

ORIGINAL**Epidemiological and clinical features of lung cancer patients from 1999 to 2009 in Tokushima Prefecture of Japan**

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Abstract : Lung cancer is the leading cause of malignancy-related death worldwide. In the present study, we reviewed the epidemiologic and clinical features of lung cancer in Tokushima Prefecture, Japan. Between January 1999 and December 2009, 2,183 patients with lung cancer were enrolled in this study. One thousand five hundred ninety-one (73%) patients were male and 592 (27%) patients were female. Median age was 70 years, with a range of 15-93 years. Seventy-six percent of patients had smoking history. One thousand nine hundred five (87%) patients were non-small cell lung cancer and the predominant histological type was adenocarcinoma (51%). Among all 2,183 patients, 702 (32%) belonged to elderly population. Four hundred seventy-one (22%), 213 (10%), 24 (1%), 116 (5%), 238 (11%), 370 (17%) and 678 (31%) patients had stage IA, IB, IIA, IIB, IIIA, IIIB and IV lung cancer, respectively. In Tokushima University Hospital, 516 (29%), 191 (11%), 58 (3%), 755 (43%) and 216 (12%) patients were initially treated with chemotherapy, chemo-radiotherapy, thoracic radiotherapy, operation and best supportive care, respectively. The median time to progression (TTP) and the median survival time (MST) of patients treated with chemotherapy and chemo-radiotherapy were 3.5 months, 13.0 months and 7.0 months, 18.0 months, respectively. The median TTP and the MST of 33 elderly patients treated with chemotherapy were 3.3 months and 18.0 months, respectively, which were comparable with those of total population. These results indicated the benefit of chemotherapy in elderly patients with advanced lung cancer by proper selection. *J. Med. Invest.* 57 : 326-333, August, 2010

Keywords : epidemiology, lung cancer, Tokushima Prefecture

Abbreviation used : TTP, time to progression ; OS, overall survival ; NSCLC, non-small cell lung cancer ; SCLC, small cell lung cancer ; MST, median survival time ; RR, response rate.

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INTRODUCTION

Lung cancer is a global public health problem of epidemic proportions, and the number of people affected is expected to grow in the near future (1). Despite improvements in survival for many other types of cancer in recent years, 5-year survival for lung cancer has remained relatively poor, mainly because by the time a diagnosis is made, lung cancer is frequently advanced and treatment options are limited (2-4).

An estimated 1.35 million people were newly diagnosed with lung cancer worldwide in 2002 (12.4% of all new cancers) (5), an increase of about 110,000 compared with the number in 2000 (6). In addition, lung cancer is the leading cause of malignancy-related death worldwide (5). In 2002 there were about 1.18 million deaths caused by lung cancer internationally (5), an increase of over 70,000 deaths since 2000 (6). Lung cancer deaths caused almost 18% of total cancer mortality (5, 7), and around 2% of all mortality worldwide during 2002 (7).

Lung cancer is, to a major extent, a disease of the elderly (8). The prevalence and societal burden of this disease will increase as more people survive into old age. Elderly patients with cancer are significantly under-represented in all clinical trials, including in those for lung cancer (9-11). A retrospective analysis of all patients enrolled onto Southwest Oncology Group trials between 1993 and 1996 demonstrated that only 25% were 65 years or older, whereas this age subgroup made up 63% of the U.S. population of patients with cancer (11). The low enrollment of patients older than 70 years was largely responsible for this discrepancy (11).

In Japan, 62,063 (45,189 male and 16,874 female) patients died of lung cancer, which consisted of 19% of all malignancy-related death in 2005, and more than half of them (53%) belonged to 75 years or older, so-called elderly patient population (12). Tokushima Prefecture, a regional area located in southeast part of Shikoku Island, Japan, had 459 (342 male and 117 female) patients who died of lung cancer in 2005, and inclined to have more elderly patients (58%) than all parts of Japan (12).

While the outlines of epidemiology of lung cancer have been reported as mentioned above, detailed epidemiologic and clinical trends in Tokushima Prefecture still remain uncertain. In the present study, we reviewed the epidemiology of lung cancer in Tokushima Prefecture focusing on 1) the incidence

by age and histology, and 2) stage, treatment modalities and clinical outcome in comparison between elderly patient and younger or total populations.

