Lung cancer in octogenarians: factors affecting long-term survival following resection

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Abstract

Objective: To identify factors associated with long-term survival following pulmonary resection for lung cancer in patients 80 years of age or older.

Methods: The medical records of all patients ≥80 years, who underwent pulmonary resection for lung cancer from 1985 to 2002, were reviewed.

Results: There were 294 patients (192 men, 102 women). Median age was 82 years (range 80—94 years). Overall 1-, 2-, and 5-year survival was 80%, 62%, and 34%, respectively. Histologic subtype, diabetes, renal insufficiency, prior myocardial infarction, congestive heart failure or stroke were not significantly associated with differences in 5-year survival. Female gender was associated with increased survival (36.2% vs 32.7% at 5 years, \( p = 0.04 \)). Extent of preoperative forced expiratory volume in 1 s (FEV1) limitation did not influence survival. However, there were no 5-year survivors amongst patients with dyspnea as their presenting chief complaint, whereas there was a 35% 5-year survival in patients presenting without dyspnea (\( p < 0.001 \)). Five-year survival by pathologic stage was IA, 48%; IB, 39%; IIA, 17%; IIB, 23%; IIIA, 9%; and IIIB, 0% (\( p < 0.001 \)). Five-year survival of patients undergoing a lobectomy was 42% versus 11% for pneumonectomy (\( p < 0.001 \)). Conclusions: Meaningful long-term survival is obtainable in elderly patients undergoing surgical resection for lung cancer. Careful patient evaluation and selection is necessary to identify patients who will benefit most from resection. Shorter survival was observed in male patients and those presenting with dyspnea. As could be expected, survival was also dependent on extent of resection and initial pathologic stage.

Keywords: Pulmonary resection; Lung cancer; Geriatric

1. Introduction

Long-term survival following resection for lung cancer in octogenarians has been reported in multiple surgical series [1—8]. While studies have repeatedly shown that surgery remains the optimal treatment for patients who are deemed to have resectable disease, even in this age group, most reports include only small patient numbers, thus limiting their ability to identify factors predicting long-term survival. The objective of this study is to elucidate predictors of long-term survival by statistical analysis of our experience in a large cohort of patients 80 years of age and older, who were selected for pulmonary resection.

2. Materials and methods

From January 1985 through September 2004, 379 patients 80 years of age or older underwent pulmonary resection with curative intent for non-small cell lung cancer (NSCLC) at Mayo Clinic, Rochester, Minnesota. To ensure sufficient time for follow-up, we restricted our present long-term analysis to patients undergoing surgical resection from January 1985 through, and including, August 2002. In order to concentrate on factors related to long-term survival, patients with operative deaths, reported previously, were excluded for purposes of statistical analysis [9]. Information on the following variables was abstracted from the medical records: age, gender, comorbidities, presenting signs and symptoms, smoking history, pulmonary function testing, extent of resection, tumor histology, and pathologic stage. For the purposes of statistical analysis, forced expiratory volume in 1 s (FEV1) values were grouped into three categories: <40% predicted, 40—70% predicted, and >70% predicted. To avoid inconsistencies related to major changes in the international staging system during the

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study period, all cases were re-staged according to the 1997 staging system [10]. This study was approved by the Mayo Clinic College of Medicine’s Institutional Review Board.

Descriptive statistics for discrete variables are presented as frequencies and percentages, whereas medians and ranges are employed for continuous measures. The Kaplan–Meier survival method was used to estimate patient survival, and the log rank test was used to assess associations between potential risk factors and survival [11,12]. The starting date in these analyses was postoperative day 31 or the date of hospital discharge — whichever was later. p-values < 0.05 were considered statistically significant.

3. Results

Operative mortality for the entire cohort (January 1985—September 2004) was 6.3% (24/379). Complications occurred in 48.0% (182/379), with atrial fibrillation and retained secretions requiring bronchoscopy being the most common [9].

In the long-term follow-up group (January 1985—August 2002), there were 294 patients including 192 men (65.3%) and 102 women (34.7%). Median age at the time of surgery was 82 years (range 80—94 years). Initial presentation was asymptomatic in 196 patients (71.5%), their tumor being incidentally discovered on screening radiologic studies obtained during routine medical examinations or as part of an evaluation for other unrelated medical problems. Of the 78 patients presenting with one or more symptoms, the most common presenting symptoms included cough in 35 (12.8%) patients, hemoptysis in 25 (9.1%), dyspnea in 16 (5.8%), chest pain in 12 (4.4%), weight loss in 5 (1.8%), and generalized muscle weakness in 1 (0.4%). Symptom data were not recorded for 20 patients.

