Stage IV non-small cell lung cancer patients aged 75 years and older

Short running title: Stage IV NSCLC in elderly patients

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Abstract

Objectives: The purpose of this study is to examine clinical and pathological features and chemotherapy in the elderly with metastatic non-small cell lung cancer (NSCLC), especially in patients aged 75 years and older.

Methods: From the databases at two teaching hospitals during the period from January 1999 to December 2013, medical records of lung cancer patients were retrospectively reviewed. The patient population was divided into two age groups: 75 years or older (the ≥75 age group) and less than 75 years (the <75 age group). Time trends were also studied in three time periods: 1999-2003, 2004-2008, and 2009-2013. The years 2004 and 2009 were chosen as cutoff points because of the introduction of gefitinib and bevacizumab respectively around these years to treat NSCLC patients.

Results: Patients aged 75 years and older comprised 27.3% of 772 consecutive stage IV NSCLC patients; there was an increase in the proportion of ≥75 age patients treated with chemotherapy; a trend of improvement in survival of these patients was found. No statistical difference was found in survival between the two age groups of patients treated with chemotherapy (p=0.883). Age ≥75 was not an unfavorable prognostic factor in multivariate analysis.

Conclusion: In order to improve survival, detection of

appropriate candidates for effective chemotherapy is indeed

essential even for the ≥75 age group of stage IV NSCLC patients.

Key words: Non-Small-Cell Lung Cancer, Elderly, Treatment,

Survival

Introduction

Lung cancer in the elderly is an increasingly common problem faced by chest physicians and thoracic surgeons [1-5]. Elderly patients tend to tolerate toxic medical treatments poorly compared to their younger counterparts, because of the comorbid diseases related to age. Clinical trials of platinum-based chemotherapy for selected "fit" elderly patients in good condition have been conducted, attracting attention to the utility of such therapy for the elderly [6-14]. Especially in non-small cell lung cancer (NSCLC), the development of new drugs such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and vascular endothelial growth factor (VEGF) inhibitors, higher standards of medical care, and wider availability of health services may change survival rates of elderly stage IV NSCLC patients.

To address the question of whether the overall survival of lung cancer patients 75 years of age or older has improved, we performed a retrospective study using clinical data from consecutive patients with NSCLC diagnosed at our two tertiary hospitals. We also focused on the role of performance status (PS), comorbid disease, and treatment modalities including chemotherapy on survival of the elderly patients aged 75 years or older.

Patients and methods

Clinicopathological data for all the consecutive patients with NSCLC were obtained by retrospective review from the databases at University of Tsukuba Hospital and Tsukuba Medical Center Hospital and Regional Cancer Center. All the patients were diagnosed pathologically and treated between 1999 and December 2013 at these two tertiary hospitals. Pathological diagnosis was defined by the WHO classification [15]. Staging was recorded for patients with NSCLC according to TNM classification [16]. Demographic data, including age, gender, and PS, were retrieved from their medical records along with the specific details of their cancer. This study conformed to the Ethical Guidelines for Clinical Studies by the Ministry of Health, Labor and Welfare of Japan. The entire patient population was divided into two age groups: 75 years or older (the ≥75 age group) at diagnosis, and less than 75 years (the <75 age group)[17-19]. The median survival time (MST) was compared between the two age groups as defined by gender, histologic subtype, stage, and therapy. Three predefined time periods, that is patients presenting between 1999 and 2003, between 2004 and 2008, and between 2009 and 2013 were used for comparison of survival. The years 2004 and 2009 were chosen as cutoff points because of the introduction of gefitinib and

bevacizumab respectively around these years to treat NSCLC patients.

Differences in distribution of subpopulations between the two age groups and three time periods 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 [20, 21]. Length of survival was defined as the interval in months from date of initial therapy or supportive care until date of death or 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. A probability value less than 0.05 was considered to be significant.

Results

Demographics

A total of 772 patients with NSCLC were registered during the 15-year period. As shown in Table 1, 211 patients (27.3%) were 75 years or older, and 72.7% of patients were younger than 75 years. Men constituted 69.7% in the ≥ 75 age group and 69.2% in the <75 age group. Non-adenocarcinomas accounted for 29.4% in the ≥75 age group and 22.1% in the <75 age group. Poor PS (2-4) accounted for 64.9% in the ≥75 age group and 37.4% in the <75 age group (P<0.001). The ≥75 age group had higher incidences of comorbid disease (respiratory, cardiovascular, neurological, and malignant disease) than those in the <75 age group. Incidences of lower serum albumin (<3.5g/dl) and elevated serum CRP level (>1.0mg/dl) at the time of NSCLC diagnosis in the ≥75 age group were higher than in the <75 age group. Best supportive care without chemotherapy or radiotherapy was also higher in the ≥75 age group than in the <75 age group. Table 2 shows the details regarding the first-line medical treatment. There were no apparent trends among the three time periods.