PATIENTS AND METHODS

Patient eligibility

The patients who had been either cytologically or histologically confirmed to have lung cancer in Tokushima University Hospital and Tokushima Prefectural Central Hospital from 1999 to 2009 were eligible for this retrospective study. Tokushima University Hospital and Tokushima Prefectural Central Hospital are two main hospitals engaging in lung cancer treatment in Tokushima Prefecture and more than 50% of lung cancer patients in Tokushima Prefecture were treated in these two hospitals. Therefore, we considered that patient population in these two hospitals was able to recapitulate the epidemiology of lung cancer in Tokushima Prefecture. We defined 74 years or younger patients as younger population and 75 years or older patients as elderly population. The study protocol was approved by the Institutional Review Board of each of the participating institution.

Evaluation of response and toxicity for treatment

Enrolled patients were appropriately treated with standard treatment modalities for lung cancer depending on their general status. Chest X-ray, complete blood count, and blood chemistry studies were repeated at least once a month for follow-up. The response was assessed based on the computed tomography scan findings that initially had been used to define the tumor extent. The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.0.

Statistical analysis

For the evaluation of the efficacy of chemotherapy, we investigated the time to progression (TTP) and overall survival (OS) of lung cancer patients who received any chemotherapeutic agents in Tokushima University Hospital. The TTP was defined as the time from diagnosis to progression or death from any cause. The OS was defined as the time from diagnosis to death from any cause or when last known to be alive. The TTP and the OS were estimated by the Kaplan-Meier method of univariate analysis. The differences between categorized groups were compared by the One-way ANOVA test. All statistical

tests were two sided, and values of $p < 0.05$ were considered to indicate statistical significance.

RESULTS

Patient population

Between January 1999 and December 2009, 2,183 patients with lung cancer from 2 institutions were enrolled in this study. The clinical characteristics of all 2,183 patients are listed in Table 1. One thousand five hundred ninety-one (73%) patients were male and 592 (27%) patients were female. Median age was 70 years, with a range of 15-93 years. Seventy-six percent of all 2,183 patients had smoking history. Causes for detection of lung cancer were as follows; medical screening (21%), symptom related to lung cancer (55%), examination during follow-up of other

diseases (24%). Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) constituted 87% and 13% of all lung cancer patients, respectively. With regard to NSCLC, the predominant histological type was adenocarcinoma (51%) followed by squamous cell carcinoma (25%), large cell carcinoma (3%) and others (8%).

As shown in Table 2, 471 (22%), 213 (10%), 24 (1%), 116 (5%), 238 (11%), 370 (17%) and 678 (31%) patients had stage IA, IB, IIA, IIB, IIIA, IIIB and IV lung cancer, respectively. In NSCLC, 783 (41%) and 1,060 (56%) patients had early (IA, IB, IIA and IIB) and advanced (IIIA, IIIB and IV) stages, respectively. In SCLC, 133 (48%) patients had distant metastasis, which was consistent with previous report (13). Among all 2,183 patients, 1,481 (68%) and 702 (32%) belonged to younger and elderly population, respectively. There was no significant difference in stage distribution between younger and elderly population in NSCLC, SCLC and total lung cancer.

Table 1. Patient characteristics

No.	2,183
Age (Year)	
Median (Range)	70 (15-93)
Gender	
Male	1,591 (73%)
Female	592 (27%)
Histology	
Non-small cell lung cancer	1,905 (87%)
Adenocarcinoma	1,112 (51%)
Squamous cell carcinoma	545 (25%)
Large cell carcinoma	69 (3%)
Others	179 (8%)
Small cell lung cancer	278 (13%)

Treatment modalities and patient survival

Next, we analyzed the first-line treatment modalities in 1,763 patients who were initially treated in two participating institutions. Five hundred sixteen (29%), 191 (11%), 58 (3%), 755 (43%) and 216 (12%) patients were treated with chemotherapy, chemoradiotherapy, thoracic radiotherapy, operation and best supportive care, respectively. As expected, there was remarkable difference of initial treatment among histological subtypes of lung cancer, namely, operation was undergone in almost half (48%) of NSCLC patients, while SCLC patients were predominantly treated with chemotherapy (60%).