Comorbidity was identified preoperatively in 188 (63.7%) patients, including congestive heart failure in 21 (7.3%), previous myocardial infarction in 19 (6.6%), previous coronary artery bypass grafting in 23 (8.0%), previous stroke in 12 (4.2%), chronic corticosteroid use in 12 (4.2%), renal insufficiency (defined as serum creatinine > 1.5 mg/dl) in 33 (11.5%), non-insulin-dependent diabetes mellitus in 16 (5.6%), and insulin-dependent diabetes in 5 (1.7%). Sixty-two patients (22%) had a history of another prior malignancy, most commonly prostate cancer. Comorbidity data were unavailable in six patients. Among the 240 patients with FEV1 data, an FEV1 < 40% of predicted was found in 17 patients (7.1%), ≥40% and <70% in 95 (39.6%), and ≥70% of predicted in 128 (53.3%).

Tumor histology was adenocarcinoma in 128 patients (43.6%), squamous cell carcinoma in 103 (35.0%), bronchoalveolar cancer in 42 (14.3%), and other in 21 (7.1%). Lobectomy or bilobectomy was performed in 196 patients (66.7%), while segmentectomy or wedge excisions were performed in 77 patients (26.2%). Pneumonecтомy was performed in 21 patients (7.1%). Complete mediastinal lymph node dissection was performed in 277 patients (94.9%). The pathologic stage was IA in 104 (35.4%) patients, IB in 92 (31.3%), IIA in 7 (2.4%), IIB in 34 (11.7%), IIIA in 38 (12.9%), IIIB in 12 (4.1%), and IV in 7 (2.4%). Only two patients (0.7%) received adjuvant chemotherapy and nine (3.3%) underwent adjuvant radiotherapy.

Follow-up data were complete in all patients with a median follow-up of 2.2 years (range 1 month—13.6 years). Eighty-three patients are currently alive and 211 have died. Among those who are alive, 7 patients have had recurrence while 76 are clinically disease-free. Cause of death was cancer-related in 65 patients (30.8%), non-cancer-related in 61 (28.9%), and unknown in 85 (40.3%).

Table 1 provides 1- and 5-year survival, with preoperative variables and presenting symptoms considered as potential risk factors. The only symptom significantly associated with worse prognosis was dyspnea (p < 0.001); 1- and 5-year survival for patients with dyspnea was 67.0% (95% confidence
group in our institution was 6.3%, with 48% of patients.

extrapolation of survival data obtained in much younger populations.

long-term outcome analysis is of paramount relevance since the predictable loss of physiologic reserve precludes easy development at least one early complication [9]. Congestive heart failure and a history of previous myocardial infarction were the only independent factors identified as associated with a significantly higher mortality risk.

Previous series reported 5-year survival rates ranging from 32% to 55% [1,2]. This wide range is likely due to a varying degree of three well-known confounding factors: (1) selection bias; (2) small sample sizes in each series (range 8–68); and (3) incompleteness of follow-up. The only report, other than the current one, to include data on completeness of follow-up was by Brock et al., in which only 1 of 68 patients was lost to follow-up, with an overall 5-year survival of 34% [7]. The overall 5-year survival in the current series was 34% as well.

Perhaps the most striking difference between our series and previous reports is the survival in those most likely to benefit from surgical resection, namely, patients with early-stage cancer. In a series of 61 octogenarians by Port et al., the 5-year estimated survival based on the 21 patients with stage IA disease was 82% [8]. This figure is far superior to the frequently quoted 67% based on the report by Mountain [10], and higher even than the 79% in a large series from the Japanese Lung Cancer Registry published by Goya et al. in 2005 [13], even though these reports are based on patients with a median age almost 20 years younger. By contrast, our study included 104 patients with pathologic stage IA, with an actuarial 5-year survival of only 48%.

