Clinicopathological characteristics and treatment strategies for young lung cancer patients

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Background: The reported age-specific survival rates of lung cancer patients have been largely inconsistent. Management strategies for younger patients and treatment outcomes are not well characterized.

Methods: Out of the 4,697 lung cancer patients with treatment history at Tokyo Medical University Hospital between January 2000 and December 2014, 266 patients were <49 years of age. Patient characteristics were investigated, and the association of overall survival (OS) with age, sex, stage, and histological type were investigated.

Results: The 1-, 3-, and 5-year survival rates in the ≤49 years age group were 82.9%, 64.6%, and 57.0%. Among surgical cases, the survival rate of patients in the ≤49 years age group was significantly better than that in the 50–69 and ≥70 years age groups (P=0.29 and P<0.0001, respectively). In comparison with the OS rate with clinical stages, I, II, and III (but not with clinical stage IV) in the older than 50 years age group, the rates in the ≤49 years age group were better. The 1-, 3-, and 5-year OS rates of females were higher than those of their males. The 1-, 3-, and 5-year OS rates for lung adenocarcinoma patients were higher than that of lung non-adenocarcinoma patients.

Conclusions: Despite the higher proportion of advanced disease, the postoperative survival rate of the younger was higher than that of the older. Aggressive multimodality treatments, including surgery, are more feasible and effective for younger patients as compared with that in older patients.

Keywords: Young lung cancer patients; lung cancer; survival; adenocarcinoma

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide regardless of sex (1). In the US, it is a particularly prominent disease in the elderly population; people <45 years of age account for <2% of all cases of lung cancer (2). According to the Japanese Ministry of Health, Labor, and Welfare, an estimated 146,000 people suffered from respiratory cancer and 73,396 deaths were attributed to respiratory cancer in 2014. According to a Japanese Lung Cancer Registry Study in 2004, patients younger than 50 years (data available since 1994) (3) accounted for between 5.0% and 8.2% of all lung cancer patients who

Page 2 of 10

Yoneyama et al. Outcome of young lung cancer patients

underwent surgical resection. Several studies have shown that post-therapeutic survival rates in younger patients with lung cancer are higher than those in their older counterparts (4-6); however, other studies have shown comparable survival outcomes among patients in different age groups (7,8). Some investigators have suggested that the course of lung cancer in young patients is more aggressive than that in older patients (9). Owing to the small number of young patients with lung cancer, their clinicopathological characteristics are not well characterized; moreover, there is no consensus on the most effective management strategies for these patients. Therefore, this study aimed to elucidate the clinicopathological characteristics and the best therapeutic strategies for lung cancer in young patients and compared them with elderly patients.

Methods

Patient selection

We retrospectively reviewed 4,733 consecutive patients with pathologically confirmed lung cancer at the Tokyo Medical University Hospital from January 2000 to December 2014. Of these, 36 patients who did not undergo therapeutic management were excluded. The remaining 4,697 patients were divided into the following three groups by age: <50 years (n=266), between 50 to 69 years (n=2,360), and ≥70 years (n=2,071). The diagnosis and treatment of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were performed in accordance with the then guidelines of the Japan Lung Cancer Society. The protocols for data collection and analyzes were approved by the institutional review board of the Tokyo Medical University. The requirement for informed consent from the patients was waived off due to the retrospective nature of the study. Confidentiality of patient data was maintained throughout the study.

Data collection

Pretreatment evaluation and treatment management included physical examination, blood examination, chest radiography, and chest and abdomen computed tomography (CT). Brain CT or magnetic resonance imaging and positron emission tomography-CT were performed if clinically indicated. Staging and pathological findings for lung cancer were determined according to the seventh TNM Classification for Lung and Pleural Tumors (10)

and the World Health Organization classification (11). The hospital charts of all patients were reviewed to collect clinicopathological data, including age; sex; smoking history; clinical T, N, and M factors; histological type; surgical procedures; epidermal growth factor receptor (EGFR) mutation status; and overall survival (OS). OS was determined as the duration from the day of initial diagnosis until the day of death from all causes. Data pertaining to patients who were alive and showed no evidence of recurrence at the end of the follow-up period were censored from the analysis.

