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Trajectory of chemotherapy for patients with EGFR wild-type advanced pulmonary adenocarcinoma: a single-institution retrospective study

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Background: Pulmonary adenocarcinoma, recently benefited by new cytotoxic and molecularly targeted drugs, has been classified by driver mutations, such as *EGFR* mutations. The aim of this study was to research the proportions of patients treated with first- to third-line chemotherapy and to find influential factors for the introduction of chemotherapy and survival benefit from chemotherapy.

Materials and methods: Data were collected retrospectively on patients who met the following criteria: adenocarcinoma, diagnosed between June 2007 and March 2015 at our hospital, stage IIIB or IV, and *EGFR* wild type. A nonchemotherapy group of patients who did not receive chemotherapy was compared with a chemotherapy group of patients who received it. The patients who had received first- to third-line chemotherapy between June 2007 and November 2015 at our hospital were also analyzed.

Results: During the study period, 46 patients did not receive chemotherapy, while 148, 89, and 48 received first-, second- and third-line chemotherapy, respectively. As predictive factors for unlikely chemotherapy, multivariate logistic analysis detected Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, hemoglobin <13.2 g/dL, creatinine clearance (Ccr) <50.4 mL/min, and CRP ≥0.53 mg/dL. As factors predicting shorter survival after chemotherapy, multivariate Cox proportional-hazard analyses detected age ≥75 years, ECOG PS ≥2, lower lymphocyte counts, and higher CRP for the first line; female, higher neutrophil counts, lower lymphocyte counts, reduced Ccr, hyponatremia, and shorter interval between first- and second-line chemotherapy for the second line; and age ≥75 years, body mass index <18.5 kg/m^2, higher neutrophil counts, lower lymphocyte counts, hyponatremia, higher lactate dehydrogenase, and higher CRP for the third line.

Conclusion: Approximately 76% of patients were treated with first-line chemotherapy. Of those patients, 61% and 34% proceeded to second- and third-line chemotherapy, respectively. For patients with poor PS, anemia, reduced Ccr, and higher CRP, it is difficult to introduce chemotherapy.

Keywords: adenocarcinoma, non-small-cell lung cancer, first-line chemotherapy, second-line chemotherapy, third-line chemotherapy, EGFR wild type

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Introduction

Pulmonary adenocarcinoma is a major histological subtype of lung cancer, and has a constant tendency to increase in Japan, irrespectively of sex. Its incidence rates were 43% and 67% of all histological types of Japanese lung cancer cases during 1999–2003 in males and females, respectively.[1]

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Over the last decade, in contrast to squamous cell carcinoma, treatment for adenocarcinoma has developed dramatically. This histology has benefited from a new cytotoxic antitumor drug, pemetrexed,[2] and a molecularly targeted antibody – bevacizumab.[3] Furthermore, adenocarcinoma has been divided into two subsets according to genetic information: adenocarcinoma harboring a driver mutation, either positive *EGFR* mutation[4] or ALK rearrangement;[5] and adenocarcinoma without these driver mutations. Nowadays, treatment strategies differ markedly between these two subsets. For the former subset, specific tyrosine-kinase inhibitors are indispensable. On the other hand, for the latter subset, cytotoxic chemotherapy remains a standard treatment. Platinum-based combination regimens with or without bevacizumab are recommended as the first-line treatment. However, almost all patients experience progression during or after first-line chemotherapy. Some of them require salvage chemotherapy.

Some survey studies have revealed a trend of patients with advanced non-small-cell lung cancer who have received first- and later-line chemotherapy.[6–15] However, there is no study that has focused on patients with *EGFR* wild-type adenocarcinoma and followed their course of chemotherapy. Our retrospective study for adenocarcinoma with wild-type *EGFR* aimed to investigate 1) what the rate of patients who had received first-, second, or third-line chemotherapy was and 2) who benefited from chemotherapy.

