Chapter 3

Stage I non-small cell lung cancer (NSCLC) in patients aged 75 years and above: Does age determine survival after radical treatment?

D. Palma[1,2], S. Tyldesley[1], F. Sheehan[1], I.G. Mohamed[3], S. Smith[4], E. Wai[4], N. Murray[5], S. Senan[2]

[1]Department of Radiation Oncology, BC Cancer Agency, Vancouver, Canada

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

[3]Department of Radiation Oncology, BC Cancer Agency, Kelowna, Canada

[4]Department of Radiation Oncology, BC Cancer Agency, Victoria, Canada

[5]Department of Medical Oncology, BC Cancer Agency, Vancouver Canada

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Abstract

Introduction

Curative treatment of stage I NSCLC in elderly patients represents a therapeutic challenge. Data examining outcomes for the elderly after radical radiotherapy (RT) or surgery in the same geographic population are limited.

Methods

Using prospective databases from British Columbia (BC), patients with stage I NSCLC treated curatively with either surgery or RT between 2000 and 2006 were identified. Kaplan-Meier, Cox regression, and competing risk analyses were used to assess overall survival (OS) and disease specific survival (DSS) in the elderly, and the relationship between age and survival outcomes.

Results

Of a total of 558 patients with stage I disease, 310 (56%) received surgery and 248 (44%) received RT. Elderly patients (age ≥ 75) were less likely to undergo resection than their younger counterparts (43% vs. 72%, p<0.0001). Actuarial OS after surgery for elderly patients was 87% at 2 years and 69% at 5 years. On multivariate analysis, OS after surgery was dependent on tumor stage (p=0.034) and performance status (p=0.03), but not age (p=0.87). After RT, actuarial OS for elderly patients was 53% at 2 years and 23% at 5 years. On multivariate analysis, age did not predict for OS after RT (p=0.43), whereas tumor stage (p=0.033), sex (p=0.044) and dose (p=0.01) were significant predictors.

Conclusions

Survival after radical treatment for stage I NSCLC is dependent on factors such as tumor stage, performance status, sex, and RT dose, but not age. Elderly patients who are sufficiently fit should not be considered ineligible for radical treatment based on age alone.

Introduction

Lung cancer is increasingly a disease of older patients. The median age of diagnosis is 70, and one in three patients is aged 75 years or older (1). Although lung cancer incidence rates are stable or falling in many countries, this has been offset by the expansion of the elderly demographic, resulting in an overall increase in the number of elderly patients with lung cancer (1-3). For example, in Canada the age-standardized incidence rates for lung cancer have decreased in men and stabilized in women between 2000 and 2005 (4), but in the same time period the number of elderly people (age ≥75) diagnosed with lung cancer increased approximately 20% (5).

Elderly patients are less likely to receive protocol-specified treatment, often due to concerns about comorbidity, frailty, or efficacy (1;6;7). Almost 70% of elderly lung cancer patients have significant comorbidities, compared to about 50% of younger patients (8). Physiologic changes that occur with aging may alter the efficacy or toxicity of treatment (9). Post-operative risks are higher in elderly patients, particularly those with impaired performance status (3;10). Non-surgical options, such as conventional external beam radiotherapy (RT) have historically demonstrated inferior outcomes when compared to surgery (11;12), with only small improvements in median survival compared to no treatment (13). This has led to instances of medically inoperable elderly patients being deferred treatment until development of symptoms (12).

Elderly patients are less often subjects of clinical trials (14;15), leading to more uncertainty about optimal management, and a greater reliance on other types of comparative effectiveness studies. Several studies have examined outcomes for elderly patients with stage I NSCLC after either surgery or RT, but no large or recent studies have reported outcomes for both treatments, with curative intent, from the same baseline population. This is an important distinction, as surgical and radiotherapeutic outcomes depend highly on patient selection. Reports on only one of these two treatment options may give an incomplete picture of outcomes for elderly patients. The aims of our study were to assess survival outcomes for elderly patients with stage I lung cancer treated with radical intent and to determine the impact of age on post-treatment survival.