Statistical analysis

Categorical variables are presented as frequencies and proportions, whereas continuous variables are presented as mean ± standard deviation. Patient characteristics were compared using the chi-squared test or Fisher exact test for categorical outcomes of continuous variables, as appropriate. OS was estimated using the Kaplan-Meier method, and between-group differences were assessed with log-rank test. P values and hazard ratios in the multivariate analyses were calculated using the Cox regression model. Between-group differences associated with P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS statistical software (version 21.0; SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Clinicopathological characteristics of patients with lung cancer from 2000 to 2014, disaggregated by age groups (≤49, 50–69, and ≥70 years) are shown in *Table 1*. In the ≤49 years age group, there were 169 (63.5%) men and 97 (36.5%) women; no significant between-group difference was observed with respect to sex distribution (P=0.809). Approximately 80% of patients with therapeutic lung cancer in the ≤49 and 50–69 years age groups had performance status 0–1, which was better than that of patients in the ≥70 years age group. A majority of the patients in all three groups were consulted us because of an abnormal chest shadow detected on routine health checkup. The proportion of "never smokers" in the ≤49 years age group (36.5%) was significantly higher than that in the other age groups. The proportion of patients with stable disease in the ≤49 years age group ranged from 5.4% to 5.9%. Regarding clinical

Table 1 Characteristics of the patients (n=4,697)

Variables	≤49 years old (n=266)		50–69 years old (n=2,360)		≥70 years old (n=2,071)		P
	n	%	n	%	n	%	
Sex							0.809
Female	97	36.5	820	34.7	733	35.4	
Male	169	63.5	1,540	65.3	1,338	64.6	
Performance status							0.0001
0	188	70.7	1,706	72.3	1,345	64.9	
1	24	9.0	210	8.9	358	17.3	
2	4	1.5	31	1.3	47	2.3	
3/4	1	0.4	21	0.9	14	0.7	
No data	49	18.4	392	16.6	307	14.8	
Symptoms							0.822
Present	66	24.8	516	21.9	429	20.7	
Absent	16	6	152	6.4	141	6.8	
Abnormal shadow in routine health check	164	61.7	1,502	63.6	1,330	64.2	
No data	20	7.5	190	8.1	171	8.3	
Smoker							0.0001
Current smoker	68	25.6	726	30.8	465	22.5	
Ex-smoker	78	29.3	827	35	855	41.3	
Never smoker	97	36.5	592	25.1	580	28.0	
No data	23	8.6	215	9.1	171	8.3	
Year of diagnosis							0.444
2000–2004 (n=1,166)	63	5.4	601	51.5	502	43.1	
2005–2009 (n=1,917)	108	5.6	979	51.1	830	43.3	
2010–2014 (n=1,614)	95	5.9	780	48.3	739	45.8	
Clinical stage							0.053
Stage I	131	49.2	1,134	48.1	1,003	48.4	
Stage II	10	3.8	228	9.7	218	10.5	
Stage III	69	25.9	573	24.3	494	23.9	
Stage IV	56	21.1	425	18.0	356	17.2	
Pathology							0.0001
Adenocarcinoma	202	75.9	1,551	65.7	1,195	57.7	
Squamous cell carcinoma	18	6.8	453	19.2	529	25.5	
Large cell carcinoma	0	0	15	0.6	13	0.6	
Non-small cell carcinoma, NOS	24	9.0	187	7.9	164	7.9	
Adenosquamous cell carcinoma	2	0.8	12	0.5	16	0.8	
Small cell carcinoma	4	1.5	128	5.4	147	7.1	
Carcinoid	9	3.4	11	0.5	6	0.3	
Others	7	2.6	3	0.1	1	0	

Table 1 (*continued*)