Materials and methods

Patients and study design

This was a single-institution retrospective study. The inclusion criteria were: 1) histologically or cytologically diagnosed with pulmonary adenocarcinoma; 2) stage IIIB or IV, defined by the seventh TNM (tumor, node, metastasis) classification of lung cancer by the Union for International Cancer Control[16] (staging by sixth edition of the UICC classification was reclassified according to seventh edition); (3) diagnosed between June 2007 and March 2015 at our institution; (4) *EGFR* wild-type status examined by LSI Medience Corporation (Tokyo, Japan) using the peptide nucleic acid-locked polymerase chain-reaction clamp method.[17] The exclusion criteria were: 1) patients who were diagnosed at our hospital, but thereafter transferred to other hospitals for aggressive treatment; 2) diagnosis and introduction of any aggressive treatment were performed at another hospital, but thereafter transferred to our hospital for later-line treatment; 3) adenocarcinoma combined with other histological types; 4) immunohistochemically positive *ALK* gene rearrangement; 5) *EGFR* mutations were not examined. In Japan, *EGFR*-mutation tests became covered by insurance in June 2007. Fluorescence in situ hybridization and immunohistochemistry for *ALK* gene rearrangement were approved in April 2012 and June 2014, respectively.

1) In order to investigate predictive factors influencing introduction of systemic chemotherapy, we compared patients who had received chemotherapy (chemotherapy group) with those who had not received chemotherapy (nonchemotherapy group). 2) To find prognostic factors influencing survival after each line of chemotherapy, we extracted three cohorts of patients who had started first-, second-, or third-line regimens between June 2007 and November 2015. We excluded chemotherapies that started after December 2015. During the study period in Japan, erlotinib, pemetrexed, bevacizumab, *nab*-paclitaxel, and nivolumab were approved for non-small-cell lung cancer in October 2007, May 2009, November 2009, February 2013, and December 2015, respectively.

Patients' background data, laboratory data, criteria and definitions of overall response rate (RR), overall survival (OS), and progression-free survival (PFS) in this study followed those of our previous studies.[18,19] In this study, we added creatinine clearance estimated by Cockcroft–Gault formula as an explanatory variable at diagnosis and at the start of each chemotherapy. We added 0.2 mg/dL to serum creatinine concentrations measured by the enzymatic method, in order to adjust the difference between creatinine values measured by the Jaffe method and the enzymatic method.[20] In principle, laboratory data comparing between the chemotherapy and nonchemotherapy groups were obtained on the last day before the examination leading to the confirmed diagnosis of malignancy. However, alkaline phosphatase (ALP) values were not measured before the examination in three and one cases in the chemotherapy and nonchemotherapy groups, respectively. Instead, we used the data on the nearest day after the examination in those four cases. Height could not be measured in three patients in the nonchemotherapy group, because they could not stand by themselves. Therefore, these three patients were excluded from comparison of body mass index. Data cutoff for RR, PFS, and OS was July 31, 2016. The Osaka Police Hospital ethics committee approved this study (number 501) and waived the requirement for informed consent, because our data were retrospective and deidentified.

Data analysis

Continuous, discrete, and categorical variables are expressed as mean ± standard deviation, median (range), and frequency, respectively. Normality of distribution and homogeneity of variances were assessed by Shapiro–Wilk and *F*-tests, respectively. Comparing relative frequencies, discrete variables, and normally distributed continuous variables between two

groups, we used χ^2 or Fisher's exact test, Mann–Whitney *U* test, and Student's *t*-test, respectively. Thereafter, all variables with a *P*-value <0.2 were included in the subsequent univariate logistic regression analysis. The laboratory data were divided by the optimal cutoff values and transformed into dichotomous variables. For receiver-operating characteristic curves and areas under the curve, cutoff points were decided as the value that gave maximal joint sensitivity and specificity. Logistic regression analysis and Cox proportional-hazard analysis were used to find factors influencing outcome variables, introduction of chemotherapy, and survival after chemotherapy, respectively. All variables with a *P*-value <0.1 in univariate analysis were included in the subsequent multivariate analysis. When a moderate-to-strong correlation (Pearson's correlation coefficient, $r \geq 0.4$) was observed between two laboratory data and a risk of multicollinearity was a concern, we arbitrarily excluded either of the coefficients from candidate explanatory variables in the multivariate analysis. Backward-stepwise selection based on *P*-value was used to select variables that were entered into the multivariate model. These results were expressed as odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs). A *P*-value <0.05 was statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).[21]

Results

Among 194 patients who met the inclusion criteria, 148 patients were able to receive chemotherapy (chemotherapy group), but 46 could not (nonchemotherapy group). On the other hand, 62 patients were excluded from analysis, because their *EGFR*-mutation status was unknown. Among these 62 patients, 19 (31%) received chemotherapy. ALK-immunohistochemistry screening was performed in 22 patients (48%) of the nonchemotherapy group and 59 (40%) of the chemotherapy group. In the chemotherapy group, 89 and 48 patients proceeded to second- and third-line chemotherapy, respectively (Figure S1).

