Lung cancer in patients aged 80 years and over

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Abstract

Objectives: The purpose of this study is to examine clinical and pathological features, treatment modality approaches in the elderly, especially in patients aged 80 years and older.

Methods: From the databases at two educational hospitals during the period from January 1978 and December 2007, medical records of lung cancer patients were retrospectively reviewed. The patient population was divided into three age groups: less than 70 years (the <70 age group), 70-79 years (the 70-79 age group), and 80 years or older (the ≥80 age group). Time trends were also studied in two-time intervals: first study period up to 1997, which represents past practice standards, the second study period up to 2007, which represents contemporary practice.

Results: Patients aged 80 years and older comprised 7.5% of 2775 consecutive patients with lung cancer, and there was a rapid increase in the proportion of patients aged 80 years or older from the earlier to the later time period. The ≥80 age group had higher proportion of poor performance status (PS) and comorbid disease than the <70 age group and the 70-79 age group. Unchanged proportion of patients with poor PS and advanced disease at presentation were observed in the ≥80 age group. The ≥80 age group was less likely to be subjected to surgery or chemotherapy, and had inferior outcomes when compared with the 70-79 age group and the <70 age group. Survival improvement was not observed in the ≥80 age group. Multivariate analysis showed good PS, early clinical stage and surgery were favorable prognostic factors in the ≥80 age group.

Conclusion: In order to improve the outcome, detection of early stage lung cancer in patients with good PS and thorough pretreatment evaluation for appropriate treatment are indeed essential even for the ≥80 age group of patients.

1. Introduction

In developed countries, populations are becoming older and the elderly have a higher incidence of malignant diseases. Among malignant diseases, the incidence and mortality of lung cancer has increased worldwide during the last few decades [1,2]. The majority of cases of lung cancer diagnosed were those between the ages of 50 and 80 years, as a result there is little data relating to the clinical characteristics, disease status, treatment modality, and survival of patients aged 80 years and over [3-5]. Too few patients older than 80 years were included in previous clinical trials to make any conclusions regarding this age group, therefore, additional studies specifically focusing on these elderly patients are required. With recent improvements in the medical management of lung cancer, the availability of many new drugs, and a better standard of medical care and more widespread health services, survival in these elderly patients might have changed. Very recently, Owonikoko et al. analyzed the outcomes for lung cancer in the very elderly using the national Surveillance, Epidemiology, and End Results Database (SEER) in U.S.A. [6]. Nevertheless, there was a lack of information on the impact of performance status (PS: ECOG), comorbid disease, and chemotherapy on survival outcomes. To address the question of whether the overall survival of lung cancer patients 80 years of age or older has improved, therefore, we here reviewed retrospectively the clinical data from the consecutive patients with lung cancer diagnosed at our two tertiary hospitals to assess the incidence and outcome of lung cancer in the very elderly. We also focused on the role of PS, comorbid disease and treatment modalities including chemotherapy on survival of the elderly patients aged 80 years or over.

2. Patients and methods

Clinicopathological data for all the consecutive patients with lung cancer were obtained by retrospective review from the databases at University of Tsukuba Hospital or Tsukuba Medical Center Hospital and Regional Cancer

Center. The patients were diagnosed pathologically and treated between January 1978 and December 2007 at these two tertiary hospitals. Pathological diagnosis was defined by the WHO classification [7]. Staging was recorded for patients with non-small cell lung cancer (NSCLC) according to TNM classification [8] and those with small cell lung cancer (SCLC) according to limited disease/extensive disease classification. Demographic data, including age, gender, and PS, were retrieved from the medical records of them along with the specific details of the cancer. We evaluated the number of comorbid disease and seriousness of comorbid disease using Charlson index (CI) score [9]. This study was approved by the Institutional Ethics Committee of each hospital. According to the recent studies on outcomes in octogenarians, the entire patient population was divided into three age groups: less than 70 years (the <70 age group), 70-79 years (the 70-79 age group), and 80 years or older (the≥80 age group) at diagnosis [6,10]. The median survival time (MST) was compared among the three age groups as defined by gender, histologic subtype, stage, and therapy. Two predefined time periods, that is patients presenting between 1978 and 1997 and between 1998 and 2007 was used for comparison of survival. The year 1998 was chosen as a cutoff point because of two reasons. One reason was third generation cytotoxic agents such as taxanes, gemcitabine, vinorelbine, and irinotecan were introduced around this time to treat both NSCLC and SCLC patients. Another reason was a very large-scale study using SEER database, which included 316,682 patients, by Owonikoko et al. chose this year as a cutoff point [6]. Differences of distribution of subpopulations between each period were analyzed using a Chi-square test. The Kaplan-Meier method was used to assess survival curves and the log-rank test to evaluate the statistical significance of differences between the two groups [11,12]. The length of survival was defined as the interval in months from the date of the initial therapy or supportive care until the date of deaths or the date of last follow-up. The Cox proportional hazard model was used to study the effects of age on survival while adjusting for other important factors. All statistical analysis were performed using SPSS 10.1 for Windows (SPSS Inc., Chicaco, IL, USA) and a probability value less than 0.05 was considered to be significant.