Page 4 of 10

Yoneyama et al. Outcome of young lung cancer patients

Table 1 *(continued)*

Variables	≤49 years old (n=266)		50–69 years old (n=2,360)		≥70 years old (n=2,071)		P
	n	%	n	%	n	%	
EGFR mutation status							0.327
Exon 19 deletion	24	0.9	128	5.4	82	4.0	
Exon 21 L858R mutation	15	5.6	141	6.0	112	5.4	
Minor mutation	4	1.5	13	0.6	11	0.5	
Wild type	67	25.2	388	16.4	305	14.7	
Unknown	156	58.6	1,690	71.6	1,561	75.4	
Initial therapy							0.0001
Surgery	110	41.4	884	37.5	870	42.0	
Surgery plus adjuvant therapy	42	15.8	506	21.4	266	12.8	
Induction therapy plus surgery	16	6.0	88	3.7	26	1.3	
Surgical procedures							0.0001
Lobectomy	146	84.4	1,298	85.6	978	82.4	
Sublobar resection	20	11.6	149	9.8	180	15.2	
Pneumonectomy	2	1.2	31	2.0	9	0.8	
Others	5	2.9	39	2.6	20	1.7	
Chemotherapy or others	98	36.8	882	37.4	909	43.9	

NOS, not otherwise specified; EGFR, epidermal growth factor receptor.

stage, 125 patients in the ≤49 years age group had advanced stage tumors at presentation, which exhibited a trend of being higher than that in the other groups (P=0.053). The percentage of adenocarcinoma and carcinoid tumors was significantly higher in the group aged ≤49 years whereas that of squamous cell carcinoma was significantly lower compared to the other groups. Squamous cell carcinoma was higher in the group aged ≥70 years than in the younger groups. Furthermore, we analyzed EGFR mutation status in a limited number of patients; the rate of patients with an EGFR mutation (particularly exon 19 deletion) in the ≤49 years age group was significantly higher than that in the other groups (12). Regarding initial therapeutic strategies, patients in the ≥70 years age group underwent more nonsurgical treatments as compared with those in the younger age groups (P=0.0001). Subsequently, sublobar resection and other less invasive surgical procedures were more frequently selected in these patients (P=0.0001).

Survival

The median follow-up time of all patients was 43.1 months (range, 0.3–189.0 months). The median follow-up time in the ≤49, 50–69, and ≥70 years age groups was 46.3, 46.6, and 38.7 months, respectively. The median follow-up time in the ≥70 years age group was significantly lower than that in the ≤49 and 50–69 years age groups (P=0.001 and P=0.045). The 1-, 3-, and 5-year survival rates in the ≤49 years age group were 82.9%, 64.6%, and 57.0% (*Figure 1A*). The 1-, 3-, and 5-year survival rates of patients in the ≤49 years age group who underwent surgery were 97.6%, 88.2%, and 81.5%, respectively (*Figure 1B*). The 1-, 3-, and 5-year survival rates of patients in the ≤49 years age group who did not undergo surgery were 55.9%, 21.1%, and 12.8%, respectively (*Figure 1C*).

The postoperative survival rate in the ≤49 age group was significantly higher than the other 50–69 and ≥70 years age groups (P=0.29 and P<0.0001, respectively) (*Figure 1B*). In the entire study population, although the survival rate in the ≤49 years age group was significantly higher than that in the ≥70 years age group (P=0.0001), it was not significantly different from that in the 50–69 years age group (P=0.439) (*Figure 1A*). Moreover, among patients who did not undergo surgery, the survival rate of those in the ≤49 years age group

	1-year survival	3-year survival	5-year survival
≤49-years old n=266	82.9%	64.6%	57.0%
50–69-years old n=2,360	84.6%	64.9%	55.3%
≥70-years old n=2,070	78.9%	56.2%	46.3%

	1-year survival	3-year survival	5-year survival
≤49-years old n=168	97.6%	88.2%	81.5%
50–69-years old n=1,478	96.2%	86.0%	77.3%
≥70-years old n=1,161	93.6%	80.5%	70.6%