Initially, we compared backgrounds and laboratory data between the chemotherapy and nonchemotherapy groups. Patients in the chemotherapy group were younger (67±9.5 vs 73.9±9.7 years, *P*<0.01), included a lower proportion of stage IV (*P*<0.01), kept better Eastern Cooperative Oncology Group (ECOG) performance status (PS) (*P*<0.01), and survived longer (median 404 vs 87 days, *P*<0.01) (Table 1). As for laboratory data, there were significant differences in absolute lymphocyte count (1,721±570 vs 1,332±562 cells/μL, *P*<0.01), hemoglobin (13.5±1.6 vs 11.9±1.8 g/dL, *P*<0.01), creatinine clearance (59.4±18.8 vs 46.3±21.6 mL/min, *P*<0.01), serum sodium concentration (139±3.3 vs 137.8±3.9, *P*=0.04), ALP (297.6±158.9 vs 351.9±184.7, *P*=0.04), and CRP (2.1±3.4 vs 4.8±3.5, *P*<0.01) (Table 1). Table S1 presents the optimal cutoff values for binarization of laboratory data. Univariate analysis detected ten variables as factors predicting difficult introduction of chemotherapy – age ≥75 years, stage IV, ECOG PS ≥2, neutrophil count ≥8,356 cells/μL, lymphocyte count <1,414 cells/μL, hemoglobin <13.2g/dL, sodium <139 mEq/L, creatinine

Table 1 Patient characteristics at diagnosis

Variables	Chemotherapy	Nonchemotherapy	*P*
n	148	46	
Age (years)			
Mean ± SD	67.0±9.5	73.9±9.7	<0.01[a]
Sex (n)			
Male/female	106/42	32/14	0.93[b]
Smoking habits (n)			
Non/ex-smokers vs current smokers	71/77	27/19	0.27[b]
Staging (n)			
IIIB/IV	31/117	1/45	<0.01[c]
ECOG PS (n)[d]			
0–1/2/3/4	121/23/4/0	11/16/15/4	<0.01[a]
BMI (kg/m²)[d]			
Mean ± SD	22.1±3	21.5±3.4[e]	0.34[f]
Charlson Comorbidity Index			
Mean ± SD	0.9±1.1	1.1±1.4	0.26[a]
Overall survival (days)[g]			
Median (95% CI)	404 (330–573)	87 (44–109)	<0.01[h]
Laboratory data[d]			
Neutrophils (cells/μL)	6,008±2,933	7,106±4,090	0.13[a]
Lymphocytes (cells/μL)	1,721±570	1,332±562	<0.01[a]
Monocytes (cells/μL)	478±194	555±291	0.24[a]
Hemoglobin (g/dL)	13.5±1.6	11.9±1.8	<0.01[f]
RDW (%)	13.7±1.1	14.0±1.6	0.24[a]
Platelets ($\times 10^3$ cells/μL)	269.2±82.1	287.3±127	0.84[a]
Ccr (mL/min)	59.4±18.8	46.3±21.6	<0.01[a]
Sodium (mEq/L)	139±3.3	137.8±3.9	0.04[a]
LDH (IU/L)	291.6±333.5	525.6±1358.1	0.41[a]
ALP (IU/L)	297.6±158.9	351.9±184.7	0.04[a]
CRP (mg/dL)	2.1±3.4	4.8±3.5	<0.01[a]

Notes: [a]Mann–Whitney *U* test; [b]χ^2 test; [c]Fisher's exact test; [d]nearest point before diagnostic examination was performed; [e]three patients were excluded because height could not be measured at diagnosis; [f]Student's *t*-test; [g]from diagnosis to death or last survival confirmation; [h]log-rank test.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CCI, Charlson Comorbidity Index; Ccr, creatinine clearance; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status; RDW, red cell distribution width; SD, standard deviation.

clearance <50.4 mL/min, ALP ≥293 IU/L, and CRP ≥0.53 mg/dL – while multivariate analysis extracted the four variables ECOG PS ≥2 (OR 0.08, 95% CI: 0.03–0.21; *P*<0.01), hemoglobin <13.2 g/dL (OR 0.13, 95% CI: 0.05–0.36; *P*<0.01), creatinine clearance <50.4 mL/min (OR 0.36, 95% CI: 0.15–0.9; *P*=0.03), and CRP ≥0.53 mg/dL (OR 0.33, 95% CI: 0.12–0.88; *P*=0.03) (Table 2).