Methods

Data Sources

The majority of cancer care in British Columbia, a province in excess of 4 million people, is provided by the BC Cancer Agency (BCCA). Treatment policy for lung cancer in the province is generated by the Lung Tumor Group and the treatment guidelines are published online (www.bccancer.bc.ca). The BC Cancer Registry (BCCR) captures all diagnoses of cancer in the province of British Columbia (case ascertainment rate of 90% between 2000-2005 (16)), along with demographic data, histology, and vital statistics. Staging data is not captured. The BCCA maintains a separate database, the Oncology Reporting System (ORS), which captures more detailed information on all patients referred to the BCCA, including clinical and pathologic stage; RT information; surgical procedures, and Eastern Cooperative Oncology Group (ECOG) performance status. Data on specific staging investigations are not included. The BCCA is the only provider of RT in the province, therefore any patient receiving RT in BC (or seeking a consultation for RT) at any time is included in this database. Information on the cause and date of death is captured by automatic reporting of death certificates to the BCCR. The last complete death update of the registry was December 31, 2007, and patients who were alive with no further follow-up after this date were censored as of that date. Institutional ethics review board approval was obtained prior to initiation of the study.

Both databases were queried in March 2009 for patients with non-small cell lung cancer diagnosed between Jan 1, 2000 and Dec 31, 2006. A total of 14338 patients with NSCLC any stage were diagnosed in the BC population during this time period, of which 9388 were referred to the BCCA.

Patients were identified at first clinical and/or pathological diagnosis of T1/T2 N0/X M0/X NSCLC, based on the 1997 AJCC definition. Patients with both clinical and surgical staging were only included if they were stage I by both methods; all surgical patients can be therefore be considered as pathologically T-staged. Patients were excluded if there was a prior history of cancer, other than non-melanoma skin cancer, in the 5 years prior to diagnosis, if the diagnosis was made post-mortem or on the date of death; or with a diagnosis of synchronous lung cancers (defined as 2 separate diagnoses of lung cancer within 6 months). Surgical patients were excluded if referred to the BCCA more than 3 months after surgery or because of recurrence. The databases were assessed for uncommon clinical scenarios (e.g. patients coded as receiving chemotherapy before or during local treatment), and those charts were reviewed manually.

Patients were classified by primary radical local treatment into 2 groups: surgery or RT. Nine patients who received surgery plus adjuvant (n=8) or neoadjuvant (n=1) RT were included in the surgery group. Patients were classified as receiving radical RT if treatment intent was coded as 'radical' and they received a dose equivalent to 40 Gy in 20 fractions or higher. Since several fractionation schemes were used with a variety of fraction sizes, RT doses were normalized to 2 Gy per fraction equivalents using the linear-quadratic formula (17).

This resulted in a final sample size of 558 patients, 310 treated with surgery and 248 treated with RT. The RT cohort includes all stage I patients treated with RT in BC. In this study era, all of these patients would have been routinely treated with three-dimensional-conformal RT as 4-dimensional CT scanning was not available, and elective nodal irradiation would not be standard. The surgical cohort only includes patients referred to the BCCA. Using data from previously administered surveys of family physicians of non-referred patients (18), we estimate that approximately 25% of stage I patients treated with surgery alone during this time period are captured in this cohort. The surgical patients included here either underwent surgery under the care of a BCCA surgeon, or were referred for any BCCA service within the time periods specified above.

Following data analysis, the accuracy of the final dataset was assessed by a random review of the charts of 10% of patients. The database was found to be highly accurate, with only minor deviations found, none of which affected inclusion in the present study or outcomes.