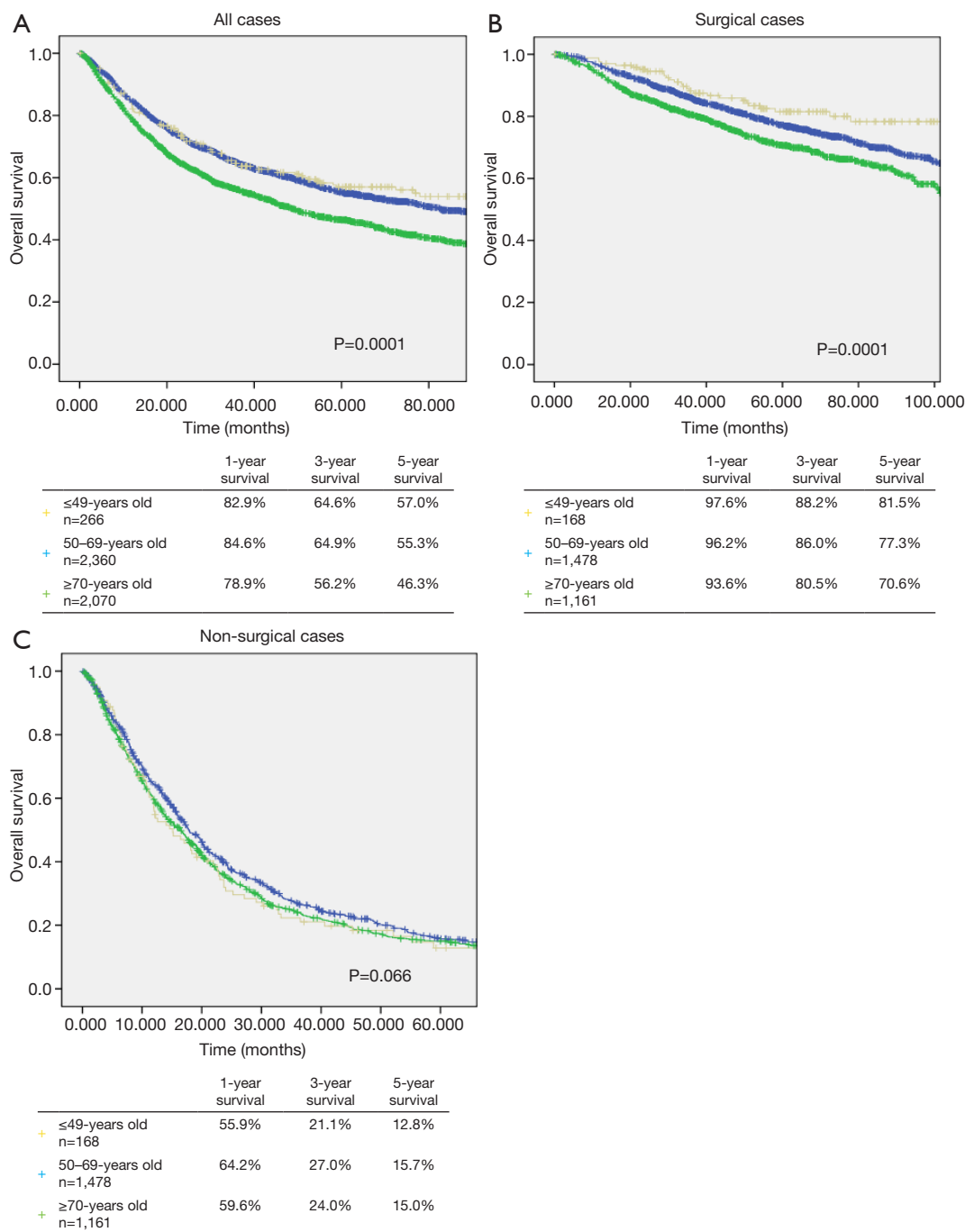|	1-year survival	3-year survival	5-year survival
≤49-years old n=168	55.9%	21.1%	12.8%
50–69-years old n=1,478	64.2%	27.0%	15.7%
≥70-years old n=1,161	59.6%	24.0%	15.0%

Figure 1 Kaplan-Meier curves for 1-, 3-, and 5-year overall survival of lung cancer patients according to (A) all patients (P=0.0001), (B) surgical cases (P=0.0001), and (C) non-surgical cases in the age group of ≤49, 50–69, and ≥70.

was not significantly different from the survival rates of those in the other age groups (P=0.066) (*Figure 1C*).