Table 3 shows pretreatment characteristics and laboratory data at the start of first-, second-, and third-line chemotherapy, respectively. Carboplatin-based combination regimens were most frequently used in the first-line setting, while nonplatinum monotherapy regimens were used in the second- and third-line settings (Table S2). Progressive disease was always the most frequent reason for discontinuation of chemotherapy. RR, disease-control rate, and PFS gradually diminished every line (Table S3).

As factors predicting OS from the start of first-, second-, and third-line chemotherapy, univariate Cox-hazard analysis detected that the variables female, ECOG PS ≥2, neutrophil count, lymphocyte count, monocyte count, creatinine clearance, sodium concentration, and CRP in first-line therapy (Table 4); age ≥75 years, male, ECOG PS ≥2, neutrophil count, lymphocyte count, monocyte count, hemoglobin, red cell distribution width (RDW), platelet count, creatinine clearance, sodium concentration, LDH, ALP, CRP, and interval between first and second lines in second-line therapy (Table 5); and ECOG PS ≥2, neutrophil count, lymphocyte count, monocyte count, sodium concentration, LDH, ALP, CRP, and interval between first and third lines in third-line therapy (Table 6).

Subsequent multivariate Cox-hazard analysis extracted age ≥75 years (HR 1.56, 95% CI: 1.01–2.39; *P*=0.04), ECOG PS ≥2 (HR 3.22, 95% CI: 1.98–5.24; *P*<0.01), lymphocyte count (HR 0.65, 95% CI: 0.47–0.89; *P*<0.01), and CRP (HR 1.07, 95% CI: 1.02–1.11; *P*<0.01) in first-line therapy (Table 4); female (HR 0.43, 95% CI: 0.24–0.77; *P*<0.01), neutrophil count (HR 1.26, 95% CI: 1.13–1.4; *P*<0.01), lymphocyte count (HR 0.42, 95% CI: 0.26–0.67; *P*<0.01), creatinine clearance (HR 0.81, 95% CI: 0.68–0.95; *P*<0.01),

Table 2 Univariate and multivariate logistic regression analyses of factors influencing receipt of chemotherapy

Variables	Univariate			Multivariate[a]		
	OR	95% CI	P	OR	95% CI	*P*
Age						
<75 vs ≥75 years	0.35	0.18–0.69	<0.01			
Staging						
IIIB vs IV	0.08	0.01–0.63	0.02			
ECOG PS						
0–1 vs 2–4	0.07	0.03–0.16	<0.01	0.08	0.03–0.21	<0.01
Neutrophils (cells/μL)						
<8,356 vs ≥8,356	0.42	0.19–0.93	0.03			
Lymphocytes (cells/μL)						
≥1,414 vs <1,414	0.26	0.13–0.53	<0.01			
Hemoglobin (g/dL)						
≥13.2 vs <13.2	0.13	0.06–0.29	<0.01	0.13	0.05–0.36	<0.01
Sodium (mEq/L)						
≥139 vs <139	0.4	0.21–0.74	<0.01			
Ccr (mL/min)						
≥50.4 vs <50.4	0.22	0.11–0.46	<0.01	0.36	0.15–0.9	0.03
ALP (IU/L)						
<293 vs ≥293	0.43	0.22–0.84	0.01			
CRP (mg/dL)						
<0.53 vs ≥0.53	0.26	0.11–0.55	<0.01	0.33	0.12–0.88	0.03

Note: [a]Explanatory variables were selected by backward-stepwise selection based on *P*-values.

Abbreviations: ALP, alkaline phosphatase; Ccr, creatinine clearance; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; PS, performance status.