Table 2. Comparison of clinical stages for lung cancer between younger and elderly patients.

Stage	Number of patients (%)								
	NSCLC			SCLC			Total		
	Younger	Elderly	Total	Younger	Elderly	Total	Younger	Elderly	Total
IA	303 (23)	146 (24)	449 (24)	11 (6)	11 (12)	22 (8)	314 (21)	157 (22)	471 (22)
IB	125 (10)	82 (13)	207 (11)	4 (2)	2 (2)	6 (2)	129 (9)	84 (12)	213 (10)
IIA	16 (1)	7 (1)	23 (1)	1 (1)	0 (0)	1 (0)	17 (1)	7 (1)	24 (1)
IIB	62 (5)	42 (7)	104 (5)	8 (4)	4 (4)	12 (4)	70 (5)	46 (7)	116 (5)
IIIA	142 (11)	66 (11)	208 (11)	21 (11)	9 (10)	30 (11)	163 (11)	75 (11)	238 (11)
IIIB	202 (16)	105 (17)	307 (16)	43 (23)	20 (22)	63 (23)	245 (17)	125 (18)	370 (17)
IV	408 (32)	137 (22)	545 (29)	94 (51)	39 (42)	133 (48)	502 (34)	176 (25)	678 (31)
unstaged	37 (3)	25 (4)	62 (3)	4 (2)	7 (8)	11 (4)	41 (3)	32 (5)	73 (3)
Total	1,295	610	1,905	186	92	278	1,481	702	2,183

NSCLC : non-small cell lung cancer, SCLC : small cell lung cancer
 younger : 74 years or younger patients, elderly : 75 years or older patients

Among 1,763 patients, 1,218 (69%) and 545 (31%) belonged to younger and elderly population, respectively. We compared the initial treatment modalities for lung cancer among these populations. The proportions of NSCLC patients treated with operation and that of SCLC patients treated with chemotherapy were comparable between younger and elderly population (48% in younger, 47% in elderly and 59% in younger, 61% in elderly, respectively). On the other hand, the proportion of patients treated with chemo-radiotherapy tended to be lower in elderly than younger population (5% vs. 11% in NSCLC ($p=0.13$), 11% vs. 27% in SCLC ($p=0.06$) and 6% vs. 13% in total lung cancer ($p=0.12$), respectively), and that of patients treated with best supportive care tended to be higher in elderly than younger population (25% vs. 8% in NSCLC ($p=0.08$), 13% vs. 3% in SCLC ($p=0.18$) and 23% vs. 7% in total lung cancer ($p=0.09$), respectively), while these differences were not significant (Table 3).

Finally, we evaluated the survival of the subgroup underwent chemotherapy in Tokushima University Hospital. Between January 1999 and December 2009, 204 and 84 patients with NSCLC were treated with chemotherapy, chemo-radiotherapy, respectively. The median TTP and the median survival time (MST) of patients treated with chemotherapy and chemo-radiotherapy were 3.5 months, 13.0 months and 7.0 months, 18.0 months, respectively (Fig. 1 and 2). Among 204 NSCLC patients treated with chemotherapy, 33 (16%) belonged to elderly population. The median TTP and the MST of 33 elderly patients treated with chemotherapy were 3.3 months and 18.0 months, respectively (Fig. 3), which were comparable with those of total population.