Statistical Analysis

Baseline differences between the elderly (age $\geq$ 75) and non-elderly patients were compared using the t-test, Fisher's Exact test, or the Chi-squared test, as appropriate. Kaplan-Meier estimates of overall survival (OS) and disease-specific survival (DSS) from date of diagnosis were generated, with differences compared using the log rank test. Cox Regression analysis was used to determine the factors associated with survival outcome after the proportional hazards assumptions were confirmed. Age was considered as a continuous variable for multivariate analysis. Due to the potential for competing risks of death influencing the DSS analysis, these were confirmed using a cumulative incidence methodology (19) and Fine and Gray's regression analysis (20) (results did not differ and are not shown). All statistical tests were two-sided with $p \leq 0.05$ indicative of statistical significance, done using the Statistical Package of Social Sciences (SPSS version 16.0, Chicago, Illinois) or R (version 2.6.0).

Results

The clinical characteristics of the 558 patients meeting the inclusion criteria are shown in Table 1, stratified by age and treatment modality. In the whole cohort, 310 patients were treated with surgery and 248 with RT, of whom 211 (38%) were age 75 or older. The median follow-up for all patients was 2.4 years (range 0.1 – 8.2 years). Older patients were much less likely to undergo surgery than their younger counterparts (72% of patients age < 75 vs. 43% of patients age ≥ 75, $p<0.0001$).

Patients treated with surgery

Of the 310 patients treated with surgery, the median age was 67 years (range 20-86 years), and 63 patients (20%) were age 75 or greater. A comparison of the older and younger age groups (shown in Table 1) revealed no significant differences in baseline characteristics.

There were 75 deaths among the patients treated with surgery. Estimated OS at 2 years was 87% and at 5 years was 69%. Figure 1 shows OS stratified by age category, with no significant difference between elderly and younger patients ($p=0.38$). In elderly patients, the OS rates were 88% at 2 years and 65% at 5 years. There were no changes in OS by era of diagnosis (before 2003 vs. 2003-2004 vs. 2005 or later) in the whole surgical cohort ($p=0.32$) or in the subset of surgical patients who were elderly ($p=0.61$). On multivariate analysis (Table 2A), age was not predictive of OS, whereas tumor stage and ECOG performance status were predictive of OS.

Of the 75 deaths, 50 were due to lung cancer. DSS was 91% at 2 years and 79% at 5 years. Figure 1B shows DSS by age category, indicating a trend toward inferior DSS in the patients aged 75 or older, but this did not meet statistical significance (log-rank $p=0.10$). On multivariate analysis tumor stage and ECOG score were predictive of DSS, whereas age was not (Table 2B).

Table 1. Clinical characteristics of 558 patients with stage 1 NSCLC, treated with radical radiotherapy or surgery, stratified by treatment and age. Percentages are by column.

	SURGERY			RADIATION		
Variable	**Age < 75**	**Age ≥ 75**	**P-value* comparing age groups**	**Age < 75**	**Age ≥ 75**	**P-value* comparing age groups**
N	247	63		100	148	
Age (median, range)	64 (20-74)	77 (75-86)		70 (49-74)	80 (75-90)	
Sex (no, %)			0.09			0.90
Male	136 (55%)	27 (43%)		60 (60%)	87 (59%)	
Female	111 (45%)	36 (57%)		40 (40%)	61 (41%)	
Stage						
1A	75 (30%)	20 (32%)	0.88	54 (54%)	74 (50%)	0.60
1B	172 (70%)	43 (68%)		46 (46%)	74 (50%)	
Years of F/U (median, range)	2.9 (0.2-7.8)	2.8 (0.2-7.5)	0.88	2.1 (0.3-7.8)	1.9 (0.1-8.2)	0.87
ECOG (no, %)						
0-1	151 (61%)	34 (54%)	0.49	51 (51%)	89 (60%)	0.30
2-3	31 (13%)	11 (18%)		18 (18%)	25 (17%)	
Unknown	65 (26%)	18 (28%)		31 (31%)	34 (23%)	
Driving time to nearest cancer center > 2 hrs (no, %)	65 (26%)	18 (29%)	0.75	26 (26%)	34 (34%)	0.65
Histology (no, %)			0.11			0.42
Squamous	54 (21%)	23 (36%)		34 (34%)	47 (32%)	
Large cell	21 (9%)	3 (5%)		5 (5%)	3 (2%)	