Table 3 Pretreatment characteristics of patients who received first- to third-line chemotherapy

Variables	First line	Second line	Third line
n	148	89	48
Age (years)[a]			
Mean ± SD	67.1±9.5	66.5±9.5	65.4±8.6
Sex			
Male/female	106/42	62/27	33/15
Staging[a]			
≤IIIB/IV	31/117	13/76	41/7
ECOG PS[a]			
0–1/2/3/4	115/29/4/0	66/19/4/0	32/13/3/0
BMI (kg/m^2)[a]			
Mean ± SD	21.8±3.1	21.9±3.1	22.1±3.1
Laboratory data[b]			
Neutrophils (cells/μL)	6,098±3,392	4,803±2,291	4,796±2,579
Lymphocytes (cells/μL)	1,632±597	1,594±639	1,591±552
Monocytes (cells/μL)	544±272	519±239	508±209
Hemoglobin (g/dL)	12.7±1.5	11.6±1.7	11.6±1.7
RDW (%)	14±1.7	14.8±2.3	15.5±2.3
Platelets (×10^3 cells/μL)	269±83.1	243.3±91.8	241.3±78.1
Ccr (mL/min)	53.2±16.5	62.5±34.3	61.5±15.4
Sodium (mEq/L)	138.6±3.6	139.7±3.1	139.4±2.8
LDH (IU/L)	309.3±470	309.1±394.7	262.1±113.1
ALP (IU/L)	325.8±263.8	283±111.7	293.2±116.4
CRP (mg/dL)	3.0±4.6	2.5±4.4	1.8±2.2

Notes: [a]At the start of each line of chemotherapy; [b]data obtained nearest to the start of each line of chemotherapy.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ccr, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; RDW, red cell distribution width; SD, standard deviation.

Table 4 Univariate and multivariate Cox-hazard analysis of factors associated with overall survival after first-line chemotherapy

Factors	Univariate			Multivariate[a]		
	HR	95% CI	P	HR	95% CI	P
Age						
<75 vs ≥75 years	1.43	0.95–2.15	0.09	1.56	1.01–2.39	0.04
Sex						
Male vs female	1.78	1.16–2.74	<0.01			
ECOG PS						
0–1 vs 2–4	4.5	2.87–7.07	<0.01	3.22	1.98–5.24	<0.01
Stage						
<IIIB vs IV	1.09	0.68–1.73	0.72			
BMI (kg/m²)						
≥18.5 vs <18.5	1.01	0.61–1.65	0.98			
Laboratory data						
Neutrophils ($\times10^3$cells/μL)[b]	1.07	1.02–1.13	<0.01			
Lymphocytes ($\times10^3$cells/μL)[b]	0.59	0.42–0.8	<0.01	0.65	0.47–0.89	<0.01
Monocytes ($\times10^2$cells/μL)[b]	1.16	1.08–1.25	<0.01			
Hemoglobin (mg/dL)	0.95	0.84–1.07	0.4			
RDW (%)	0.9	0.78–1.05	0.17			
Platelets ($\times10^5$ cells/μL)	0.87	0.69–1.09	0.22			
Ccr (×10 mL/min)	0.87	0.77–0.98	0.02			
Sodium (mEq/L)	0.65	0.43–0.98	0.04			
LDH ($\times10^2$ IU/L)	1.03	0.99–1.07	0.12			
ALP ($\times10^2$ IU/L)	1.06	0.99–1.12	0.07			
CRP (mg/dL)	1.09	1.06–1.13	<0.01	1.07	1.02–1.11	<0.01

Notes: [a]Explanatory variables were selected by backward-stepwise selection based on *P*-value; [b]a significant correlation was observed between neutrophil and monocyte counts (r=0.72, 95% CI: 0.64–0.79; P<0.01), while no significant correlation was found between neutrophil and lymphocyte counts (r=–0.05, 95% CI: –0.21 to 0.11; P=0.51) or between lymphocyte and monocyte counts (r=0.03, 95% CI: –0.13 to 0.19; P=0.74). Monocyte count was not selected as an explanatory variable in the multivariate analysis. Coded as 1 (age ≥75 years, female, ECOG PS 2–4, stage IV, BMI <18.5 kg/m²) and as 0 (age <75 years, male, ECOG PS 0–1, stage I–III, BMI ≥18.5 kg/m²).

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; PS, performance status; RDW, red cell distribution width.

