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Improvement in the survival of patients with stage IV non-small-cell lung cancer: Experience in a single institutional 1995–2017

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ABSTRACT

Objectives: In the past two decades several antineoplastic agents have been approved for the treatment of advanced non-small-cell lung cancer (NSCLC), and the management of these patients has drastically changed. However, there is limited information regarding the impact of these advances on patient survival in clinical practice.

Materials and methods: We analyzed the survival of patients with stage IV NSCLC who received any treatment in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR) between January 1, 1995 and March 1, 2017. A total of 1,547 consecutive patients were included in this case series. In this analysis, five diagnostic periods were evaluated: 1995–1999 (period A), 2000–2004 (period B), 2005–2009 (period C), 2010–2014 (period D), and 2015–2017 (period E). We compared overall survival (OS) between the periods before and after propensity score matching (PSM) and in patients with EGFR mutation, with ALK fusion gene, or without driver mutation.

Results: In the past two decades the OS of patients with stage IV NSCLC improved. The median OSs for periods A, B, C, D, and E were 9.0, 11.0, 13.7, 17.9 months, and not reached, respectively. After PSM with known baseline characteristics, the trend of improvement in OS was similar. However, the OS of patients with EGFR mutation or ALK fusion gene did not improve between periods, despite the availability of several tyrosine kinase inhibitors in Japan. The OS of patients without a driver mutation was slightly longer in the period E.

Conclusion: The introduction of new classes of drugs has significantly improved the survival of patients with stage IV NSCLC. However, the approval of similar types of drugs may not be associated with further improvement in survival.

1. Introduction

Lung cancer is a leading cause of death due to cancer in many countries, including Japan [1]. Non-small-cell lung cancer (NSCLC) accounts for 85–90% of lung cancers [2]. Approximately 70% of NSCLC patients are diagnosed with advanced or metastatic disease that is not amenable to surgical resection, and the prognosis remains poor [3]. However, in the previous two decades several new antineoplastic agents have been approved for the treatment of NSCLC in Japan (Fig. 1). In the 1990s, several cytotoxic agents (CAs) were approved, and the role of chemotherapy in the treatment of stage IV NSCLC was established by 1995 [4].

Gefitinib was the first epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) approved in 2002. Active EGFR mutations were identified in 2004, and the EGFR mutation test has been reimbursed in Japan since 2007 [5,6]. Three additional EGFR-TKIs—namely erlotinib, afatinib, and osimertinib—were approved in 2007, 2013, and 2016, respectively.

In 2009 the antivascular endothelial growth factor (anti-VEGF) antibody (Ab) bevacizumab was approved as the first angiogenesis inhibitor (AI) for the treatment of non-squamous NSCLC. The second AI, ramucirumab (anti-VEGFR2 Ab), was approved in 2016 [7,8]. In 2012 the first anaplastic lymphoma kinase (ALK) TKI (crizotinib) was

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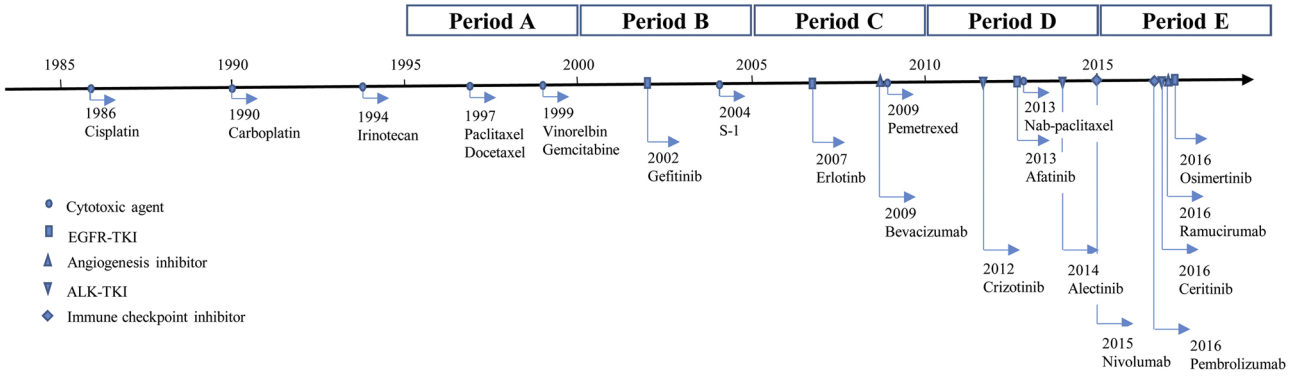

Fig. 1. Year of approval of multiple agents for the treatment of advanced non-small-cell lung cancer (NSCLC) in Japan.

approved for the treatment of NSCLC patients with the ALK fusion gene [9,10]. Two additional ALK-TKIs (alectinib and ceritinib) were approved in 2014 and 2016, respectively.

More recently, the use of immune checkpoint inhibitors (ICIs), including anti-programmed cell death 1 (PD-1) Ab, for the treatment of NSCLC has been widespread. In 2015, nivolumab—a fully human IgG4 anti-PD-1 Ab—was approved as the first ICI against NSCLC [11,12].

Despite the approval and availability of several new classes of agents in the previous two decades, information regarding their impact on the survival of patients with stage IV NSCLC in clinical practice is limited. Therefore, the objective of the present study was to analyze the survival of patients with stage IV NSCLC treated at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR).