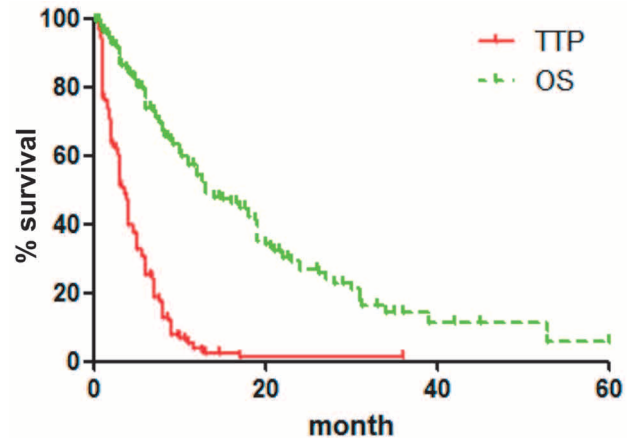


Figure 1. The survival of NSCLC patients treated with chemotherapy. The survival of 204 NSCLC patients treated with chemotherapy was calculated according to the Kaplan-Meier method. The median TTP and MST were 3.5 months and 13.0 months, respectively.

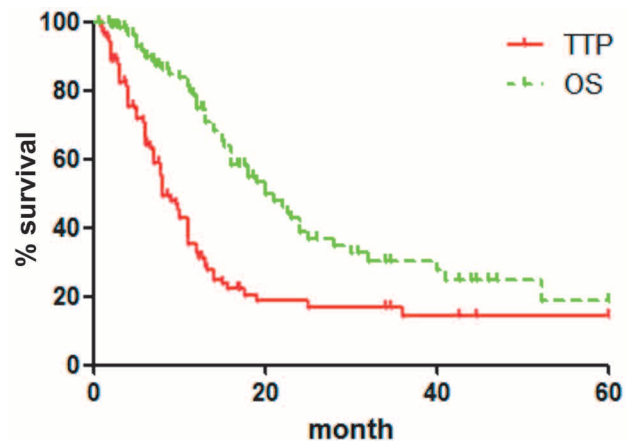


Figure 2. The survival of NSCLC patients treated with chemo-radiotherapy. The survival of 84 NSCLC patients treated with chemo-radiotherapy was calculated according to the Kaplan-Meier method. The median TTP and MST were 7.0 months and 18.0 months, respectively.

Table 3. Comparison of treatment modalities for lung cancer between younger and elderly patients.

Treatment	Number of patients (%)								
	NSCLC			SCLC			Total		
	Younger	Elderly	Total	Younger	Elderly	Total	Younger	Elderly	Total
Chemotherapy	311 (29)	71 (15)	382 (25)	90 (59)	44 (61)	134 (60)	401 (33)	115 (21)	516 (29)
Chemo-radiotherapy	116 (11)	26 (5)	142 (9)	41 (27)	8 (11)	49 (22)	157 (13)	34 (6)	191 (11)
Thoracic radiotherapy	17 (2)	36 (8)	53 (3)	2 (1)	3 (4)	5 (2)	19 (2)	39 (7)	58 (3)
Operation	513 (48)	221 (47)	734 (48)	14 (9)	7 (10)	21 (9)	527 (43)	228 (42)	755 (43)
Best supportive care	87 (8)	116 (25)	203 (13)	4 (3)	9 (13)	13 (6)	91 (7)	125 (23)	216 (12)
Others	22 (2)	3 (1)	25 (2)	1 (1)	1 (1)	2 (1)	23 (2)	4 (1)	27 (2)
Total	1,066	473	1,539	152	72	224	1,218	545	1,763

NSCLC : non-small cell lung cancer, SCLC : small cell lung cancer
 younger : 74 years or younger patients, elderly : 75 years or older patients

