cancer but were treated for a solitary metastasis of a prior malignancy. However, even if patients with metastases were included inadvertently in our cohort, it

Table 3. Key Advantages of Stereotactic Radiotherapy Compared With Surgery in Elderly Patients

1. Stereotactic radiotherapy is well tolerated in patients with significant comorbidity
2. Treatment-related morbidity and mortality are uncommon
3. No planned hospitalization is required
4. Less risk of significant deterioration in quality of life

**Figure 2.** Actuarial (cumulative [Cum]) overall survival is illustrated for patients aged ≥ 75 years who underwent stereotactic radiotherapy with ($n = 75$) or without ($n = 118$) histologic proof of malignancy.

would have had a negative impact on our outcomes. The exclusion of such patients would only support the conclusion that SRT is a good treatment option in elderly patients.

Our findings suggest that SRT should be compared systematically with surgery in stage I NSCLC, and a randomized clinical trial comparing surgery with SRT in patients who are fit to undergo surgery currently is in progress.³⁴ However, the relatively short follow-up in many reports, including ours, must be acknowledged. Because the elderly are a group in which the acute mortality and morbidity associated with surgery are unacceptably high, we would argue that the current results of SRT are sufficiently convincing to be discussed as a treatment alternative for elderly patients with significant comorbidity. The latter is important, because the elderly often are excluded or are under represented in clinical trials for lung cancer.³⁵ Physicians who counsel elderly patients need realistic data about the risks and long-term benefits of lung operations and of alternatives to surgery, such as SRT. Elderly patients, particularly those with multiple comorbidities and an impaired performance status, are at high operative

risk and do not have the same survival benefits observed in younger patients.^{2,3,20} Several factors that predict for prolonged length of hospital stay (PLOS) have been identified,³⁶ and our cohort of mainly elderly men who were smokers with COPD and had high average comorbidity scores, by definition, have a high PLOS score. Hospitalization is the single largest component of net costs for elderly patients with cancer during any phase of care, and it is estimated that more than half the cost of initial lung cancer care consists of hospitalization costs.^{37,38} A systematic review indicated that even when thoracic surgery is performed using video-assisted thoracoscopic surgery, the mean duration of hospitalization was 8.3 days.¹⁶ Counseling of elderly patients should include information about the likelihood of convalescence at an extended care facility, because approximately 24% of octogenarians are transferred to extended care facilities after undergoing pulmonary resection, and physicians should be aware of the added costs.²

Steps to standardize the delivery of SRT are essential to ensure the safe use of this technique.³⁴ Although the capital expenditure in stereotactic radiation equipment and well trained, specialized staff is considerable, the cost-effectiveness of the short outpatient procedure in the setting of an aging population is self evident. Caution is required when applying SRT to unselected patient groups. For example, attempts to treat central tumors that overlap mediastinal structures with these SRT schedules using large fraction sizes has resulted in increased morbidity.³⁹ More data are needed for SRT outcomes in tumors that are not located in the lung periphery.

In conclusion, in a population of frail, elderly patients aged ≥ 75 years for whom surgical treatment often is not feasible or is accompanied by high morbidity and high hospitalization costs, curative SRT achieved high local control rates with minimal toxicity. This indicates that active diagnostic and therapeutic approaches are justified in frail, elderly patients with stage I NSCLC, and SRT should be considered and discussed with such patients as a curative treatment alternative.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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