2. Patients and methods

2.1. Study design and patient selection

We selected patients with stage IV NSCLC who received any treatment, including best supportive care (BSC) alone, between January 1, 1995 and March 1, 2017 using the database of the JFCR. The clinical and pathological information from eligible patients—including the date of NSCLC diagnosis, sex, age at the time of diagnosis, smoking history, histological subtype, clinical stage of disease diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and treatments—was retrospectively collected from the database and medical records. Overall survival (OS) time was calculated from the date of diagnosis to the date of death.

This study was approved by the Institutional Review Board of the JFCR (2017-1131).

2.2. Statistical methods

This study evaluated the OS in all patients with stage IV NSCLC in the following five periods: period A: 1995–1999, period B: 2000–2004, period C: 2005–2009, period D: 2010–2014, and period E: 2015–2017. Surviving patients were censored in March 2017, and those lost to follow-up without data regarding mortality were censored on the date of the last follow-up. Additional analysis included comparison of the OS in stage IV NSCLC patients with EGFR mutation or ALK fusion gene or absence of identified driver mutations between the periods. Differences in the baseline characteristics of patients between the periods were tested using the Pearson's χ^2 test or the t-test for categorical and continuous variables, respectively. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival curves. Cox regression analysis was used to test the association between treatment and demographic variables with OS in the univariate analysis. Variables with a $p \leq 0.05$ in the univariate analysis were included in the multivariate model. Propensity score matching (PSM) was used to adjust for known baseline characteristics. The propensity score was calculated on the basis of a multiple logistic regression for receiving a given treatment. The model included the following variables: age, sex, smoking history, histology, and ECOG PS. Patients were matched for variables and compared for survival outcomes among the investigated periods. All statistical analyses were performed using the JMP software version 11.0.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

We compiled a case series of 1,547 consecutive patients with stage IV NSCLC treated in our hospital. The patient characteristics are shown in Table 1, and the patient diagram is shown in Supplementary Fig. S1. In periods A, B C, D, and E, a total of 149, 237, 378, 542, and 241 patients, respectively, were identified. At the end of the study period (March 1, 2017), 1,197 patients had expired, 246 patients were alive, and 104 patients were lost to follow-up.

The median age of patients in periods A, B C, D, and E was 64, 64, 63, 63, 65, and 67 years, respectively. Patients in period E were significantly older than those in periods B, C, and D. The percentage of elderly patients (aged ≥75 years) in periods A, B, C, D, and E was 9%, 8%, 6%, 11%, and 17%, respectively. The percentage of females in each period was 34%, 36%, 38%, 39%, and 37%, respectively. No significant difference was observed between the periods. Although the percentage of patients who had never smoked increased throughout the previous decades, only 33% of the patients were included in this category, even in the most recent periods (i.e., D and E). The incidence of adenocarcinoma was not significantly changed during the periods with the exception of period D.

Patients with EGFR mutation were identified from period C because the EGFR mutation test was approved in 2007. The percentage of EGFR-mutation-positive patients reached its plateau after period D (approximately 30%). Patients with the ALK fusion gene were identified from period C because the ALK fusion test was approved in 2012, and the percentage of ALK-positive patients reached its plateau in periods D and E.

3.2. Antineoplastic agents used during the five periods examined in this study

The patient populations treated with each of the antineoplastic agents (i.e., CA, EGFR-TKI, ALK-TKI, AI, and ICI) are shown in Table 2. Among the 1,547 patients identified, 247 patients (16%) did not receive any antineoplastic agents, 1,109 patients (72%) received CAs, 601 patients (39%) received molecular targeted agents (EGFR-TKI (35%) and ALK-TKI (4%)), 174 patients (11%) received AIs, and 123 patients (8%) received anti-PD1/PD-L1 Abs (Table 2). The percentage of patients who did not receive any antineoplastic agents decreased from period A to

Table 1
Characteristics of all patients enrolled in this study.

Characteristics	Total *n*	Period A *n* (%)	Period B *n* (%)	Period C *n* (%)	Period D *n* (%)	Period E *n* (%)
Number of patients	1547	149	237	378	542	241
Age at diagnosis						
Median, years (range)	64 (22–90)	64 (33–87)	63 (29–82)	63 (30–81)	65 (22–90)	67 (26–87)
< 75 (%)	1388 (90)	135 (91)	218 (92)	356 (94)	480 (89)	199 (83)
≥75 (%)	159 (10)	14 (9)	19 (8)	22 (6)	62 (11)	42 (17)
Sex						
Male	965	99 (66)	152 (64)	233 (62)	329 (61)	152 (63)
Female	582	50 (34)	85 (36)	145 (38)	213 (39)	89 (37)
Smoking status						
Current or former	987	76 (51)	111 (47)	273 (72)	365 (67)	162 (67)
Never smoked	441	26 (17)	57 (24)	102 (27)	177 (33)	79 (33)
Unknown	119	47 (32)	69 (29)	3 (1)	–	–
Histological subtype						
Adenocarcinoma	1206	110 (74)	186 (78)	278 (74)	445 (82)	187 (78)
Other	341	39 (26)	41 (22)	100 (26)	97 (18)	54 (22)
ECOG PS						
0 or 1	1252	106 (71)	172 (73)	326 (86)	457 (84)	191 (79)
≥2 or unknown	295	43 (29)	65 (27)	52 (13)	85 (16)	50 (21)
EGFR mutation						
Positive	294	0	0	49 (13)	171 (32)	74 (31)
ALK fusion gene						
Positive	61	0	0	2 (1)	45 (8)	14 (6)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Table 2
Study population treated with anti-neoplastic agents.