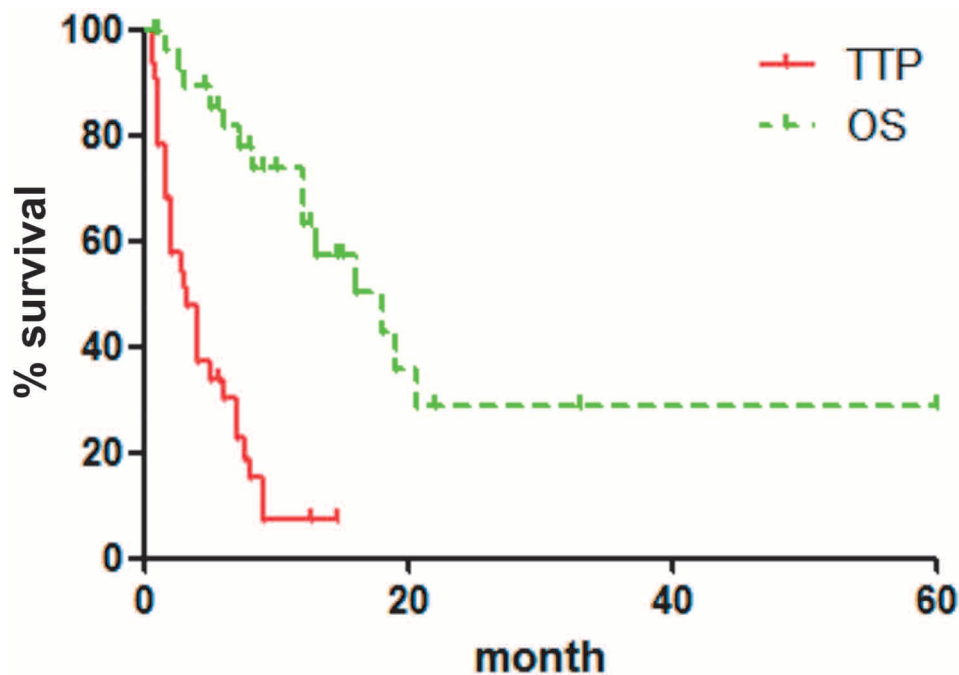


Figure 3. The survival of elderly NSCLC patients treated with chemotherapy.

The survival of 33 elderly NSCLC patients treated with chemotherapy was calculated according to the Kaplan-Meier method. The median TTP and MST were 3.3 months and 18.0 months, respectively.

DISCUSSION

Lung cancer has been the most common cancer in the world since 1985 (14), and by 2002, there were 1.35 million new cases, representing 12.4% of all new cancers. It was also the most common cause of death of cancer, with 1.18 million deaths, or 17.6% of the world total. The prognosis for people diagnosed with lung cancer remains poor worldwide, with 5-year relative survival typically between 6 to 14% among males and 7 to 18% among females (15).

The incidence and mortality of lung cancer are very much influenced by past exposure to tobacco smoking (16). For the year 2000, an estimated 85% of lung cancer in men and 47% of lung cancer in women is the consequence of tobacco smoking. A higher proportion of lung cancer deaths were attributable to smoking than for any other disease (17). It has been estimated that nearly three quarters (71%) of lung cancer deaths worldwide were caused by smoking in 2000 (17). By 2015, this would result in a projected 1.18 million smoking related lung cancer deaths per year (7). In this study, 76% of lung cancer patients had smoking history, indicating that the high prevalence of tobacco smoking in Tokushima Prefecture was closely related to the occurrence and morbidity of lung cancer in consistent with previous reports.

Lung cancer is, to a major extent, a disease of the elderly (8). The prevalence and societal burden of this disease will increase as more people survive into old age. Given that the population older than 65 years constitutes the fastest-growing segment and is projected to double by the year 2030 (18), elderly lung cancer patients are anticipated to be going to increase hereafter. Worldwide during 2002, 5% of lung cancer cases were diagnosed among people aged 0 to 44 years, 14% in the 45 to 54 age group, 25% in the 55 to 64 age group, and 55% among those aged 65 years and over (19). In all parts of Japan and Tokushima Prefecture, 33,165 and 265 elderly (75 years or older) patients died of lung cancer in 2005, respectively. The proportions of elderly patients in all parts of Japan and Tokushima Prefecture constituted 53% and 58% of all lung cancer-related death, respectively (12), suggesting that around half of lung cancer patients belonged to elderly population in Japan. In the present study, 32% (702/2,183) of lung cancer patients was elderly population. As Tokushima University Hospital and Tokushima Prefectural Central Hospital are highly specified hospitals to the intensive cancer treatment, advanced lung cancer patients who are considered to be intolerable to intensive treatment owing to poor performance status and/or high age tend to be avoided for referral to our two institutions by primary doctors. Therefore, the discrepancy of the

proportion of elderly patient population between previous reports and our study might be explained by the under-estimation of the number of elderly lung cancer patients in the present study.