Ratio of the elderly patients who received chemotherapy and survival

Among the ≥75 age group of patients, 12 (26.1%) of 46 patients received chemotherapy in 1999 to 2003, 37 (40.7%) of

91 patients received chemotherapy in 2004 to 2008, and 37 (50%) of 74 patients received chemotherapy in 2009 to 2013. The ratio of the elderly patients who received chemotherapy increased significantly (p=0.034). Figure 1 shows the survival curves of the ≥75 age group of patients. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009 to 2013 was 4.7, 5.7, and 6.1 months, respectively. Figure 2 shows the survival curves of the ≥75 age group of patients who were treated with chemotherapy. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009 to 2013 was 9.0, 11.9, and 13.5 months, respectively. There was improvement in survival but it was not statistically significant in the log-rank test.

Comparison of survival between the elderly and the younger patients

Figure 3 shows the comparison of survival between the two age groups of patients with chemotherapy. There was no statistically significant difference between them (11.9 months vs 12.5 months, p=0.883), although the elderly patients in all had poorer survival than younger patients (5.4 months vs 8.8 months, p<0.001). There was no statistically significant difference in survival between the two age groups of patients with supportive care only (3.0 months vs 2.6 months, p=0.560).

Prognostic factors

Table 3 summarizes the relationship between clinical

variables and survival. In univariate analysis, age more than 75 years old, male gender, smoking habit, poor PS (PS 2-4), non-adenocarcinoma, comorbid respiratory and neurological disease, lower level of serum albumin, elevated serum CRP level, and no chemotherapy as initial therapy were unfavorable prognostic factors. In multivariate analysis, only poor PS, lower level of serum albumin, elevated serum CRP level, and no chemotherapy as initial therapy were unfavorable prognostic factors, but ≥75 age was not an unfavorable prognostic factor.

Discussion

There has been increasing interest in the treatment of elderly patients with lung cancer [1-5]. However, information regarding clinical trends in stage IV NSCLC patients aged ≥75 years treated with chemotherapy and their survival has not been fully available. Aging is associated with a high prevalence of comorbid diseases [5, 22-24]. In particular, 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 [25-27]. Therefore, there is considerable scientific uncertainty regarding the risks and benefits of chemotherapy in NSCLC patients aged ≥75 years. It is debatable whether elderly NSCLC patients will do as well as younger patients when chemotherapy is administered for their metastatic disease.

The majority of elderly patients have been denied potentially beneficial treatment and participation in clinical trials because of the physician perception that they are too frail to withstand treatment. On the other hand, some trials indicated that 'fit' elderly patients benefit from chemotherapy. Gridelli et al. reported that there was a survival advantage for patients receiving vinorelbine aged 70 years or older in the ELVIS trial [6], but non-platinum doublets did not improve survival compared to monotherapy in the MILES study [7].

Furthermore, some researchers suggested that platinum-based doublet chemotherapy benefits elderly patients as well as younger patients. Langer et al. suggested that response and survival in 'fit' elderly patients receiving cisplatin plus either etoposide or paclitaxel appear to be similar to those in younger patients, although patients 70 years old or older have more comorbidities and can expect more leukopenia and neuropsychiatric toxicity [8]. Lilenbaum et al. reported that the combination of carboplatin and paclitaxel improves response, and there was no survival difference in elderly patients compared to younger patients [9]. Blanchard et al. reported that patients aged 70 years or older derived initial benefit from chemotherapy with cicplatin plus vinorelbine and carboplatin plus paclitaxel [10]. Belani et al. reported that cisplatin plus docetaxel chemotherapy showed similar survival outcomes in elderly and younger patient with advanced NSCLC; elderly patients tolerated the combination therapy well despite experiencing slightly more toxicity than younger patients [11]. Ansari et al. reported that overall survival in patients aged <70 years and those ≥70 years was similar in doublet chemotherapy and that doublet chemotherapy is feasible among carefully selected elderly patients with good PS [12]. Recently, Quoix et al. reported that carboplatin and weekly paclitaxel doublet chemotherapy was associated with survival benefits

compared with vinorelbine or gemcitabine monotherapy in patients aged 70-89 years [13]. Due to the results of this trial, the recommendations of the National Comprehensive Cancer Network regarding NSCLC chemotherapy in elderly patients were modified [14].