Treatment	Total *n*	Period A *n* (%)	Period B *n* (%)	Period C *n* (%)	Period D *n* (%)	Period E *n* (%)
Total		149	237	378	542	241
Cytotoxic chemotherapy	1109	86 (58)	168 (71)	331 (86)	400 (74)	124 (51)
Molecular target agent	601	4 (3)	89 (15)	171 (45)	243 (45)	94 (39)
EGFR-TKI	535	4 (3)	89 (15)	168 (44)	201 (37)	73 (30)
ALK-TKI	62	0	0	0	43 (8)	19 (8)
Other molecular agent	10	0	0	3 (1)	5 (1)	2 (1)
AI	174	0	0	34 (9)	120 (22)	20 (8)
ICI	123	0	0	2 (1)	45 (8)	76 (32)
No anti-neoplastic agent	247	62 (42)	54 (32)	32 (8)	64 (12)	35 (15)

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; AI, angiogenesis inhibitor; ICI, immune checkpoint inhibitor.

period C; however, it was slightly increased after period C (i.e., period A: 42%; period B: 32%; period C: 8%; period D: 12%; and period E: 15%). After period A, > 70% of patients received CAs. Patients treated with molecular targeted agents were identified from period A and the percentage of patients in periods C–E was 39–45%. The percentage of patients treated with EGFR-TKI increased from period A to period C, and this percentage in periods C–E was 30–44%. Before period C, there were no patients treated with ALK-TKI. In periods C and D, 8% of patients received treatment with ALK-TKI. Use of AI was recorded from period C, and 22% of the patients in period D were treated with AI. Patients who received ICI were identified from period C. In period E, the percentage of patients treated with ICI was 32%.

3.3. Survival outcomes in each period

The median follow-up times in periods A, B, C, D, and E were 8.9, 19.3, 34.8, 30.0, and 9.2 months, respectively. The OS curves of all patients with stage IV NSCLC in each period are shown in Fig. 2A. The OS improved gradually. The median OSs for periods A, B, C, and D were 9.0, 11.0, 13.7, and 17.9 months, respectively. Of note, the median OS for period E was not reached (NR). The hazard ratios (HRs) between periods A and B, B and C, C and D, and D and E were 0.81 (95%CI: 0.66–1.00, $p = 0.048$), 0.81 (95%CI: 0.68–0.96, $p = 0.012$), 0.75 (95%CI: 0.65–0.87, $p \leq 0.001$), and 0.77 (95%CI: 0.59–1.01, $p = 0.061$), respectively.

3.4. Clinical factors associated with OS

Cox univariate and multivariate analyses were performed to identify clinical factors associated with OS during the examined periods (Table 3A and B).

The clinical factors associated with OS in the univariate analysis were sex, smoking status, histology, ECOG PS, and the use of CA, EGFR-TKI, ALK-TKI, AI, and ICI in the entire period of investigation (overall) (Table 3A). However, sex and smoking status were not significant factors in period A. In period B, histology was not a significant factor. In periods C and D, all factors were significant (use of ALK-TKI was not analyzed in period C). In period E, the use of CA and ICI was not a significant factor (Table 3A). Additionally, multivariate analyses were performed in the overall period and each period (Table 3B). In these models, we included variables with a $p \leq 0.05$ in the univariate analyses. For the overall period, sex, histology, ECOG PS, and the use of CA, EGFR-TKI, ALK-TKI, AI, and ICI remained significant factors. In period A histology, ECOG PS, and the use of EGFR-TKI remained significant factors. Use of EGFR-TKI exhibited the greatest impact on OS (HR = 0.28, 95%CI: 0.07–0.7, $p < 0.01$). In period B, ECOG PS and the use of EGFR-TKI remained significant factors. ECOG PS exhibited the greatest impact on OS (HR = 0.47, 95%CI: 0.33–0.66, $p < 0.01$). In period C, sex, histology, ECOG PS, and the use of CA, EGFR-TKI, and AI remained significant factors. ECOG PS and the use of CA exhibited the greatest impact on OS (HR = 0.42, 95%CI: 0.30–0.61 and 0.29–0.62, respectively, $p < 0.01$). In period D, histology, ECOG PS, and the use of CA, EGFR-TKI, ALK-TKI, and ICI remained significant factors. Use of ALK-TKI exhibited the greatest impact on OS (HR = 0.30, 95%CI: 0.19–0.46, $p < 0.01$). In period E, ECOG PS and the use of EGFR-TKI and ALK-TKI remained significant factors. ECOG PS and the use of ALK-