3. Results

3.1. Demographics

A total of 2775 patients with lung cancer were registered during the 31-year period; 209 patients (7.5%) were 80 years or older (median, 82 years), 37.6%were 70-79 years (median, 74 years), and 54.9% of patients were younger than 70 years (median, 62 years) (Table 1). Men constituted approximately 76.1%, and distribution was comparable among the three age groups (Table 1). Poor PS (2-4) accounted for 15.3% in the <70 age group, 18.8% in the 70-79 age group and 45.0% in the ≥80 age group. 49.3% of the 209 elderly patients had two or more comorbid disease. Poor PS, number of comorbid disease, and number of CI in the ≥80 age group were significantly higher than those in other two control groups of patients (Table 1).

3.2. Histology and staging

NSCLC accounted for 87.6% in the <70 age group, 84.9% in the 70-79 age group and 89.0% in the 80 age group. Adenocarcinoma and squamous cell histology represented approximately 40-50% and 20-30% of patients in each of the three age groups (Table 1). In NSCLC patients, stage distribution at the time of diagnosis was similar for the three groups; stages IIIB or IV represented approximately half of patients in each of the three groups (Table 2). In SCLC patients, extensive disease at the time of diagnosis was similar for the three age groups; extensive disease represented more than half of patients in each of the three groups (Table 2).

3.3. Initial therapy for NSCLC and SCLC

In NSCLC, overall, 50.7%, 44.9%, and 18.3% of the <70 age group, the 70-79 age group, and the 80 age group, respectively, received surgery; 6.0%, 13.8%, and 30.6%, respectively, received radiation; and 32.1%, 22.1%, and 5.9%, respectively, received chemotherapy. In contrast, 11.2% of the <70 age group, 19.2% of the 70-79 age group, and 45.2% of the 80 age group received supportive care (Table 2). In SCLC, overall, 83.1%, 83.5%, and 73.9% of the <70 age group, the 70-79 age group, and the 80 age group, respectively,

received chemotherapy. In contrast, 5.3% of the <70 age group, 8.9% of the 70-79 age group, and 21.7% of the 80 age group received supportive care only (Table 2).

3.4. Survival

In overall lung cancer, MST was 21months for the <70 age group, 18 months for the 70-79 age group, and 12 months for the 80 age group. Similarly, the 80 age group had the worst outcome among both men and women; MST were 9 and 14 months in men and women, respectively, compare with 18 and 20 months, respectively, in the <70 age group (Table 3). In NSCLC, analysis by stage demonstrated the lowest survival rates in the 80 age group (Table 3). Table 4 shows survival analysis based on treatment modality. In NSCLC patients who received chemotherapy, the 80 age group had a worse survival than the <70 age group (Table 4). In SCLC, overall MST was 13 months for the <70 age group, 9 months for the 70-79 age group, and 9 months in the 80 age group. In overall SCLC patients, the 80 age group had poorer survival than the <70 age group (Table 3).

3.5. Temporal trend analysis

The 80 age group constituted a higher proportion of total patient cases (9.9%) in the more recent period, 1998-2007, compared with the earlier period of 1978-1997, in which they made up 4.4% (Table 1). The proportion of the 70-79 age group in the earlier and later time periods was 33.7% and 40.5%, respectively (Table 1). In the 80 age group, there were no changes in proportion of patients with poor PS, number of comorbid disease 2, number of CI 2 between the earlier and later time periods. On the other hand, there were significant increases in good PS (PS: 0-1) in the <70 age group and