We previously reviewed the clinical data of the consecutive elderly lung cancer patients diagnosed between 1978 and 2007 at our hospitals [28]. In the study, the ≥80 age group had higher prevalence of comorbid disease than the 80< age groups. The elderly ≥80 age group was less likely to undergo surgery or chemotherapy, and had inferior outcomes compared to the 70-79 age group and the <70 age group. Survival improvement was not observed in the ≥80 age group. Multivariate analysis showed that good PS, early clinical stage, and surgery were favorable prognostic factors in the ≥80 age group. We could not evaluate whether chemotherapy was the prognostic factor due to the small number of elderly patients in the previous study. In order to clarify the contribution of chemotherapy to survival in the elderly, we performed the present study. This time, elderly stage IV NSCLC patients were divided into two age groups: the ≥75 age group and the <75 age group, which is the most used division method with regard to age [17-19].

In the present study, 211 (27.2%) of 772 stage IV NSCLC patients were aged ≥75 years. In the ≥75 age group, a higher

ratio of patients with poor PS and comorbid diseases was observed compared to the <75 age group of patients. We revealed a trend of increase in patients being treated with chemotherapy in the ≥75 age group, and improvement in survival in the ≥75 age group. In stage IV NSCLC patients who received chemotherapy, there was no statistical difference in survival between the ≥75 age group and the <75 age group, although survival in all of the ≥75 age group of patients was shorter than that in the <75 age group. In univariate analysis, age more than 75 years old, male gender, smoking habit, poor PS (PS 2-4), non-adenocarcinoma, lower level of serum albumin, elevated serum CRP level, and no chemotherapy as initial therapy were unfavorable prognostic factors. In multivariate analysis, only poor PS, lower level of serum albumin, elevated serum CRP level, and no chemotherapy as initial therapy were unfavorable prognostic factors. However, Age ≥75 was not an unfavorable prognostic factor. Considering this, the improvement in survival shown in our study might be dependent on the introduction of relatively less toxic drugs such as molecular targeting agents, the improvement in supportive care, and the construction of widely available health services.

Our study suffers from limitations imposed by its retrospective nature and limited number of patients, but we believe that it is important to report clinicopathological

features and outcomes of stage IV NSCLC in the elderly. The increase in number of elderly NSCLC patients will continue, and progress in both basic and clinical research for the elderly with NSCLC will be required.

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Figure legends

Fig 1. Survival curves of the ≥75 age group of patients in three time periods. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009- 2013 was 4.7, 5.7, and 6.1 months, respectively.

Fig 2. Survival curves of the ≥75 age group of patients who were treated with chemotherapy in three time periods. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009- 2013 was 9.0, 11.9, and 13.5 months, respectively.