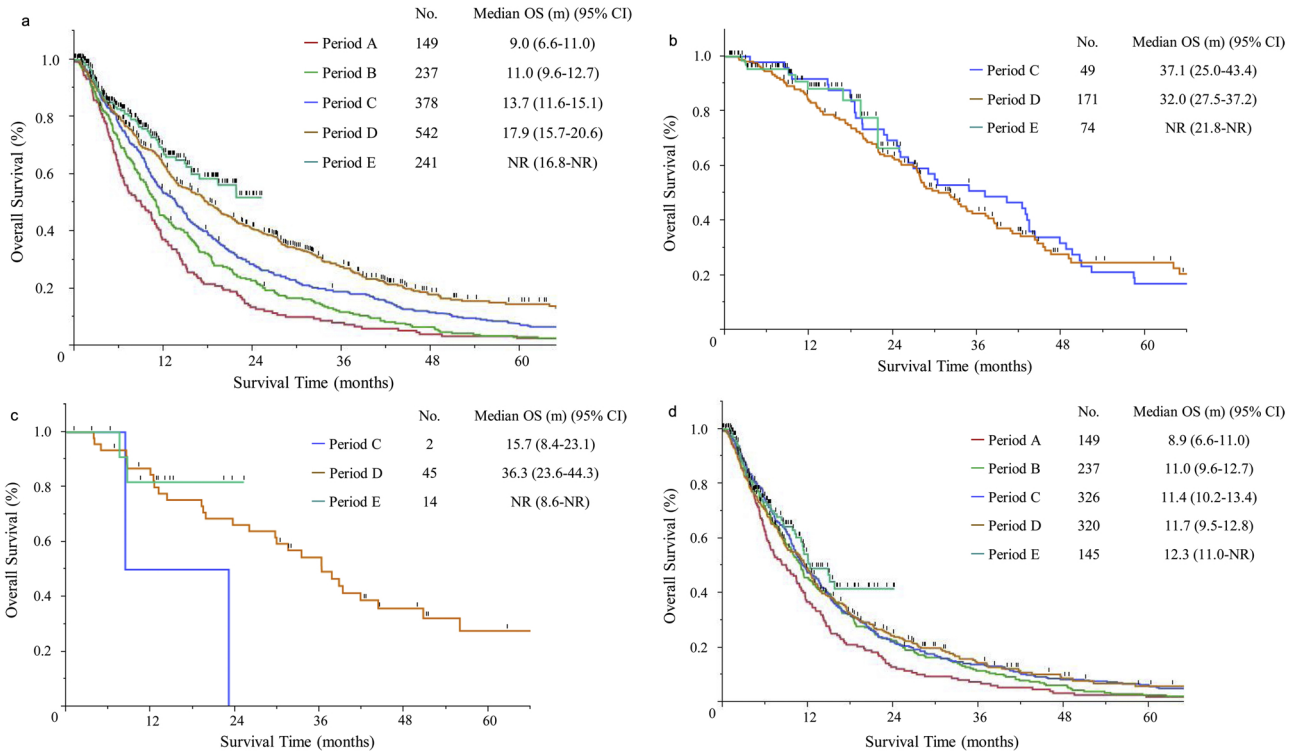

Fig. 2. Overall survival (OS) of patients with stage IV non-small-cell lung cancer (NSCLC) in each period: (A) all patients treated in our hospital; (B) patients with epidermal growth factor receptor (EGFR) mutations; (C) patients with anaplastic lymphoma kinase (ALK) rearrangement; (D) without driver mutation patients. CI, confidence interval.

TKI exhibited the greatest impact on OS (HR = 0.12 and 0.13, 95%CI: 0.07–0.20 and 0.03–0.42, respectively, $p < 0.01$).

3.5. Survival outcomes in patients with and without driver mutation during the examined periods

A total of 294 patients with EGFR mutation were identified in periods C–E. Of those, 292 patients (99.3%) received treatment with more than one EGFR-TKI. The OS curve of patients with EGFR mutation between periods C and E is shown in Fig. 2B. The median OS for periods C, D, and E was 37.1 months, 32.0 months, and not reached, respectively, and the observed difference was not statistically significant (C versus D, HR = 1.02, 95%CI: 0.71–1.44, $p = 0.931$; D versus E, HR = 0.69, 95%CI: 0.32–1.34, $p = 0.309$).

A total of 61 patients with the ALK fusion gene were identified in the periods C–E. Of those, 55 patients (90.1%) received treatment with more than one ALK-TKI. The OS curve of patients with the ALK fusion gene between periods C and E are shown in Fig. 2C. The median OS for periods C, D, and E was 15.7 months, 36.3 months, and not reached, respectively. However, the observed differences were not statistically significant because of the limited number of patients with the ALK fusion gene (C: $n = 2$, D: $n = 45$, and E: $n = 14$).

In the overall period, 1,177 patients without driver mutations were identified. The OS curves of patients without driver mutations between periods A and E are shown in Fig. 2D. The median OS was 8.9, 11.0, 11.4, 11.7, and 12.3 months, respectively. The OS was significantly improved from period A to B (A versus B; HR = 0.81; 95%CI: 0.66–1.00, $p = 0.047$). However, no differences were observed between periods B and D. Although the follow-up time was short, survival in period E was improved versus those observed in the other periods (E versus D; HR = 0.79; 95%CI: 0.58–1.06, $p = 0.119$). Cox univariate and multivariate analyses were performed in patients without driver mutations (Supplementary Table S1). Female sex, presence of adenocarcinoma, good ECOG PS, and treatment with CA, AI, and ICI were selected as independent clinical factors associated with improved OS in the multivariate analyses.