Table 5 Univariate and multivariate Cox-hazard analysis of factors associated with overall survival after second-line chemotherapy

Factors	Univariate			Multivariate[a]		
	HR	95% CI	P	HR	95% CI	P
Age						
<75 vs ≥75 years	1.93	1.14–3.28	0.01			
Sex						
Male vs female	0.5	0.29–0.85	0.01	0.43	0.24–0.77	<0.01
ECOG PS						
0–1 vs 2–4	3.68	2.15–6.31	<0.01			
Stage						
<IIIB vs IV	0.72	0.38–1.35	0.31			
BMI (kg/m²)						
≥18.5 vs <18.5	1.28	0.69–2.39	0.43			
Laboratory data						
Neutrophils ($\times10^3$cells/μL)[b]	1.25	1.14–1.38	<0.01	1.26	1.13–1.4	<0.01
Lymphocytes ($\times10^3$cells/μL)[b]	0.54	0.36–0.82	<0.01	0.42	0.26–0.67	<0.01
Monocytes ($\times10^2$cells/μL)[b]	1.22	1.1–1.35	<0.01			
Hemoglobin (mg/dL)[b]	0.83	0.71–0.97	0.02		–	
RDW (%)[b]	1.09	1.01–1.18	0.02		–	
Platelets ($\times10^5$ cells/μL)	1.47	1.12–1.92	<0.01			
Ccr (×10 mL/min)	0.86	0.75–1	0.048	0.81	0.68–0.95	<0.01
Sodium (mEq/L)	0.12	0.05–0.27	<0.01	0.24	0.09–0.6	<0.01
LDH ($\times10^2$ IU/L)	1.11	1.05–1.17	<0.01			
ALP ($\times10^2$ IU/L)	1.43	1.16–1.77	<0.01			
CRP (mg/dL)	1.13	1.08–1.18	<0.01			
Interval between first- and second-line chemotherapy (months)[c]	0.87	0.8–0.94	<0.01	0.88	0.8–0.95	<0.01

Notes: [a]Explanatory variables were selected by backward-stepwise selection based on *P*-value. [b]Significant correlations were observed between neutrophil and monocyte counts (r=0.55, 95% CI: 0.39–0.68; P<0.01), lymphocyte and monocyte counts (r=0.25, 95% CI: 0.05–0.44; P=0.02), and hemoglobin and red cell distribution width (r=–0.35, 95% CI: –0.52 to –0.15; P<0.01), while no significant correlation was found between neutrophil and lymphocyte counts (r=0.02, 95% CI: –0.19 to 0.23; P=0.85). Monocyte count was not selected as an explanatory variable in the multivariate analysis. [c]From the start of first-line chemotherapy to the start of second-line chemotherapy. Coded as 1 (age ≥75 years, female, ECOG PS 2–4, stage IV, BMI <18.5 kg/m²) and as 0 (age <75 years, male, ECOG PS 0–1, stage I–III, BMI ≥18.5 kg/m²).

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; PS, performance status; RDW, red cell distribution width.

sodium concentration (HR 0.24, 95% CI: 0.09–0.6; P<0.01), and interval between first- and second-line chemotherapy (HR 0.88, 95% CI: 0.8–0.95; P<0.01) in second-line therapy (Table 5); age ≥75 years (HR 3.33, 95% CI: 1.3–8.53; P=0.01), body mass index (HR 3.26, 95% CI: 1.27–8.36; P=0.01), neutrophil count (HR 1.26, 95% CI: 1.06–1.51; P=0.01), lymphocyte count (HR 0.42, 95% CI: 0.19–0.92; P=0.03), sodium concentration (HR 0.06, 95% CI: 0.01–0.27; P<0.01), LDH (HR 1.4, 95% CI: 1.03–1.90; P=0.03), and CRP (HR 1.45, 95% CI: 1.21–1.73; P<0.01) in third-line therapy (Table 6).

Discussion

This retrospective study is the first to clarify the trajectory of patients with advanced adenocarcinoma with *EGFR* wild-type status. We found several factors leading to introduction of chemotherapy and longer survival after first-, second-, and third-line chemotherapy.