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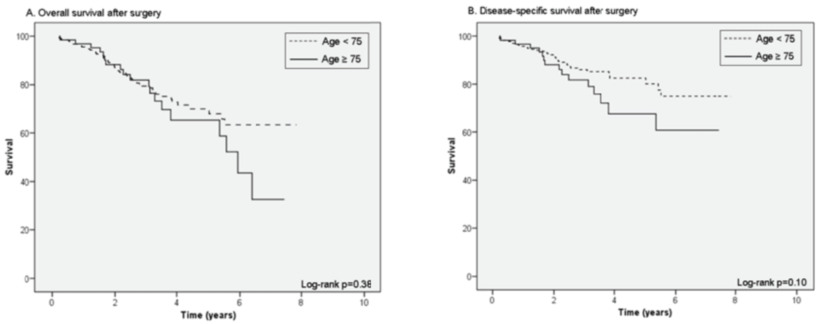
Adenocarcinoma	145 (59%)	31 (49%)			18 (18%)	36 (24%)	
NSCLC not otherwise specified/other	27 (11%)	6 (10%)			43 (43%)	62 (42%)	
Mediastinoscopy (no, %)	129 (52%)	31 (49%)	0.68		19 (19%)	16 (11%)	0.09
Surgical Procedure			0.21				
Lobectomy	206 (83%)	56 (89%)			N/A	N/A	
Pneumonectomy	19 (8%)	1 (2%)			N/A	N/A	
Segmental resection	22 (9%)	6 (9%)			N/A	N/A	
Radiotherapy Dose (normalized to 2 Gy per fraction) (median, range)	N/A	N/A			58 Gy (42-76)	58 (42-70)	0.132

*T-test, Fisher's Exact test, or Chi-Squared test as appropriate

Figure 1. A. Overall survival and **B.** Disease-specific survival for 310 patients with stage I NSCLC treated with surgery.



Patients treated with Radical RT

The median age of the 248 patients in the RT cohort was 76 years (range 49-90 years), and 148 (60%) were age 75 or greater. The diagnosis of NSCLC was made by cytology or pathology in 229 cases (93%). Comparison of the older and younger age groups revealed no significant differences in baseline characteristics (Table 1).

Most patients received hypofractionated RT regimens. The most common dose-fractionation regimens were: 55 Gy in 20 fractions (49% of patients); 50 Gy in 20 fractions (13%); 52.5 Gy in 20 fractions (6%); 60 Gy in 25 fractions (4%); and 60 Gy in 30 fractions (4%). Four patients (1.6%) received chemotherapy as part of their initial treatment. The median normalized dose was 58 Gy in 2 Gy fractions.

There were 174 deaths in the RT cohort. The estimated OS for RT patients at 2 years was 55.3% and at 5 years was 20.3%. A comparison of OS by age category is shown in Figure 2A. The overall survival rates for the elderly patients were 53% at 2 years and 22% at 5 years. There was no difference between the older and younger groups in OS (log-rank p=0.88), and there were no differences in OS by era of diagnosis (before 2003 vs. 2003-2004 vs. 2005 or later) in the whole RT cohort (p=0.44) or in the elderly RT cohort (p=0.65). On multivariate analysis (Table 2C), factors predictive of OS were tumor stage, sex, and dose, while age was not a significant predictor.