3.6. Impact of antineoplastic treatment on the survival of patients with NSCLC

We further investigated the effect of treatments on the improvement in survival in each of the five periods. Patients were matched for known prognostic factors (i.e., age, sex, smoking history, histology, and ECOG PS) in each period using PSM (A versus B; B versus C; C versus D; and D versus E) (Supplementary Fig. S1). Following the PSM, a trend of improvement in OS was observed between the periods, except in the B versus C comparison (Fig. 3A–D).

For period A versus period B, the median OS was 9.0 versus 10.2 months, respectively (HR = 0.85; 95%CI: 0.67–1.07; $p = 0.156$; Fig. 3A) and the OS curve in period B was slightly higher than that observed for period A. There were no significant differences in OS observed between the matched pairs B versus C. For period B versus C, the median OS was 13.2 versus 13.9 months, respectively (HR = 0.92; 95%CI: 0.74–1.14; $p = 0.451$; Fig. 3B). In contrast, significant differences in OS were observed between the matched pairs C versus D. For period C versus D, the median OS was 13.8 versus 17.5 months, respectively (HR = 0.80; 95%CI: 0.68–0.94; $p < 0.006$; Fig. 3C). For period D versus E, additional follow-up is warranted for the precise estimation of median OS in period E. However, the OS curve in period E was higher than that observed for period D. The median OS was 18.0 months versus NR, respectively (HR = 0.78; 95%CI: 0.57–1.05; $p = 0.099$; Fig. 3D).

4. Discussion

In this study we report a significant improvement in the OS of patients with advanced NSCLC treated between 1995 and 2017 in the Cancer Institute Hospital of the JFCR.

Table 3
(A) Univariate analysis of overall survival (OS) in patients with non-small-cell lung cancer (NSCLC); (B) multivariate analysis of OS in NSCLC patients.

Characteristics	Total				Period A				Period B			
	No.	HR	95% CI	*p* value	No.	HR	95% CI	*p* value	No.	HR	95% CI	*p* value
(A)												
Age (years)												
< 75	1388	0.85	0.71–1.04	0.12	135	0.87	0.52–1.59	0.64	218	0.93	0.65–1.69	0.75
≥75	159	–	–	–	14	–	–	–	19	–	–	–
Sex												
Female	965	0.64	0.56–0.72	< 0.01	50	0.73	0.51–1.03	0.07	85	0.67	0.51–0.88	< 0.01
Male	582	–	–	–	99	–	–	–	152	–	–	–
Smoking status												
Never	441	0.60	0.53–0.68	< 0.01	26	0.74	0.47–1.12	0.16	57	0.68	0.50–0.92	0.01
Other	1106	–	–	–	123	–	–	–	180	–	–	–
Histology												
Adenocarcinoma	1206	0.53	0.46–0.60	< 0.01	110	0.54	0.38–0.80	< 0.01	186	0.76	0.56–1.08	0.12
Other	341	–	–	–	39	–	–	–	51	–	–	–
ECOG PS												
0 or 1	1252	0.32	0.28–0.37	< 0.01	106	0.43	0.30–0.62	< 0.01	172	0.38	0.28–0.53	< 0.01
Other	295	–	–	–	43	–	–	–	65	–	–	–
Chemotherapy												
Yes	1109	0.61	0.53–0.69	< 0.01	86	0.61	0.44–0.86	< 0.01	168	0.66	0.50–0.88	< 0.01
No	438	–	–	–	63	–	–	–	69	–	–	–
EGFR-TKI												
Yes	535	0.49	0.43–0.55	< 0.01	4	0.24	0.06–0.65	< 0.01	89	0.49	0.37–0.64	< 0.01
No	1012	–	–	–	145	–	–	–	148	–	–	–
ALK-TKI												
Yes	62	0.35	0.24–0.50	< 0.01	0	–	–	–	0	–	–	–
No	1485	–	–	–	149	–	–	–	237	–	–	–
AI												
Yes	174	0.46	0.38–0.55	< 0.01	0	–	–	–	0	–	–	–
No	1373	–	–	–	149	–	–	–	237	–	–	–
ICI												
Yes	123	0.33	0.24–0.45	< 0.01	0	–	–	–	0	–	–	–
No	1424	–	–	–	149	–	–	–	237	–	–	–