The detailed survival data of patients with NSCLC of different TNM stages are summarized in *Figure 2*. From the point of clinical staging, 1-, 3-, and 5-year survival rates of patients with stage I lung cancer in the ≤49 years age group were 98.5%, 95.0%, and 88.4%, respectively (*Figure 2A*). The 1-, 3-, and 5-year survival rates of patients with stage
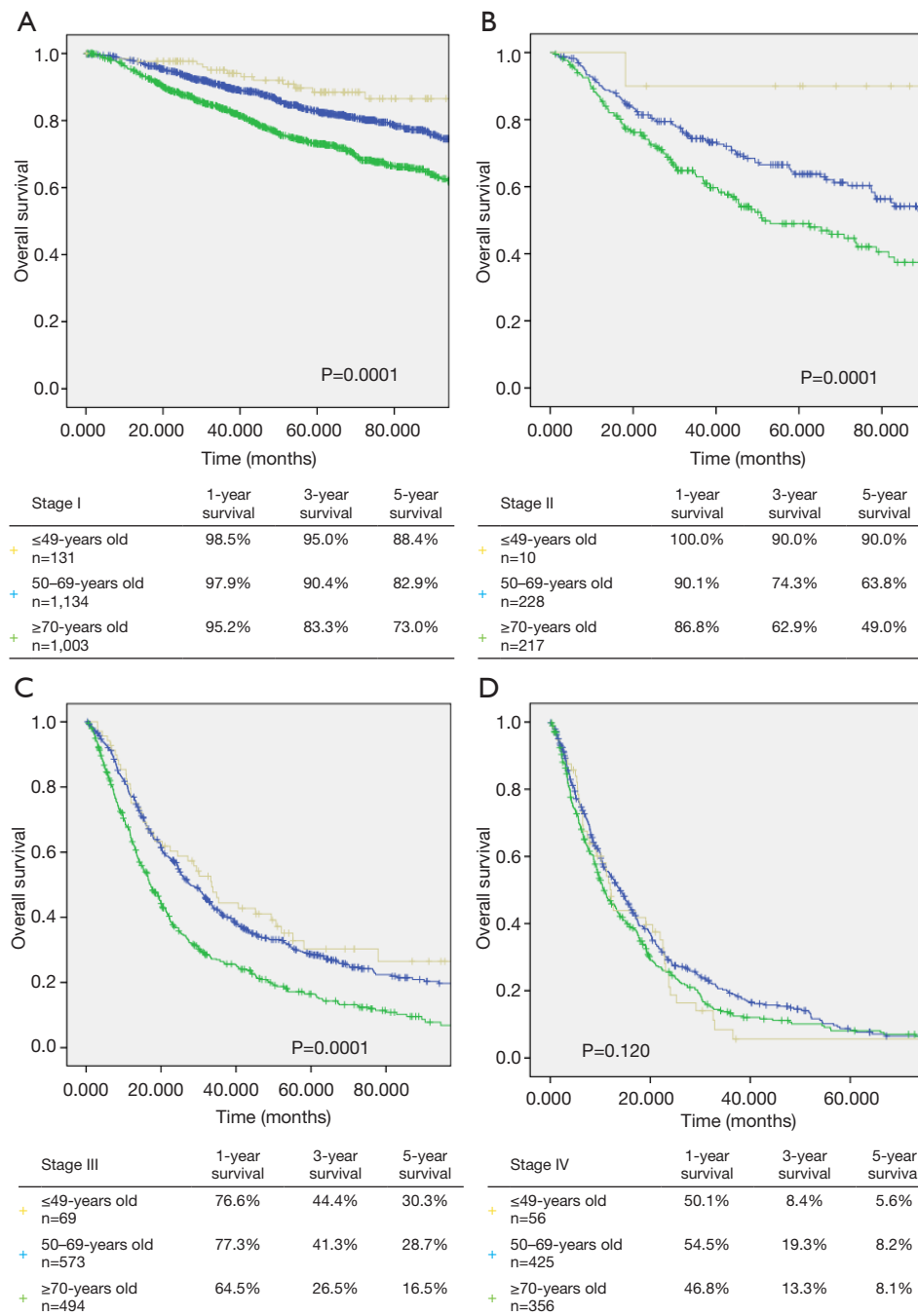
Page 6 of 10