There is little previous information regarding predictors of long-term survival. Osaki et al. found that postoperative cardiac and pulmonary complications portend lower survival rates [2]. Brock et al. reported that FEV1, American Society of Anesthesiology (ASA) class, and pathologic stage were associated with significant differences in survival [7]. In the present study there were no differences in survival according to FEV1 category. This may be due to a lack of power to determine a true difference (beta error) since only 17 of our patients had an FEV1 less than 40% of those predicted. Pulmonary function is, indeed, a fundamental consideration in preoperative evaluation, as illustrated by the fact that, in interval = 54, 82) and 0%, as opposed to 80.6% (95% confidence interval = 77, 85) and 34.9% (95% confidence interval = 29, 38) in those without dyspnea on presentation. The presence of cough, hemoptysis, chest pain, weight loss, or asymptomatic presentation was not associated with significant differences in survival. Preoperative limitation of FEV1 was not significantly associated with poorer survival (p = 0.20). The presence of the listed comorbidities did not portend a worse prognosis, and neither did advancing age. Thus, other than dyspnea, the only preoperative factor significantly associated with a poor prognosis was male gender.

Survival by cell type, pathologic stage, and extent of resection was analyzed (Table 2). There was no statistically significant association between histologic cell types of NSCLC and survival. Increased survival was observed for patients undergoing lobectomy or bilobectomy, as compared with sublobar resections and pneumonectomy (p = 0.0001). Long-term survival was closely associated with pathologic stage (p < 0.0001). There was no statistical difference in the long-term survival of patients undergoing resection during the first half of the study period (1985–1993) versus the second half of the study period (1994–2002).

### 4. Discussion

As life expectancy increases, so will the incidence of lung cancer in octogenarians and the demand for appropriate modes of treatment. The conventional bias against surgical therapy in the elderly, and in octogenarians in particular, is being challenged as acceptable outcomes in selected cohorts have been reported [1–9]. In this special patient population, long-term outcome analysis is of paramount relevance since the predictable loss of physiologic reserve precludes easy extrapolation of survival data obtained in much younger populations.

As previously reported, operative mortality for this age group in our institution was 6.3%, with 48% of patients developing at least one early complication [9]. Congestive heart failure and a history of previous myocardial infarction were the only independent factors identified as associated with a significantly higher mortality risk.

Previous series reported 5-year survival rates ranging from 32% to 55% [1,2]. This wide range is likely due to a varying degree of three well-known confounding factors: (1) selection bias; (2) small sample sizes in each series (range 8–68); and (3) incompleteness of follow-up. The only report, other than the current one, to include data on completeness of follow-up was by Brock et al., in which only 1 of 68 patients was lost to follow-up, with an overall 5-year survival of 34% [7]. The overall 5-year survival in the current series was 34% as well.

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our series, there were no 5-year survivors in the group of patients presenting with dyspnea.

Pathologic stage was, as expected, the most important predictive factor of survival (Table 2). The relatively high survival of stage IV patients (28.6%) may be explained by the fact that most of the seven patients within this category were deemed stage IV by virtue of a synchronous pulmonary metastasis found incidentally in a different lobe. All were of the same histologic cell type as the index cancer. Battafarano et al. have shown that this subgroup of stage IV lesions tends to have an improved survival if resected [14]. Nevertheless, this degree of survival with such a high stage in a group of octogenarians was completely unexpected and may also be an indicator of the high degree of selection that is generally seen in these patients.

When analyzing outcomes by extent of resection, the best 5-year survival is achieved in patients undergoing lobectomy or bilobectomy (40.8%). Sublobar resections were associated with a 5-year survival of only 24%. Here again a selection bias may be an important confounding factor. In this retrospective series, it is likely that limited resections were a surrogate for patients with more severe preexisting respiratory compromise, leading to less extensive pulmonary resections. Those undergoing pneumonectomy also had a poorer long-term survival with a 10.6% 5-year survival. This likely demonstrates the effect due to both the extent of disease requiring a pneumonectomy for complete resection and the limited ability of these elderly patients to withstand, over the long-term, the loss of pulmonary function involved in a pneumonectomy.

The strengths of our study include its relatively large size, the completeness (100%) of follow-up, and the inclusion of clinical presentation and comorbidities in the analysis of prognostic factors. Limitations include its retrospective nature and, by implication, its inherent risk of significant selection bias. Furthermore, given the data available to us for this present study, we were unable to address an important consideration in all surgical interventions but especially in geriatric populations: quality-of-life measures after surgery. As the number of octogenarians with lung cancer increases, the attention of clinicians and investigators will focus more toward developing accurate, large databases and prospective trials to overcome these limitations.