Characteristics	Period C				Period D				Period E			
	No.	HR	95% CI	*p* value	No.	HR	95% CI	*p* value	No.	HR	95% CI	*p* value
(A)												
Age (years)												
< 75	356	0.81	0.53–1.32	0.37	480	0.82	0.61–1.14	0.22	199	0.56	0.33–1.00	0.052
≥75	22	–	–	–	62	–	–	–	42	–	–	–
Sex												
Female	145	0.61	0.49–0.75	< 0.01	213	0.64	0.52–0.79	< 0.01	89	0.52	0.29–0.87	0.01
Male	233	–	–	–	329	–	–	–	152	–	–	–
Smoking status												
Never	102	0.57	0.45–0.72	< 0.01	177	0.63	0.51–0.78	< 0.01	79	0.53	0.30–0.91	0.02
Other	276	–	–	–	365	–	–	–	162	–	–	–
Histology												
Adenocarcinoma	278	0.5	0.40–0.64	< 0.01	445	0.45	0.36–0.58	< 0.01	187	0.51	0.31–0.88	0.02
Other	100	–	–	–	97	–	–	–	54	–	–	–
ECOG PS												
0 or 1	326	0.32	0.24–0.44	< 0.01	457	0.31	0.24–0.40	< 0.01	191	0.16	0.10–0.26	< 0.01
Other	52	–	–	–	85	–	–	–	50	–	–	–
Chemotherapy												
Yes	331	0.35	0.26–0.49	< 0.01	400	0.53	0.43–0.67	< 0.01	124	0.99	0.61–1.62	0.96
No	47	–	–	–	142	–	–	–	117	–	–	–
EGFR-TKI												
Yes	168	0.48	0.39–0.60	< 0.01	201	0.52	0.42–0.64	< 0.01	73	0.26	0.12–0.49	< 0.01
No	210	–	–	–	341	–	–	–	168	–	–	–
ALK-TKI												
Yes	0	–	–	–	43	0.43	0.28–0.64	< 0.01	19	0.37	0.09–0.99	0.047
No	378	–	–	–	499	–	–	–	222	–	–	–
AI												
Yes	34	0.46	0.31–0.65	< 0.01	120	0.56	0.44–0.71	< 0.01	20	0.45	0.14–1.09	0.08
No	344	–	–	–	422	–	–	–	221	–	–	–
ICI												
Yes	2	0.16	0.01–0.71	0.01	45	0.32	0.20–0.49	< 0.01	76	0.72	0.42–1.20	0.21
No	376	–	–	–	497	–	–	–	165			

Characteristics	Total				Period A				Period B			
	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*

(*continued on next page*)

Table 3 (*continued*)

Characteristics	Total				Period A				Period B			
	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*
(B)												
Age (years)												
< 75	1388	–	–	–	135	–	–	–	218	–	–	–
≥75	159	–	–	–	14	–	–	–	19	–	–	–
Sex												
Female	965	0.84	0.72–0.97	0.01	50	–	–	–	85	0.75	0.55–1.02	0.06
Male	582	–	–	–	99	–	–	–	152	–	–	–
Smoking status												
Never	441	0.98	0.83–1.15	0.81	26	–	–	–	57	–	–	–
Other	1106	–	–	–	123	–	–	–	180	0.95	0.67–1.36	0.77
Histology												
Adenocarcinoma	1206	0.79	0.68–0.92	< 0.01	110	0.59	0.36–0.87	< 0.01	186	–	–	–
Other	341	–	–	–	39	–	–	–	51	–	–	–
ECOG PS												
0 or 1	1252	0.43	0.36–0.50	< 0.01	106	0.54	0.36–0.81	< 0.01	172	0.47	0.33–0.66	< 0.01
Other	295	–	–	–	43	–	–	–	65	–	–	–
Chemotherapy												
Yes	1109	0.77	0.66–0.89	< 0.01	86	0.70	0.49–1.00	0.051	168	0.94	0.69–1.29	0.70
No	438	–	–	–	63	–	–	–	69	–	–	–
EGFR-TKI												
Yes	535	0.49	0.43–0.57	< 0.01	4	0.28	0.07–0.77	< 0.01	89	0.6	0.44–0.82	< 0.01
No	1012	–	–	–	145	–	–	–	148	–	–	–
ALK-TKI												
Yes	62	0.29	0.19–0.42	< 0.01	0	–	–	–	0	–	–	–
No	1485	–	–	–	149	–	–	–	237	–	–	–
AI												
Yes	174	0.65	0.53–0.79	< 0.01	0	–	–	–	0	–	–	–
No	1373	–	–	–	149	–	–	–	237	–	–	–
ICI												
Yes	123	0.33	0.24–0.45	< 0.01	0	–	–	–	0	–	–	–
No	1424	–	–	–	149	–	–	–	237	–	–	–

Characteristics	Period C				Period D				Period E			
	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*	No.	HR	95% CI	*p*
(B)												
Age (years)												
< 75	356	–	–	–	480	–	–	–	199	–	–	–
≥75	22	–	–	–	62	–	–	–	42	–	–	–
Sex												
Female	145	0.75	0.56–0.99	0.04	213	0.92	0.70–1.19	0.51	89	0.71	0.36–1.33	0.29
Male	233	–	–	–	329	–	–	–	152	–	–	–
Smoking status												
Never	102	0.88	0.65–1.22	0.46	177	0.88	0.67–1.16	0.39	79	–	–	–
Other	276	–	–	–	365	–	–	–	162	0.69	0.34–1.45	0.32
Histology												
Adenocarcinoma	278	0.64	0.49–0.83	< 0.01	445	0.68	0.52–0.90	< 0.01	187	0.93	0.54–1.67	0.80
Other	100	–	–	–	97	–	–	–	54	–	–	–
ECOG PS												
0 or 1	326	0.42	0.30–0.61	< 0.01	457	0.42	0.31–0.56	< 0.01	191	0.12	0.07–0.20	< 0.01
Other	52	–	–	–	85	–	–	–	50	–	–	–
Chemotherapy												
Yes	331	0.42	0.29–0.62	< 0.01	400	0.53	0.40–0.70	< 0.01	124	–	–	–
No	47	–	–	–	142	–	–	–	117	–	–	–
EGFR-TKI												
Yes	168	0.65	0.50–0.84	< 0.01	201	0.39	0.30–0.50	< 0.01	73	0.17	0.07–0.36	< 0.01
No	210	–	–	–	341	–	–	–	168	–	–	–
ALK-TKI												
Yes	0	–	–	–	43	0.30	0.19–0.46	< 0.01	19	0.13	0.03–0.42	< 0.01
No	378	–	–	–	499	–	–	–	222	–	–	–
AI												
Yes	34	0.57	0.38–0.81	< 0.01	120	0.84	0.64–1.10	0.21	20	–	–	–
No	344	–	–	–	422	–	–	–	221	–	–	–
ICI												
Yes	2	0.32	0.02–1.46	0.17	45	0.29	0.18–0.45	< 0.01	76	–	–	–
No	376	–	–	–	497	–	–	–	165	–	–	–