the 70-79 age group (Table 1). In NSCLC, there was no significant change in the stage distribution across the three age groups, and no trend toward increased use of radiation or chemotherapy was observed (Table 2). There seemed to be increased use of surgery in the 80 age group between the two time periods, but it did not reach statistical significant difference (Table 2) ($p = 0.1866$). The survival pattern was similar during both time periods; the <70 age group had the best outcome, followed by the 70-79 age group and then the 80 age group (Table 3). In NSCLC, except for the 80 age group, there

was a trend of better overall survival in the recent period, 1998-2007 for the <70 age group and the 70-79 age group (Table 3). With regard to treatment modality for NSCLC, there was a substantial improvement in disease outcome for the <70 age group and the 70-79 age group with surgery, that for septuagenarians with radiation, and that for the <70 age group with chemotherapy, but the improvement was not observed in the 80 age group with any treatment (Table 4). In SCLC, overall, there was not a trend of better overall survival in the recent period for any three age groups (Table 3). However, there was a substantial improvement in disease outcome for the <70 age group with chemotherapy, but the improvement was not observed in the 70-79 age group and the 80 age group (Table 4).

3.6. Multivariate analysis

Table 5 summarizes the relationship between clinical variables and survival. In univariate analysis, age less than 80 years old, female gender, NSCLC, good PS, early clinical stage, number of comorbid disease, CI, and surgical treatment were statistically significant favorable prognostic factors. According to a multivariate Cox proportional hazards model, female gender, good PS, early clinical stage and surgery showed a statistical significance in survival. But number of comorbid disease, CI revealed no statistical significance in survival. Same analysis included only the ≥80 age group revealed good PS ($p = 0.001$, 95% confidence interval: 1.642-4.184), early clinical stage ($p = 0.001$, 95% confidence interval: 1.843-5.195), and surgical treatment ($p = 0.004$, 95% confidence interval: 1.561-10.70) were statistically significant favorable prognostic factors.

4. Discussion

There has been an increasing interest in the treatment of elderly patients with lung cancer [5,6,10,13-31].However, clinical information regarding lung cancer patients aged 80 years and over has not been fully available since such patients are not usually included in clinical trials and retrospective care analysis. Therefore, there is a great amount of scientific uncertainty regarding the risks and benefits of lung cancer treatment in patients aged 80 and older. Using the SEER database, Owonikoko et al. studied the burden and outcome of lung cancer in the elderly, particularly for patients aged 80 years and older [6]. Nevertheless, there was a lack of information on the impact of PS, comorbid disease, and chemotherapy on survival outcomes. We here reviewed retrospectively the clinical data from the consecutive patients with lung cancer diagnosed at our two tertiary hospitals to assess the incidence and outcome of lung cancer in the very elderly. According to the same analyses as previous studies [6,10], this study characterized lung cancer presentation and outcome in the very elderly patient population and compared it with that of septuagenarians and with the younger patient population. It is noteworthy that the ≥80 age group account for 7.5% of all lung cancers. This proportion was lower than 14% of the study by Owonikoko et al. [6], but there was a rapid increase in the proportion of the ≥80 age group from the earlier to the later time period. The ≥80 age group had higher proportion of patients with poor PS, and presence of severe comorbid disease than those in septuagenarians and patients younger than 70 years of age. In addition, there was unchanged proportion of patients with poor PS and advanced disease at presentation aged 80 years or older. Aging is associated with a high prevalence of comorbid diseases [17,18,27,31]. Particularly those patients with a long smoking history are predisposed to comorbid diseases such as chronic obstructive pulmonary disease and cardiovascular disease, as well as other smoking-related malignancies [19]. Findlay et al. reported the incidence of these comorbid diseases in patients with SCLC over the age of 70 years [19], which was almost same incidence as our results. The univariate analysis showed a significant association of number and severity of comorbid disease with a survival in our series of