Yoneyama et al. Outcome of young lung cancer patients

Stage I	1-year survival	3-year survival	5-year survival
≤49-years old n=131	98.5%	95.0%	88.4%
50–69-years old n=1,134	97.9%	90.4%	82.9%
≥70-years old n=1,003	95.2%	83.3%	73.0%

Stage II	1-year survival	3-year survival	5-year survival
≤49-years old n=10	100.0%	90.0%	90.0%
50–69-years old n=228	90.1%	74.3%	63.8%
≥70-years old n=217	86.8%	62.9%	49.0%

Stage III	1-year survival	3-year survival	5-year survival
≤49-years old n=69	76.6%	44.4%	30.3%
50–69-years old n=573	77.3%	41.3%	28.7%
≥70-years old n=494	64.5%	26.5%	16.5%

Stage IV	1-year survival	3-year survival	5-year survival
≤49-years old n=56	50.1%	8.4%	5.6%
50–69-years old n=425	54.5%	19.3%	8.2%
≥70-years old n=356	46.8%	13.3%	8.1%

Figure 2 Kaplan-Meier curves for 1-, 3-, and 5-year overall survival of lung cancer patients according to (A) stage 1 (P=0.0001), (B) stage 2 (P=0.0001), (C) stage 3 (P=0.0001), and (D) stage 4 in the age group of ≤49, 50–69, and ≥70.

II lung cancer in the ≤49 years age group were 100.0%, 90.0%, and 90.0%, respectively (*Figure 2B*). The 1-, 3-, and 5-year survival rates of patients with stage II lung cancer in the ≤49 years age group were 76.6%, 44.4%, and 30.3%,

respectively (*Figure 2C*). The 1-, 3-, and 5-year survival rates of patients with stage IV lung cancer in the ≤49 years age group were 50.1%, 8.4%, and 5.6%, respectively (*Figure 2D*). The OS rates of lung cancer patients with
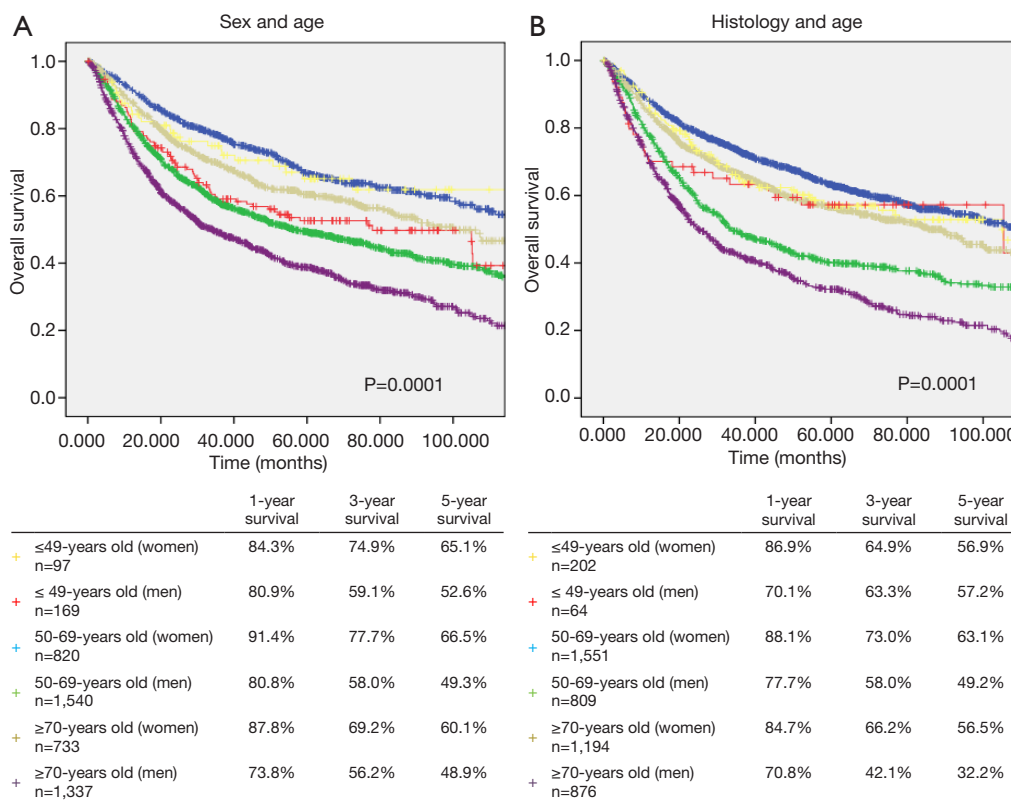
	1-year survival	3-year survival	5-year survival
≤49-years old (women) n=97	84.3%	74.9%	65.1%
≤ 49-years old (men) n=169	80.9%	59.1%	52.6%
50-69-years old (women) n=820	91.4%	77.7%	66.5%
50-69-years old (men) n=1,540	80.8%	58.0%	49.3%
≥70-years old (women) n=733	87.8%	69.2%	60.1%
≥70-years old (men) n=1,337	73.8%	56.2%	48.9%