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; AI, angiogenesis inhibitor; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval.

We used PSM to compare survival outcomes adjusted for differences in baseline characteristics and treatment selection bias. In PSM patients the trend of improvement in survival was maintained, especially over the previous decade. Furthermore, in the Cox multivariate analysis the use of CA, EGFR-TKI, ALK-TKI, AI, and ICI remained a significant factor related to survival benefit in all patients. Therefore, these data

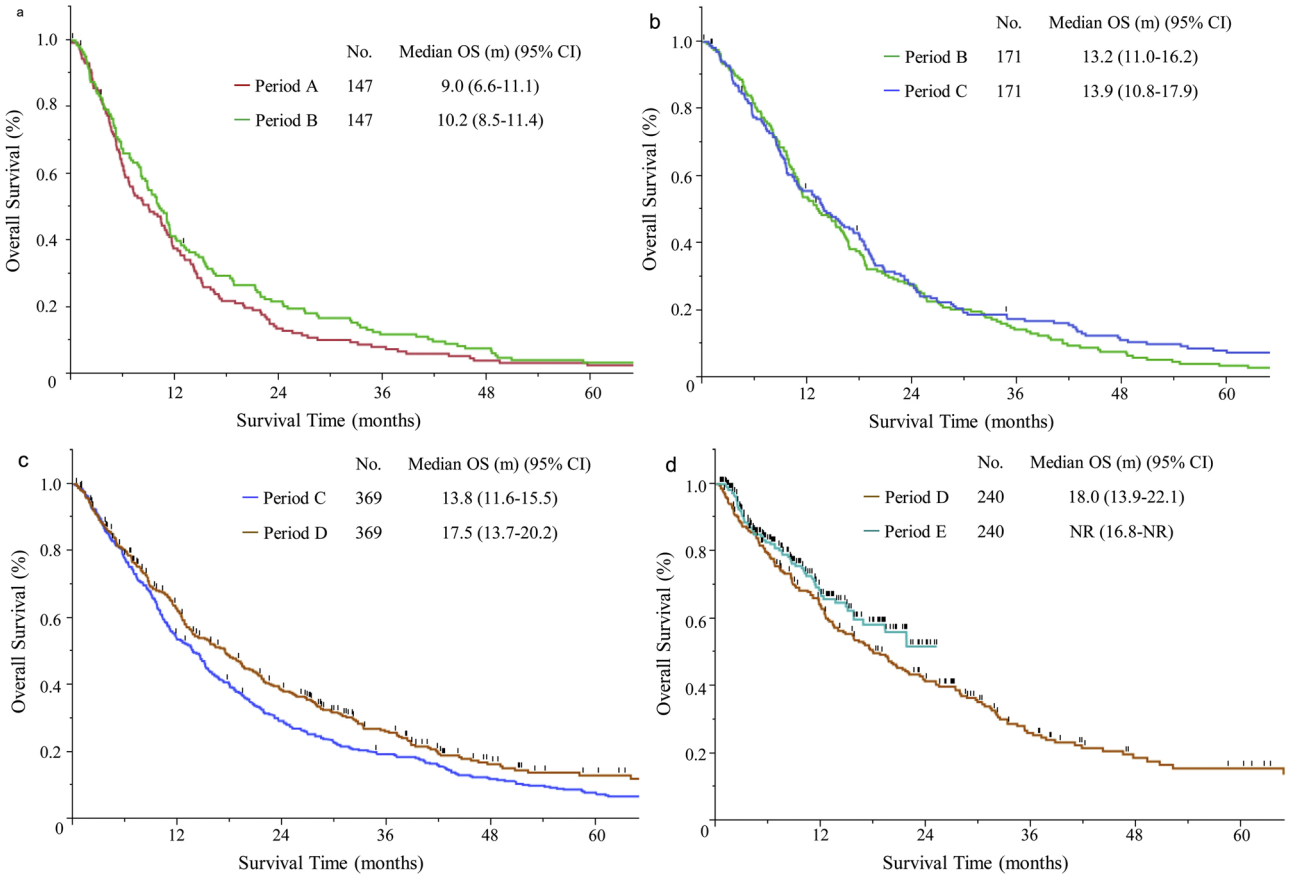

Fig. 3. Comparison of overall survival (OS) of propensity score-matched patients with non-small-cell lung cancer (NSCLC) in each period. Matching for baseline characteristics: (A) patients in period A versus period B; (B) patients in period B versus period C; (C) patients in period C versus period D; (D) patients in period D versus period E.

demonstrated the effect of each new class of drugs on the improvement of survival.