Our study revealed a flow of patients with adenocarcinoma with *EGFR* wild-type status. No other study has

Table 6 Univariate and multivariate Cox-hazard analysis of factors associated with overall survival after third-line chemotherapy

Factors	Univariate			Multivariate[a]		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
<75 vs ≥75 years	2.09	0.9–4.86	0.09	3.33	1.3–8.53	0.01
Sex						
Male vs female	0.75	0.37–1.51	0.42			
ECOG PS						
0–1 vs 2–4	2.4	1.24–4.61	<0.01			
Stage						
<IIIB vs IV	1.13	0.47–2.74	0.78			
BMI (kg/m^2)						
≥18.5 vs <18.5	2.05	0.93–4.55	0.08	3.26	1.27–8.36	0.01
Laboratory data						
Neutrophils (×10^3 cells/μL)[b]	1.21	1.06–1.39	<0.01	1.26	1.06–1.51	0.01
Lymphocytes (×10^3 cells/μL)[b]	0.27	0.13–0.59	<0.01	0.42	0.19–0.92	0.03
Monocytes (×10^2 cells/μL)[b]	1.16	1–1.35	0.049			
Hemoglobin (mg/dL)	0.86	0.71–1.04	0.11			
RDW (%)	1.04	0.9–1.19	0.64			
Platelets (×10^5 cells/μL)	1.3	0.86–1.96	0.21			
Ccr (×10 mL/min)	0.99	0.82–1.21	0.95			
Sodium (mEq/L)	0.28	0.08–0.95	0.04	0.06	0.01–0.27	<0.01
LDH (×10^2 IU/L)	1.43	1.11–1.84	<0.01	1.4	1.03–1.9	0.03
ALP (×10^2 IU/L)	1.41	1.03–1.94	0.03			
CRP (mg/dL)	1.31	1.15–1.49	<0.01	1.45	1.21–1.73	<0.01
Interval between first- and third-line chemotherapy (months)[c]	0.92	0.86–0.99	0.02			

Notes: [a]Explanatory variables were selected by backward-stepwise selection based on *P*-value. [b]A significant correlation was observed between neutrophil and monocyte counts (r=0.50, 95% CI: 0.25–0.68; P<0.01), while no significant correlation was found between neutrophil and lymphocyte counts (r=–0.11, 95% CI: –0.38 to 0.18; P=0.46) or between lymphocyte and monocyte counts (r=–0.03, 95% CI: –0.31 to 0.26; P=0.86). Monocyte count was not selected as an explanatory variable in the multivariate analysis. [c]From the start of first-line chemotherapy to the start of third-line chemotherapy. Coded as 1 (age ≥75 years, female, ECOG PS 2–4, stage IV, BMI <18.5 kg/m^2) and as 0 (age <75 years, male, ECOG PS 0–1, stage I–III, BMI ≥18.5 kg/m^2).

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; PS, performance status; RDW, red cell distribution width.

focused on these selected patients. 1) 76% of patients who had been diagnosed with adenocarcinoma with *EGFR* wild-type status received chemotherapy. This proportion was higher than 67%, the proportion of patients with squamous cell carcinoma during the same study period in our hospital.[19] However, we are afraid that this proportion might be overestimated. We did not examine *EGFR*-mutation status intentionally in some patients with poor general condition and/or severe complications at diagnosis. Therefore, our non-chemotherapy group excluded some patients who appeared unfit for both aggressive treatment and tyrosine-kinase inhibitors at diagnosis. 2) 61% and 34% of patients who received first-line chemotherapy proceeded to second- and third-line chemotherapy, respectively. When calculating these proportions, we excluded three and three patients who remained not to progress after first- and second-line chemotherapy, respectively. These proportions were consistent with 65% and 34%, those of patients with advanced pulmonary squamous cell carcinoma in our previous study.[19] Therefore, the receipt rate of salvage chemotherapy was not affected by histological type. Oncologists should keep in mind that approximately a third of our patients may drop out of chemotherapy during or after the ongoing line. Therefore, we should select the best regimen at the upcoming line for each patient, rather than the best sequence of later-line regimens.

We detected some predictive markers for unlikely introduction of chemotherapy and survival benefit of each line of chemotherapy. 1) Patients with poor PS, low hemoglobin concentration, low creatinine clearance, and higher CRP value were unlikely to receive chemotherapy. Irrespective of histology, PS was a common predictive factor.[18,19] Low hemoglobin was also common with squamous cell carcinoma,[19] while this study additionally detected low creatinine clearance and CRP as influential factors. 2) In our previous study of squamous cell carcinoma,[19] PS was a common predictive factor at any time of the chemotherapeutic course. On the other hand, in this study, absolute lymphocyte count was a common predictive factor from first- to third-line chemotherapy. Ratios of neutrophils[22–27] or monocytes to lymphocytes have been reported to be predictive markers for OS in advanced lung cancers. We did not assess ratios of these leukocyte differentiations as predictive markers in this study.