older patients. However, they were not confirmed in the multivariate analysis. Several factors may account for the lower prognostic relevance of number and severity of comorbid diseases after 80 years of age. The patients aged 80 years or older might undergo a strict selection process before being scheduled for correct diagnosis of lung cancer [6,17,18]. Correct diagnosis of lung cancer is established by pathological specimens, which are usually obtained via transbronchial or transthoracic approach. Elderly patients with severe comorbid disease may be excluded in these processes of correct diagnosis. A frequent reason for withholding invasive diagnostic procedures from elderly patients with severe comorbid disease are the fears of complications, which can be a genuine, but not always justified, concern. Breen et al. showed the presence of comorbid condition (CI≥6) tended to be associated with poor survival in NSCLC patients, which was inconsistent with our results [31]. In their study, 41.2% of the elderly patients had CI ≥6, but there were only 5 of 209 patients with CI ≥6 in our study. Low frequency of severe comorbid disease in our elderly patients might influence on the results of multivariate analysis. The ≥80 age group was less likely to be subjected to surgery or chemotherapy, and had inferior outcomes when compared with the 70-79 age group and the <70 age group. A previous analysis of the linked SEER-Medicare database of patients with lung cancer who were older than 65 years and diagnosed between 1994 and 1999 revealed that elderly patients older than 75 years were less likely to receive chemotherapy [32]. Owonikoko et al. observed a consistent trend of lower rates of surgery and radiation therapy with increased age, whereby more than 80% of the younger population received this active therapy compared with 70% of septuagenarians and with only 50% of the very elderly [6]. But their analysis could not address all forms of therapy, especially chemotherapy. Our results were consistent with these large scale studies. It is a debatable question of whether the elderly patients will do as well as younger patients when standard therapy is administered for their stage of disease. Majority of elderly patients have been denied potentially beneficial treatment and participation in clinical trials solely because of chronological age and because of the physician perception that they are too frail to withstand treatment [24,25]. On the contrary, the benefit of standard therapy is well demonstrated in the elderly population in general and is comparable to the benefit obtained by younger patients [22-24,26]. In a

SEER-Medicine database study, the ≥80 age group had worse survival outcomes than the 70-79 age group and the <70 age group. Our results in both genders were consistent with this large scale study. O'Brien et al. recently reported the trends in the chemotherapeutic outcome in patients age ≥70 years with SCLC and NSCLC [14,15]. There was no improvement in survival in their NSCLC patients. On the other hand, there was a significant improvement in survival for elderly SCLC patients treated by chemotherapy in the past 20 years [14,15]. Their study included only 26 (8.0%) of 322 patients aged 80 years and over and the MST in the former study period was too short to compare. In the analysis by Owonikoko et al., there was a trend of better overall survival during 1998-2003 for all age groups, although they noted no substantial change in stage distribution of disease across these time periods [6]. As Owonikoko et al. suggested, the improved survival in the more recent period may also be a reflection of better supportive care measures or merely a function of stage migration resulting from advanced imaging modalities [6].We showed a trend of better overall survival only for the 70-79 age group and the <70 age group. There was an inconsistence between their results and ours. Survival improvement in our patients might be associated with improvement in radiotherapy for the 70-79 age group, and that chemotherapy for the <70 age group, and that in surgery for these age groups. Although we do not know why we did not show any trend of better survival for the 80 age group, we speculate that chronological age, unchanged high proportion of poor PS and advanced disease at presentation might be the reasons for which influenced on the outcome. In addition to them, physician's and patient's belief of shorter life expectancy in the elderly and increased adverse effect of intensive treatment might influence on the treatment selection and prognosis of the aged patients [20,21].

It has been generally accepted that female, good PS, early clinical stage, surgical resection are favorable prognostic factors in the all lung cancer patients [4,13,33]. Asmis et al. reported that comorbid condition (Charlson index ≥1) was associated with poor survival [13]. They used clinical data in 1255 NSCLC patients, who were enrolled in prospective randomized trials of systemic chemotherapy in Canada [13]. On the other hand, Coebergh et al. showed gender and number of comorbid disease had no prognostic effect using a cancer registry records data on 4072 NSCLC patients in The

Netherlands [33]. Our multivariate analysis showed that female, good PS, early clinical stage, surgical resection are favorable prognostic factors in the all lung cancer patients. In ≥80 age group, however, female and comorbidity (number of comorbid disease ≤1, number of Charlson index ≤1) were not favorable prognostic factors, which were consistent with that by Coebergh et al. [33]. We do not know the exact reason why they were not prognostic factors in our patients aged 80 years or over, but we speculate that difference in study population and that in index studied (ex. number of comorbid disease and number of Charlson index) might influence on these results. Our study suffers from limitations imposed by its retrospective nature and limited number of patients, but we suppose that it is important to report clinicopathological features and outcome of lung cancer in the very elderly. The ≥80 age group account for 7.5% of all lung cancers, were increased rapidly. They were less likely to be subjected to surgery or chemotherapy, compared with the 70-79 age group and the <70 age group. In order to improve the outcome, detection of early stage lung cancer and thorough pretreatment evaluation for appropriate treatment is indeed essential even for the≥80 age group of patients.

Conflict of interest

All the authors have no conflict of interest which could inappropriately influence on this work.