Table 2. Cox multivariate analysis of factors predictive of overall survival (OS) and disease-specific survival (DSS) after radical treatment for stage 1 lung cancer with surgery (**A**. OS and **B**. DSS) or radiotherapy (**C**. OS and **D**. DSS). HR: Hazard Ratio; CI: Confidence Interval

Surgical Patients				
	Factor	HR	95% CI	p-value
A. OS				
	Age (per year increase)	1.002	0.98-1.02	0.87
	Tumor stage T2 (vs. T1)	**1.76**	**1.04-2.95**	**0.034**
	ECOG score >1 (vs. 0-1)	**1.06**	**1.01-1.13**	**0.03**
	Female sex	0.70	0.44-1.10	0.12
	Squamous histology (vs. non-squamous)	0.76	0.43-1.36	0.32
	Distance from cancer centre > 2 hrs	0.97	0.57-1.63	0.89
B. DSS	Age	0.997	0.97-1.02	0.81
	Tumor stage T2	**1.96**	**1.01-3.78**	**0.045**
	ECOG score >1	**1.06**	**1.01-1.12**	**0.03**
	Female sex	0.70	0.39-1.22	0.20
	Squamous histology	1.05	0.55-1.99	0.89
	Distance from cancer centre > 2 hrs	1.08	0.57-2.03	0.82

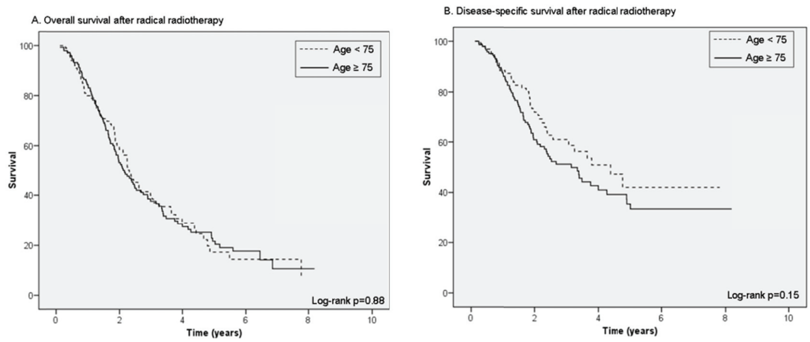
(Table 2 continued)

Radiotherapy Patients

	Factor	HR	95% CI	p-value
C. OS				
	Age	1.01	0.99-1.03	0.43
	Tumor stage T2	**1.39**	**1.03-1.87**	**0.033**
	Normalized dose (per 1 Gy increase)	**0.95**	**0.91-0.99**	**0.01**
	ECOG score >1	1.12	0.94-1.33	0.21
	Female sex	**0.73**	**0.54-0.99**	**0.044**
	Squamous histology	1.17	0.82-1.69	0.35
	Distance from cancer centre > 2 hrs	0.89	0.62-1.29	0.55
D. DSS	Age	1.01	0.99-1.04	0.27
	Tumor stage T2	**1.49**	**1.06-2.07**	**0.02**
	Normalized dose	0.96	0.91-1.003	0.06
	ECOG score >1	1.06	0.87-1.31	0.56
	Female sex	0.80	0.56-1.14	0.21
	Squamous histology	1.21	0.78-1.92	0.30
	Distance from cancer centre > 2 hrs	0.89	0.59-1.34	0.58

Of the 174 deaths, 110 were due to lung cancer. The estimated DSS at 2 years was 65.2% and at 5 years was 38.1%. Kaplan-Meier estimates of DSS by age category are shown in Figure 2B. There was no significant difference between the older and younger groups in DSS (p=0.15). On multivariate analysis (Table 2D), the only factor predictive of DSS was tumor stage, whereas RT dose approached significance and age was not predictive.

Figure 2. A. Overall survival and **B.** Disease-specific survival for 248 patients with stage I NSCLC treated with radical RT.



Discussion

We present a large study of 558 patients with stage I lung cancer treated with curative intent, either with surgery or radical RT, using prospectively collected data. To our knowledge, this is the largest study addressing outcomes after both radical surgery and RT in elderly stage I patients. Our analysis is unique in capturing outcomes in patients who were fit for surgery and underwent resection, but also those who were unfit or declined surgery and proceeded to radical RT instead. Although other studies have compared outcomes between patients treated with surgery vs. RT, often the RT cohort included patients treated both radically and palliatively (3), obscuring outcomes for radical RT.