At this time, there do not appear to be more promising evidence-based options to treat lung cancer in octogenarians. While there are only a few surgical series in populations of this age, the published research in radiation and medical oncology remains even more limited. Radiotherapy alone in patients 70 years or older with clinical stage I NSCLC has achieved 5-year survival of 34% [15] — a result inferior to the survival after surgical resection in all available studies, including the current one. No study was found reporting results of chemotherapy for NSCLC in octogenarians. Several salient issues related to chemotherapy in the elderly must, however, be emphasized. First, in the present study, only 2 of 294 patients underwent chemotherapy. Besides reflecting the high proportion of early-stage cancers in our cohort, this likely illustrates the reluctance to offer or accept chemotherapy in the 98 patients with stage II or higher. Secondly, for locally advanced lung cancer, the significant risk of short-term toxicities in older patients may outweigh the survival rate benefit. Radiation alone, therefore, may be the best choice in aged patients who are perceived to be poor operative candidates [16].

In summary, while resection for lung cancer remains the treatment of choice in all patients with clinically resectable NSCLC, including octogenarians, 5-year survival in stage IA disease within this cohort is considerably lower than is seen in younger cohorts. Decreased survival was associated with two preoperative factors: dyspnea as a presenting sign and male gender. Extent of resection and pathologic stage also had a significant prognostic value in terms of long-term survival.

References


Appendix A. Conference discussion

Dr B. Passlick (Freiburg, Germany): I have one short question: Did you present us the cancer-related survival or was that overall survival — that means death from any cause?

Dr Dominguez-Ventura: What I have presented is the overall survival. Looking at our data, we were able to define the cause of death in roughly two-thirds of the patients. Of those two-thirds in which we knew the reason they died, half died of a cancer-related cause and half died of some other non-cancer cause.
Dr D. Branscheid (Grobhansdorf, Germany): What is your net survival rate? Net survival rate is the survival rate according to cancer and according to normal life expectancy of an 80-year-old American guy or girl.

Dr Dominguez-Ventura: We did not present those numbers. An otherwise healthy American who reaches the age of 80 is expected to live until the age of 88. Our overall survival is 34% at 5 years versus, I would estimate, something like 15% for the general population.

Dr Branscheid: 43% net survival rate. That’s incredible.

Dr Dominguez-Ventura: 34%.

Dr T. Lerut (Leuven, Belgium): This is a real nice study on a large cohort of patients. But obviously these patients, as you said, are a result of a selection both from an oncological and a medical point of view. What is the bottom-line? How many of the referred patients and who were potentially candidates from an oncological point of view had to be refused because they were medically not fit for surgery?

Dr Dominguez-Ventura: We did not evaluate the denominator, in other words, the total number of patients referred. Our database for this study project includes patients whom we operated on, not necessarily everybody who was seen in the clinic.

Dr Lerut: I thought that the Mayo Clinic had the biggest database in the world.

Dr M. Beshay (Bielefeld, Germany): There were 77 patients who received sublobectomy resection in the form of segmentectomy or wedge resection. What were the selection criteria? Is this based on patient condition, comorbidity, or on the lung function of these patients? It would be good if you would give us your selection criteria. I know it’s a retrospective study, but how would you suggest to operate on some patients and to reject others?

Dr Dominguez-Ventura: In a retrospective-type study it can be difficult to exactly determine the selection criteria used for these patients. Most of these sublobar resections were wedge excisions and the patients were selected based on the individual surgeon’s evaluation. There have been nine thoracic surgeons in our division over the course of the 18 years of this study.

Dr Beshay: But do you do a routine cardiological examination for these 80-year-old patients?

Dr Dominguez-Ventura: In general our evaluation is the same for every patient. If they meet the requirements for operability and resectability, they will qualify for surgery regardless of age. To determine this we perform certain standard testing including pulmonary function tests, cardiac testing individualized to each patient’s particular symptoms, and risk factors.

Dr J. Thorpe (Leeds, United Kingdom): There was a paper several years ago from Edinburgh that showed that the over 75-year patient is at a higher risk of stroke and myocardial infarct. How do you assess the cardiac-risk patients? What do you do? Do you repeat angiograms in patients with previous coronary arterial disease or do you just look at left ventricular function? How do you assess that difficult group of cardiac high-risk patients?

Dr Dominguez-Ventura: We don’t have a specific or generic protocol. In general, for the octogenarian patient, we obtain a history and physical, and if the patient has no evidence of cardiac disease and has a good functional status, we obtain a dobutamine or stress echocardiographic examination. If the patient does have symptoms, they will undergo a full workup individualized to their symptoms, risk factors, and clinical findings.