Fig 3. Survival curves compared between the ≥75 age group and <70 age group of patients who received chemotherapy. There was no statistically significant difference between them (11.9 months vs 12.5 months, p=0.883).
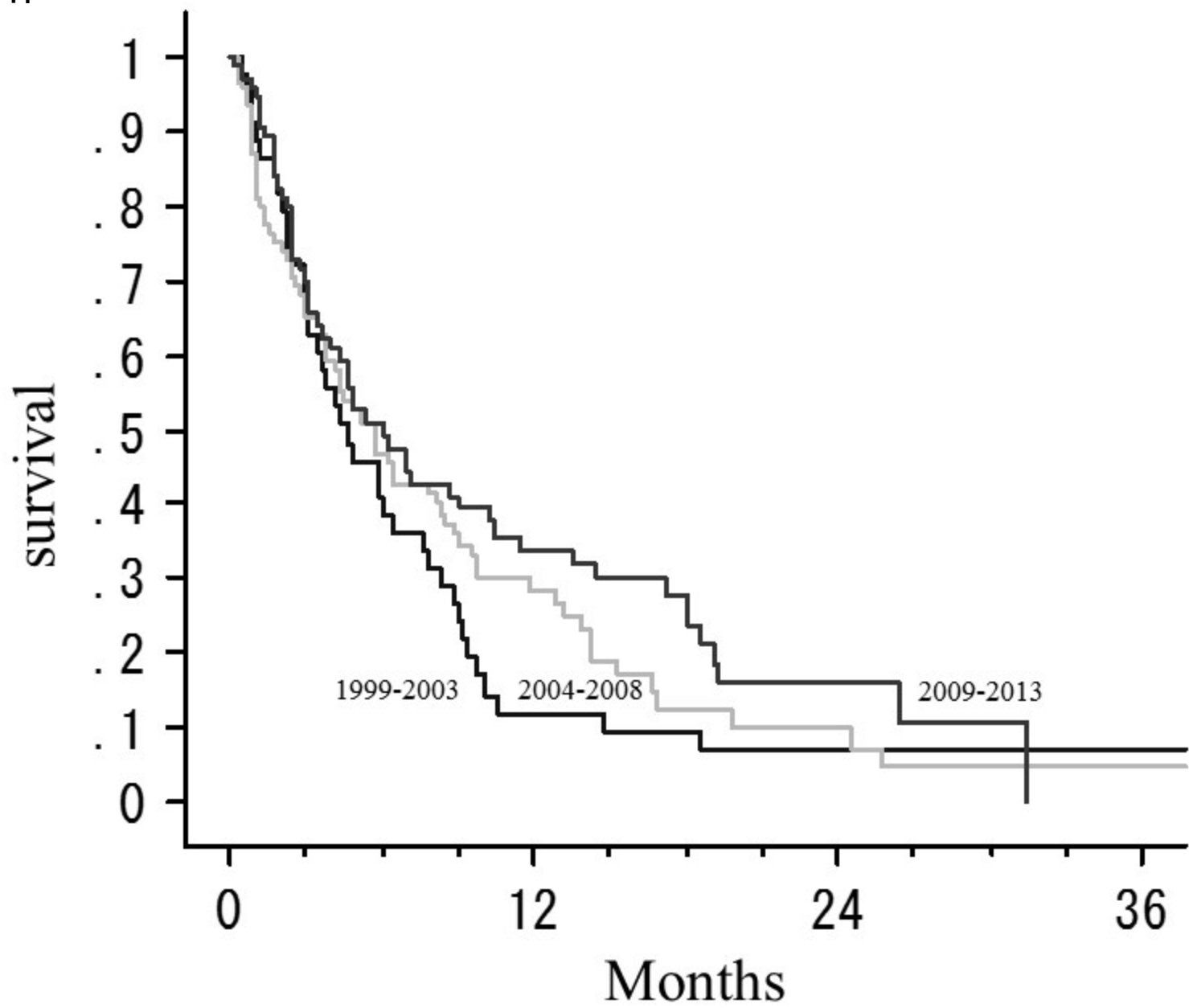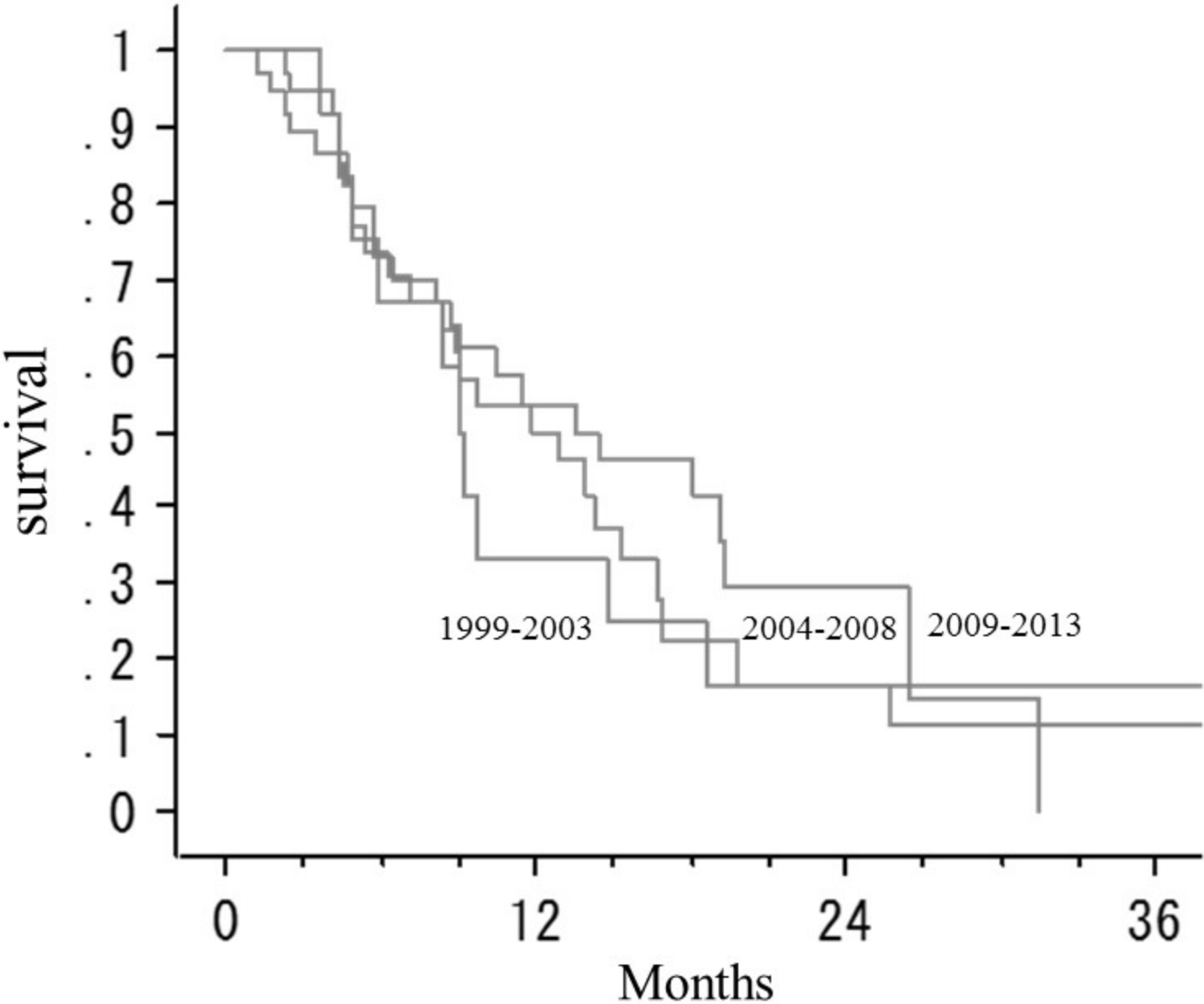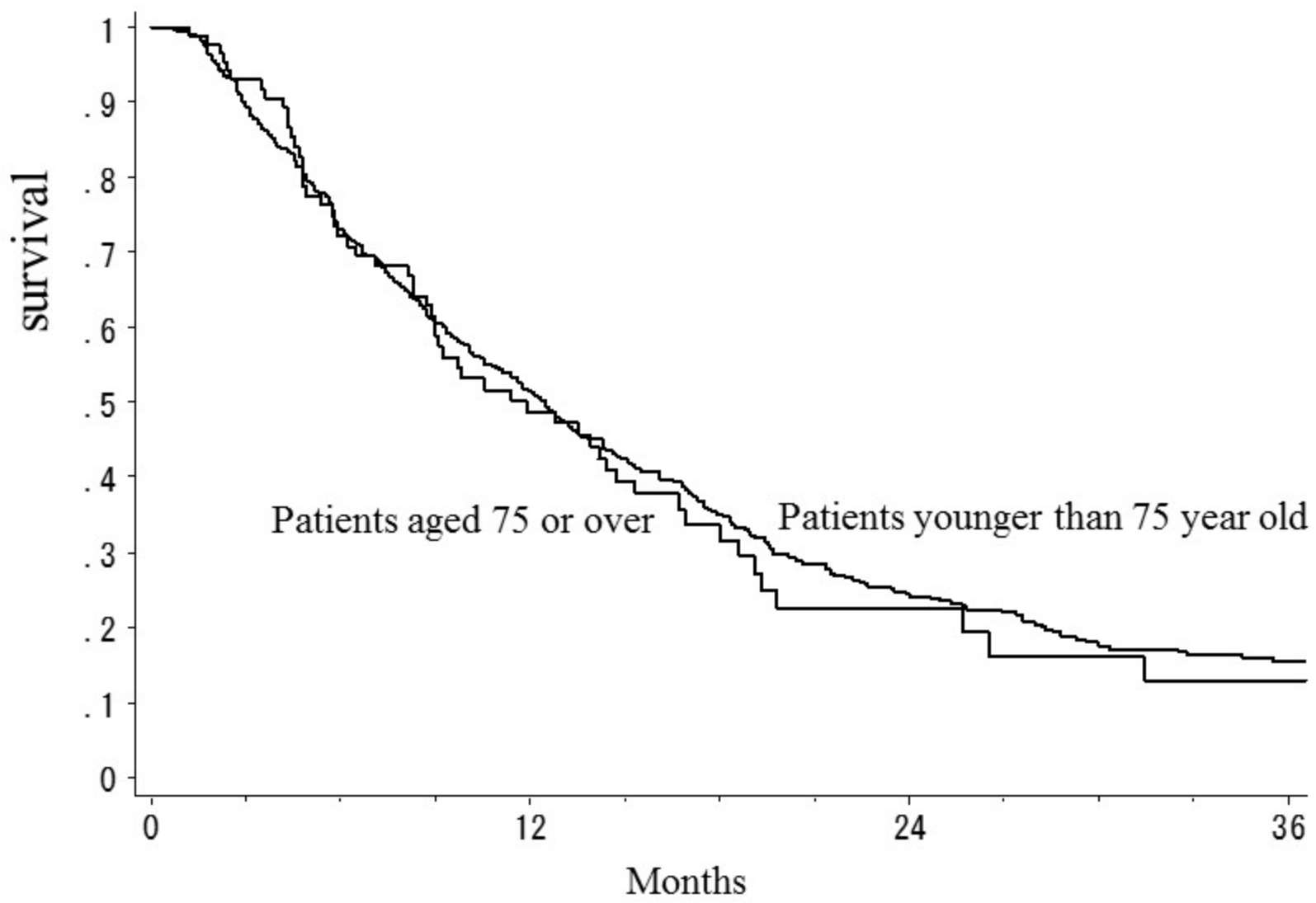
Fig 1.