Our data confirm that elderly patients are much less likely to receive surgery than their younger counterparts – only 30% of elderly patients in this study underwent resection, compared to 71% of younger patients. However, when stratified by treatment, survival rates in the elderly compare very favorably with their younger counterparts who underwent the same therapies, and age was not found to be predictive of survival outcomes on multivariate analysis. Although the Kaplan-Meier estimates of DSS appeared to show trends towards inferior survival in older patients, after controlling for other factors on multivariate analysis these trends were no longer apparent. Instead, the factors predictive of survival outcomes were tumor stage and ECOG performance score for surgical patients, and tumor stage, dose, and sex for RT patients. These findings indicate that if elderly patients are fit enough to be referred and selected for radical treatment, whether surgery or RT, then age does not contribute significantly to survival outcomes.

Although outcomes for elderly patients with stage I NSCLC are variable and strongly reflective of the baseline patient population, the OS estimates in our study are consistent with published data (21-23). Comparisons between outcomes RT and surgery are very difficult, and were not done in this study. Although the outcomes after RT appear to be inferior to surgery, the exact difference in outcomes between the two treatments cannot be easily ascertained. The two treatment populations differ in baseline characteristics and staging (pathological vs. clinical). Furthermore, the presence of 'confounding by indication' is very difficult, if not impossible, to address (24).

Most series have indicated that long-term survival after surgery or RT for early stage lung cancer is not affected by age (3;25), although some studies have found an inferior prognosis with advanced age (26). The largest study, by Siegel *et al*, examined over 27,000 patients with Stage I NSCLC from the Surveillance, Epidemiology and End Results (SEER) database. They found that elderly patients who underwent resection have similar survival to younger patients (3). The only previous study, to our knowledge, that examined both surgery and radical RT in elderly stage I patients was published in 1988 with 138 patients, and reported that age did not affect post-treatment survival (27).

Although age does not appear to predict survival in patients who receive radical treatment, age does impact upon whether patients are referred for treatment, and whether curative treatment is offered. Rates of referral and radiotherapy utilization have been shown to decrease with age (7). As a result, the patients included in studies examining outcomes after radical treatments represent a selected group that likely differs from the baseline population of elderly patients. Our data did not allow us to draw conclusions on elderly patients with stage I NSCLC who were never referred for treatment.

Treatment options for elderly patients with stage I NSCLC have evolved over the past 10 years, and newly diagnosed patients may have more options available than the patients in this cohort. Minimally invasive surgery using video-assisted thoracic surgery (VATS) decreases operative morbidity and can allow for resection in elderly patients who would otherwise be unfit for surgery (28). Fitness for surgery and operative mortality risks can be assessed pre-operatively using validated instruments (29). There has been a change in the RT treatment paradigm, with the delivery of large ablative doses using stereotactic body radiation therapy (SBRT). SBRT has been shown to achieve high rates of local control in elderly patients, with a good side-effect profile (30).

The findings of this study should be considered in the context of its strengths and limitations. As is common with the use of large administrative databases, data was not recorded for all variables of interest, particularly co-morbidities, weight loss at presentation, toxicity, and quality of life. Patients with stage I disease who received palliative RT or no treatment are not included, and these patients may be more likely to be elderly (7). The surgical data is not population-based, and elderly patients may have been less likely to be referred to a BCCA surgeon, or referred after surgery for consideration of adjuvant therapy. PET scanning was not widely available in BC until 2004, and therefore most patients in this cohort did not undergo PET scans.

In conclusion, our study shows that survival outcomes for elderly patients after radical treatment for stage I NSCLC are similar to those of younger patients, whether treated with surgery or RT. In making decisions regarding treatment for elderly patients, oncologists should consider the individual characteristics of each patient, and elderly patients who are sufficiently fit should be considered for curative treatments.

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