	1-year survival	3-year survival	5-year survival
≤49-years old (women) n=202	86.9%	64.9%	56.9%
≤ 49-years old (men) n=64	70.1%	63.3%	57.2%
50-69-years old (women) n=1,551	88.1%	73.0%	63.1%
50-69-years old (men) n=809	77.7%	58.0%	49.2%
≥70-years old (women) n=1,194	84.7%	66.2%	56.5%
≥70-years old (men) n=876	70.8%	42.1%	32.2%

Figure 3 Kaplan-Meier curves for 1-, 3-, and 5-year overall survival of lung cancer patients according to (A) sex and age (P=0.0001) and (B) histology and age (P=0.0001) in the age group of ≤49, 50–69, and ≥70.

clinical stages I, II, and III in the ≤49 years age group were better than those of their counterparts older than 50 years.

Regarding sex differences, the 1-, 3-, and 5-year OS rates in females were higher than that in males (*Figure 3A*).

The 1-, 3-, and 5-year OS rates of patients with adenocarcinoma were better than that of patients with non-adenocarcinoma. In the non-adenocarcinoma group, the 3- and 5-year OS rates of younger patients were higher than those of older patients (*Figure 3B*).

Discussion

Lung cancer mostly occurs in patients of older age (13). Therefore, lung cancer in young patients is recognized to be relatively rare and to comprise a distinct oncological entity.

Owing to the reported increase in the incidence of lung cancer among young patients in Europe and Japan (14,15), there is an urgent need to characterize young lung cancer patients. Several studies have compared the clinicopathological features and prognoses of young NSCLC patients of different ages (9,16-19). In general, epidemiological observations have been explained by the time period required for the environmental toxins to induce genetic damage that ultimately leads to cancer. Therefore, many studies have suggested that lung cancer in the young may constitute a distinct clinicopathological entity with a different sex distribution, stage at diagnosis, pathological features, and prognosis, although the reported data are frequently discordant (3,8,9,16-20).

At our institution, a total of 266 patients in the ≤49 years age group were registered between 2000 and 2014, which accounts for 5.7% of all cases (*Table 1*). This is consistent with a previous nationwide Japanese cohort (6) that was stable over the last 15 years. The young patients included 169 men and 97 women; the male:female ratio of 1.74:1 (*Table 1*) is similar to that in a Japanese nationwide cohort reported in 2004 (3), and comparable with that in the older age groups in the present study. We also found that the histological type in almost 80% of the younger patients was

Page 8 of 10

Yoneyama et al. Outcome of young lung cancer patients

adenocarcinoma (*Table 1*). It is possible that there are less cases of smoking-related squamous carcinoma or small cell carcinoma in young patients.