Fig 2.

Fig 3.

Table 1. Comparison of clinicopatholofical features between aged ≥75 and <75 years stage IV non-small lung cancer patients.

Variables	patients aged ≥75	patients aged <75	
Number of patients	211	561	
Male patients	147 (69.7%)	388 (69.2%)	
Smoking habit: present	154 (73.0%)	412 (73.4%)	
Performance status: 2-4	137 (64.9%)	210 (37.4%)	**
Non-adenocarcinoma	62 (29.4%)	124 (22.1%)	*
Comorbidity			
Respiratory disease	63 (29.9%)	121 (21.6%)	*
Cardiovascular disease	123 (58.3%)	176 (31.4%)	**
Neurological disease	30 (14.2%)	33 (5.9%)	**
Diabetes mellitus	44 (20.9%)	91 (16.2%)	
Malignant disease#	34 (16.1%)	51 (9.1%)	**
Serum albumin (<3.5g/dl)	95 (45.0%)	190 (33.9%)	**
Serum CRP (>1.0ml/dl)	314 (58.7%)	91 (38.4%)	**

*: $p<0.05$, **: $p<0.01$ #Malignant disease included past and concurrent diseases.

Table 2. Detail of 1st line treatment given in each time period.

Treatment	1999-2003		2004-2008		2009-2013	
	<75	≥75	<75	≥75	<75	≥75
Platinum doublet	74 (46.5%)	2 (4.3%)	131 (63.3%)	13 (14.3%)	133 (68.2%)	15 (20.3%)
with Bevacizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (5.6%)	1 (1.4%)
Single agent	4 (2.5%)	3 (6.5%)	10 (4.8%)	21 (23.1%)	6 (3.1%)	11 (14.9%)
EGFR-TKI	15 (9.4%)	6 (13.0%)	12 (5.8%)	2 (2.2%)	29 (14.9%)	11 (14.9%)
Other	2 (1.3%)	1 (2.2%)	1 (0.5%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Supportive care only	64 (40.3%)	34 (73.9%)	53 (25.6%)	54 (59.3%)	27 (13.8%)	37 (50.0%)

EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor

Table 3. Univariate and multivariate analyses of prognostic factors in 211 aged ≥75 patients with stage IV non-small cell lung cancer

Factors	Univariate analysis (log-rank test) P-value	Multivariate analysis (Cox`s proportional hazards model)		
		hazard ratio	95%CI	P-value
Age ≥75 years	<0.001	0.83	0.68-1.01	0.060
Male	<0.001	1.19	0.92-1.53	0.182
Smoking habit: present	<0.001	1.08	0.82-1.41	0.583
Performance status: 2-4	<0.001	1.87	1.54-2.26	<0.001
Non-adenocarcinoma	<0.001	1.14	0.94-1.39	0.187
Comorbid respiratory disease	0.038	1.04	0.86-1.26	0.711
Comorbid neurological disease	0.040	0.95	0.69-1.32	0.776
Serum albumin<3.5g/dl	<0.001	1.29	1.07-1.55	0.007
Serum CRP>1.0mg/dl	<0.001	1.65	1.37-2.00	<0.001
Supportive care only	<0.001	2.92	2.38-3.59	<0.001

95%CI: 95% confidence interval