According to cancer registry data in National Cancer Center, Japan (12), age-standardized lung cancer mortality rates (per 100,000) in 2005 were comparable between all parts of Japan (15.63) and Tokushima Prefecture (15.57). But Tokushima Prefecture had a tendency to have more elderly patients who died of lung cancer than all parts of Japan. The proportions of elderly patients in total population, male and female were 53% and 58%, 51% and 55%, and 60% and 67% in all parts of Japan and Tokushima Prefecture, respectively (Table 4). These epidemiologic data might reflect the trend that elderly population in Tokushima Prefecture had been growing faster than cross-sectional population of Japan.

In the present study, there was no difference in the proportion of NSCLC patients initially treated with operation between younger and elderly population (48% and 47%, respectively), suggesting that operation could be actively performed even in elderly lung cancer patients after consideration for its indication. Similarly, the proportion of SCLC patients treated with chemotherapy was also comparable between younger and elderly population (59% and 61%, respectively), reflecting the fact that SCLC is characterized by significant sensitivity to initial chemotherapy (20). On the other hand, the proportion of patients initially treated with chemo-radiotherapy tended to be lower in elderly than younger population (5% vs. 11% in NSCLC, 11% vs. 27% in SCLC

and 6% vs. 13% in total lung cancer, respectively), and that of patients initially treated with best supportive care tended to be higher in elderly than younger population (25% vs. 8% in NSCLC, 13% vs. 3% in SCLC and 23% vs. 7% in total lung cancer, respectively), while these differences were not significant (Table 3). Elderly lung cancer patients commonly have poor performance status and higher incidence of smoking-related comorbidities, such as cardiovascular diseases, chronic pulmonary emphysema, pulmonary fibrosis and so on. These factors might lead to the physician's discretion to avoid aggressive anti-cancer treatment in these patients.

A number of randomized clinical trials support the conclusion that the combined modality of chemotherapy and radiotherapy improve survival compared with either chemotherapy or radiotherapy alone for locally advanced NSCLC (21, 22). The response rate (RR) and MST in the phase III trials that use chemo-radiotherapies have been reported to be 49-84% and 14.5-16.5 months, respectively (23, 24). In this study, the MST of 84 patients treated with chemo-radiotherapy was 18.0 months, which was comparable with previous phase III studies.

The standard chemotherapy regimen for advanced NSCLC is considered to be two-drug combination chemotherapy with platinum agents and new-generation non-platinum antitumor agents, such as paclitaxel, docetaxel, gemcitabine, and vinorelbine. The RR, TTP and MST in the phase III trials that use these combination chemotherapies have been reported to be 17-28%, 3-4 months and 7-9 months, respectively (25-27). In this study, the

Table 4. Comparison of epidemiologic trends of lung cancer between all parts of Japan and Tokushima Prefecture in 2005.

Population	Lung cancer-related death			ASR
	Younger No. (%)	Elderly No. (%)	Total No. (%)	
Total				
Japan	28,898 (47)	33,165 (53)	62,063 (100)	15.63
Tokushima	194 (42)	265 (58)	459 (100)	15.57
Male				
Japan	22,196 (49)	22,993 (51)	45,189 (100)	24.97
Tokushima	155 (45)	187 (55)	342 (100)	26.49
Female				
Japan	6,702 (40)	10,172 (60)	16,874 (100)	7.13
Tokushima	39 (33)	78 (67)	117 (100)	5.88

cited from reference 12

younger : 74 years or younger patients, elderly : 75 years or older patients

ASR : age-standardized lung cancer mortality rate (per 100,000)

median TTP and the MST of patients treated with chemotherapy were 3.5 months, 13.0 months, respectively, in consistent with previous phase III studies. Moreover, it is noteworthy that the median TTP and the MST of 33 elderly patients treated with chemotherapy were shown to be 3.3 months, 18.0 months, respectively, which were comparable with those of total population. These results indicated the significant findings that chemotherapy had survival benefit even in elderly patients if they were properly selected for the indication of chemotherapy. Further studies should be warranted to elucidate the therapeutic efficacy and safety of chemotherapy in elderly patients with advanced NSCLC.

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