The therapeutic strategy is sometimes constrained in older patients because of existing comorbidities, which may not be the case with younger patients.

Regarding the clinical TNM staging of young lung cancer patients in this series, there were 131 stage I, 10 stage II, 69 stage III, and 56 stage IV patients; the proportion of patients with stages III–IV advanced lung cancer was higher than that in the older age groups (P=0.053) (*Table 1*). In comparison with elderly patients, it has suggested that lung cancer in young patients tends to be more aggressive in nature; however, the performance status of these young patients tends to be better (6,19,21,22).

The present study suggests that surgical resection was more frequently selected as the first-line treatment for younger patients as compared with that in the other age groups. The higher rates of neoadjuvant chemotherapy in the younger group may reflect the higher proportion of patients with operable stage III advanced disease, which is a prime indication for induction therapy (6); moreover, young patients tend to show better tolerance for such treatment owing to better functional status of organs. The rate of neoadjuvant chemotherapy in the younger group was more than two-fold higher than that in the older group. Radzikowska *et al.* also reported similar results with more aggressive treatment in younger patients (4). These results indicate that planned active multimodal strategies in younger patients result in good performance status. In addition, among patients who underwent surgical resection, the 5year survival rates in the ≤49 years age patients group was the highest at 81.5%; the corresponding rates in the 50–69 and ≥70 years age groups were significantly lower at 77.3% and 70.6%, respectively (P=0.0001) (*Figure 1B*). Therefore, more aggressive multimodality treatments, including surgery, are feasible for young patients with lung cancer and are highly recommended in our daily practice.

The tendency for a higher survival rate in female patients and in patients with adenocarcinoma was similar to that seen with the analyses of all ages (6) (*Figure 3*). Adenocarcinoma *in situ* showing ground-glass opacity on CT, which is currently classified as adenocarcinoma *in situ* or minimally invasive adenocarcinoma (23), is generally considered as a slow-growing, low-grade adenocarcinoma and a unique subtype associated with a never-smoking history and female sex (24). Although CT data were not analyzed in the present study cohort, higher proportions of adenocarcinoma and females in the young patient group might affect the patients' characteristics, with a higher rate of adenocarcinoma *in situ* with lower malignant behavior.

Limitations

This single institutional study of a large number of surgically and non-surgically treated lung cancer patients has several limitations. As it is a retrospective study, we cannot clarify the prognostic effects of multimodal therapy in young patients owing to limited comprehensive data, including data pertaining to chemotherapy regimens or molecular targeted therapy during their entire treatment course. Other limitations are the persistence of patient-selected treatment bias and time-to-detection bias that may have worsened prognostic outcomes in elderly patients. Moreover, we could not analyze the treatment outcomes after recurrence in the present study; young patients with good performance status might have more chance to receive secondary or more chemotherapy in combination with radiation or immunotherapy. Further prospective, multi-institutional investigations and substantial clinical analyzes are required to clarify the cause underlying the better prognosis of younger patients who receive treatment as compared with patients in the other age groups (25).

Conclusions

We retrospectively reviewed 4,697 consecutive patients with pathologically confirmed lung cancer who received surgical and nonsurgical treatment at the Tokyo Medical University Hospital between January 2000 and December 2014. We compared the clinicopathological characteristics and survival outcomes of younger patients and older patients.

We interestingly found better postoperative survival of these young lung cancer patients, although the proportion of patients with advanced disease was higher compared with that in the older group.

Clinical practice points

❖ Especially to postoperative patients, the survival rate is better than older group.
❖ Longer-term follow-up is essential for primary cancer and associating health care problems (26-28).
❖ Data storage system including specimen sample is needed expecting to treatment options in future.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocols for data collection and analyzes were approved by the institutional review board of the Tokyo Medical University. The requirement for informed consent from the patients was waived off due to the retrospective nature of the study.

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Page 10 of 10

Yoneyama et al. Outcome of young lung cancer patients

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