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Table 1. Characteristics of lung cancer patients 80 years and over

No. of patients	209
Gender	M : F 145 : 64
Age(year)	median 82, range 80-94
Performance status	
0-1	115
2-4	94
Histology	
Adenocarcinoma	102
Squamous cell carcinoma	76
Large cell carcinoma	7
Others	1
Small cell carcinoma	23
Clinical stage	
IA-B	52
IIA-B	15
IIIA	15
IIIB	60
IV	67
Comorbid diseases	
Hypertention	65
Cardiovascular	62
Pulmonary	49
Cerebrovascular	29
Diabetes	24
Malignant (Meta, and/or Synchronous)	24

Table 2. Uni- and multi-variate analyses of prognostic factors in elderly patients with lung cancer

Factors	Uni-variate analysis (logrank test)	Multi-variate analysis (Cox`s proportional hazard model)		
	p-value	hazard ratio	95%CI	p-value
Age(80-84, 85≥)	0.0270	1.681	1.056 - 2.677	0.029
Gender(female, male)	0.0967	0.958	0.596 - 1.542	0.861
Pathology(NSCLC, SCLC)	0.0163	1.435	0.781 - 2.639	0.245
Performance status(0-1, 2-4)	0.0001	2.621	1.642 - 4.184	0.001
Stage(IA-IIIA, IIIB-IV)	0.0001	3.094	1.843 - 5.195	0.001
No. of comorbid disease(0-1, 2≥)	0.0090	1.404	0.851 - 2.315	0.184
Charlson index score(0, 1≥)	0.0030	1.064	0.600 - 1.888	0.831
Treatment(surgery, others)	0.0001	4.090	1.561 - 10.70	0.004

95%CI: 95%confidence interval, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer

Table 3. Trends in gender, performance status, and stage according to period at diagnosis

	NSCLC			SCLC		
	1978-1990	1991-2000	2001-2007	1978-1990	1991-2000	2001-2007
No.of patients	27	40	119	5	2	16
Gender						
M	18(66.7%)	29(72.5%)	77(64.7%)	5(100%)	2(100%)	14(87.5%)
F	9(33.3%)	11(27.5%)	42(35.3%)	0(0%)	0(0%)	2(12.5%)
Performance status						
0-1	16(59.3%)	25(62.5%)	62(52.1%)	2(40.0%)	1(50.0%)	9(56.3%)
2-4	11(40.7%)	15(37.5%)	57(47.9%)	3(60.0%)	1(50.0%)	7(43.8%)
Stage						
IA-IIIA	10(37.0%)	20(50.0%)	51(42.9%)			
IIIB	10(37.0%)	11(27.5%)	32(26.9%)			
IV	7(25.9%)	9(22.5%)	36(30.3%)			

Table 4. Trends in treatment modalities according to period at diagnosis

	NSCLC			SCLC		
	1978-1990	1991-2000	2001-2007	1978-1990	1991-2000	2001-2007
No.of patients	27	40	119	5	2	16
Treatment modalities						
Surgery	1(3.7%)*	6(15.0%)	27(22.7%)	0(0%)	0(0%)	0(0%)
Radiotherapy	11(40.7%)#	13(32.5%)	33(27.7%)#	0(0%)	0(0%)	1(6.3%)
Chemotherapy	3(11.1%)**	0(0%)	8(6.7%)**	5(100%)	2(100%)	10(62.5%)
Supportive Care	12(44.4%)	21(52.5%)	51(42.9%)	0(0%)	0(0%)	5(31.3%)

*p=0.0279 **p=0.4271 #p=0.2477

Table 5. Survival in lung cancer according to period at diagnosis

	NSCLC			SCLC		
	1978-1990	1991-2000	2001-2007	1978-1990	1991-2000	2001-2007
No.of patients	27	40	119	5	2	16
MST(Mo)	12	16	14	8	6	9
1-year survival	9(33.3%)	12(30.0%)	38(31.9%)	2(40.0%)	0(0%)	2(12.5%)
2-year survival	3(11.1%)	9(22.5%)	20(16.8%)	0(0%)	0(0%)	0(0%)
3-year survival	2(7.4%)	5(12.5%)	9(7.6%)	0(0%)	0(0%)	0(0%)

p=0.2088 p=0.7418 p=0.7015 p=0.4984

p=0.3633 p=0.8455

NSCLC : Non-small cell lung cancer
SCLC : Small cell lung cancer
MST : Median survival time