During the previous two decades a major shift has occurred in the pharmacological agents used for the treatment of patients with advanced NSCLC (Fig. 1). These patients are able to undergo treatment using their preferred drug among numerous anticancer agents. As demonstrated in pivotal studies, these new classes of drugs significantly extend progression-free survival. However, the use of these agents did not result in a marked difference in patient survival [7,10,13–17]. In those pivotal studies treatment crossover was permitted (i.e., patients received various drugs). Demonstrating the extent of improvement in survival outcomes induced by one of these drugs is therefore challenging. The present study revealed superior outcomes in patients with EGFR mutation treated with gefitinib and ALK-positive patients treated with crizotinib compared with those observed before the approval of these drugs. This finding is consistent with those of previous reports [18,19].

This study also has a limitation. This was a retrospective analysis, and the clinical characteristics in each period were slightly unbalanced. For example, the percentage of BSC was high in period A and decreased with the passage of time. This trend may be attributed to the administration of anticancer treatment in period A. There may be a considerable number of cases that did not receive therapeutic agents because of the lack of anticancer drug options (other than cytotoxic chemotherapy) at that time. It is logical to assume that the different rates of BSC observed between periods may have affected the OS of patients. However, based on the observed decrease in BSC between the examined periods, it is suggested that the broadening of the available anticancer therapeutic options was beneficial to patients. Therefore, the introduction of a new class of drugs would improve patient survival. To confirm this hypothesis, we used Cox multivariate analysis and PSM to compare survival outcomes adjusted for differences in baseline characteristics. We noticed that the proportion of patients treated with a new class of drugs increased with the passage of time (Supplementary Table S2). Therefore, the present results indicate that the use of the new classes of drugs and the paradigm shift observed in the treatment of advanced NSCLC from 1995 to 2017 contributed to the improvement in patient survival.

In contrast, no significant improvement in the survival of patients with EGFR mutation was observed from 2005. This lack of improvement was observed despite the approval of erlotinib and afatinib (after the approval of gefitinib) in Japan in 2002. Previously, prospective randomized trials compared the efficacy of erlotinib or afatinib with that of gefitinib. However, they failed to show a significant benefit in survival over gefitinib [17,20,21]. The present findings are consistent with those of the previous randomized trials and suggest that the approval of multiple EGFR-TKIs was not responsible for the observed improvement in the survival of patients with EGFR mutation. Although the median OS of patients with EGFR mutation in period E was not reached at the data cut-off, we hypothesize that the use of new agents (i.e., osimertinib) may prolong the survival of patients with EGFR mutation. This hypothesis is based on the significantly greater efficacy of osimertinib compared with that of platinum-doublet chemotherapy demonstrated in patients with EGFR Thr790Met (T790M) point mutation—the most frequently reported mechanism of acquired resistance to first-line treatment with EGFR-TKI [22].

Furthermore, the EML4-ALK fusion oncogene, which was described in 2007, represents one of the molecular targets in NSCLC. In 2012 crizotinib was the first ALK-TKI to be approved for the treatment of ALK-positive patients with advanced NSCLC [9]. Subsequently,

alectinib and ceritinib were approved in Japan. Currently, ALK-TKIs are considered the standard first-line treatment for ALK-positive patients. In our study, the proportion of patients treated with ALK-TKIs increased after period C. However, the number of patients was insufficient to demonstrate the superiority of alectinib or ceritinib versus crizotinib in terms of survival. In prospective analyses, alectinib, ceritinib, brigatinib, and lorlatinib demonstrated clinical efficacy in ALK-positive patients with disease progression while receiving treatment with crizotinib [16,23–25]. The development of next-generation ALK-TKIs may overcome the resistance mechanisms in these patients. Consequently, this may lead to an improvement in the survival of ALK-positive patients.

Our data also showed that non-significant differences in survival were observed among patients without driver mutations between periods B and D. This finding suggests that the approval of multiple CAs during the previous two decades may not be responsible for the improvement in the survival of patients without driver mutations. Although the follow-up time was short, we found that the survival of patients diagnosed in period E tended to be longer than that of patients diagnosed in other periods. Nivolumab, the first ICI, was approved in 2015 for the treatment of previously treated NSCLC patients. The approval of nivolumab provided a new treatment option for patients with advanced NSCLC. In a prospective phase III trial, treatment with nivolumab showed a significantly longer survival compared with docetaxel [11,12]. The findings of the present study are consistent with those of previous trials, suggesting that the approval of nivolumab may be responsible for the prolonged OS observed in patients with advanced NSCLC without driver mutations. In 2016 and 2017, pembrolizumab and atezolizumab, respectively, were also approved in Japan. Use of these agents may contribute further to the extension of patient survival.

5. Conclusions

In conclusion, this study demonstrated an improvement in the survival of patients with advanced NSCLC during the previous decades. This effect was associated with the approval of several new classes of drugs and marked shifts in the treatment of patients with advanced NSCLC. Moreover, our study revealed the absence of significant improvement in survival in recent years among patients with EGFR mutation and those without driver mutations. This finding indicates that the development of similar types of drugs may not exert a great benefit on the improvement in patient survival. We expect that in the future the prognosis of patients may improve through treatment with new classes of antineoplastic agents such as ICIs and next-generation molecular targeted agents.

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Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2019.03.008.

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