Our study had several limitations. It was a single-institution, small-sample, retrospective study. As described earlier, we did not examine *EGFR*-mutation status in all patients with adenocarcinoma. There might be biases for patients with unknown mutation status. We did not evaluate variables related to nutrition status, such as serum albumin concentration, because we did not measure these data routinely. Poor nutrition status may affect both introduction of chemotherapy and survival after chemotherapy. Our analyses focused exclusively on medical and physical conditions. Whether or not to start chemotherapy might depend not only on medical conditions but also on many other issues.

Conclusion

Approximately 76% of patients with adenocarcinoma with *EGFR* wild-type status were treated with first-line chemotherapy. Of those patients, 61% and 34% proceeded to second- and third-line chemotherapy, respectively. Patients with poor PS, low hemoglobin concentration, low creatinine clearance, and higher CRP value tended not to receive chemotherapy. Absolute lymphocyte count was a common predictive factor from first- to third-line chemotherapy.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Receiver-operating characteristic curve analysis for optimal cutoff values of laboratory data at diagnosis for the introduction of chemotherapy

Variables	Cutoff	Sensitivity	Specificity	AUC	95% CI
Neutrophils (cells/μL)	8,356	0.28	0.86	0.58	0.48–0.67
Lymphocytes (cells/μL)	1,414	0.63	0.7	0.68	0.59–0.77
Hemoglobin (g/dL)	13.2	0.8	0.65	0.76	0.68–0.84
Ccr (mL/min)	50.4	0.7	0.66	0.7	0.61–0.8
Sodium (mEq/L)	139	0.54	0.68	0.6	0.5–0.69
ALP (IU/L)	293	0.59	0.63	0.6	0.5–0.7
CRP (mg/dL)	0.54	0.78	0.52	0.66	0.57–0.76

Abbreviations: ALP, alkaline phosphatase; AUC, area under the curve; Ccr, creatinine clearance; CI, confidence interval.

Table S2 Regimens

Regimen	First line	Second line	Third line
n	148	89	48
Platinum-based	139	8	7
Platinum			
Cisplatin-based	37	1	1
Carboplatin-based	102	7	6
Partner agent			
Pemetrexed	57	1	1
Paclitaxel	66	5	2
Nab-paclitaxel	2	1	1
S1	1		2
Gemcitabine	3		
Docetaxel	2	1	1
CPT11	1		
Bevacizumab	22	1	
Maintenance			
Pemetrexed	33		
Gemcitabine	6		
Nonplatinum doublets		37	7
Gemcitabine + vinorelbine		4	4
Docetaxel + S1		2	
S1 + bevacizumab		15	1
Pemetrexed + bevacizumab			1
Pemetrexed + erlotinib		16	
CPT11 + erlotinib			1
Nonplatinum monotherapy	9	44	33
Pemetrexed	1	14	5
Docetaxel	1	12	16
EGFR TKI	1	15	6
S1	6	3	6
Concurrent thoracic radiotherapy	8	1	

Abbreviation: TKI, tyrosine-kinase inhibitor.

Table S3 Treatment response and discontinuation

	First line	Second line	Third line
n	148	89	48
Efficacy			
Response			
Complete response (n)	3	0	1
Partial response (n)	50	11	1
Stable disease (n)	48	25	17
Progressive disease (n)	33	45	25
Not evaluated (n)	14	8	4
Overall response rate, % (95% CI)	35.8 (28.1–44.1)	12.4 (6.3–21)	4.2 (0.5–14.3)
Disease-control rate, % (95% CI)	68.2 (60.1–75.6)	40.4 (30.2–51.4)	39.6 (25.8–54.7)
Progression-free survival (days)[a]			
Median (95% CI)	157 (127–167)	81 (50–123)	92 (61–114)
Overall survival (days)[a]			
Median (95% CI)	366 (275–529)	346 (209–403)	315 (177–365)
Reasons of discontinuation (n)			
Progressive disease	72	53	28
Completion of predefined courses	20	3	3
Adverse effects	27	14	5
Patient refusals	2	3	1
Transfer to other hospitals	1	1	0
Cancer-related deteriorated condition	19	11	7
Comorbidity-related deteriorated condition	6	1	3
Ongoing	1	3	1

Note: [a]From initiation of first-, second-, or third-line chemotherapy.
Abbreviation: CI, confidence interval.

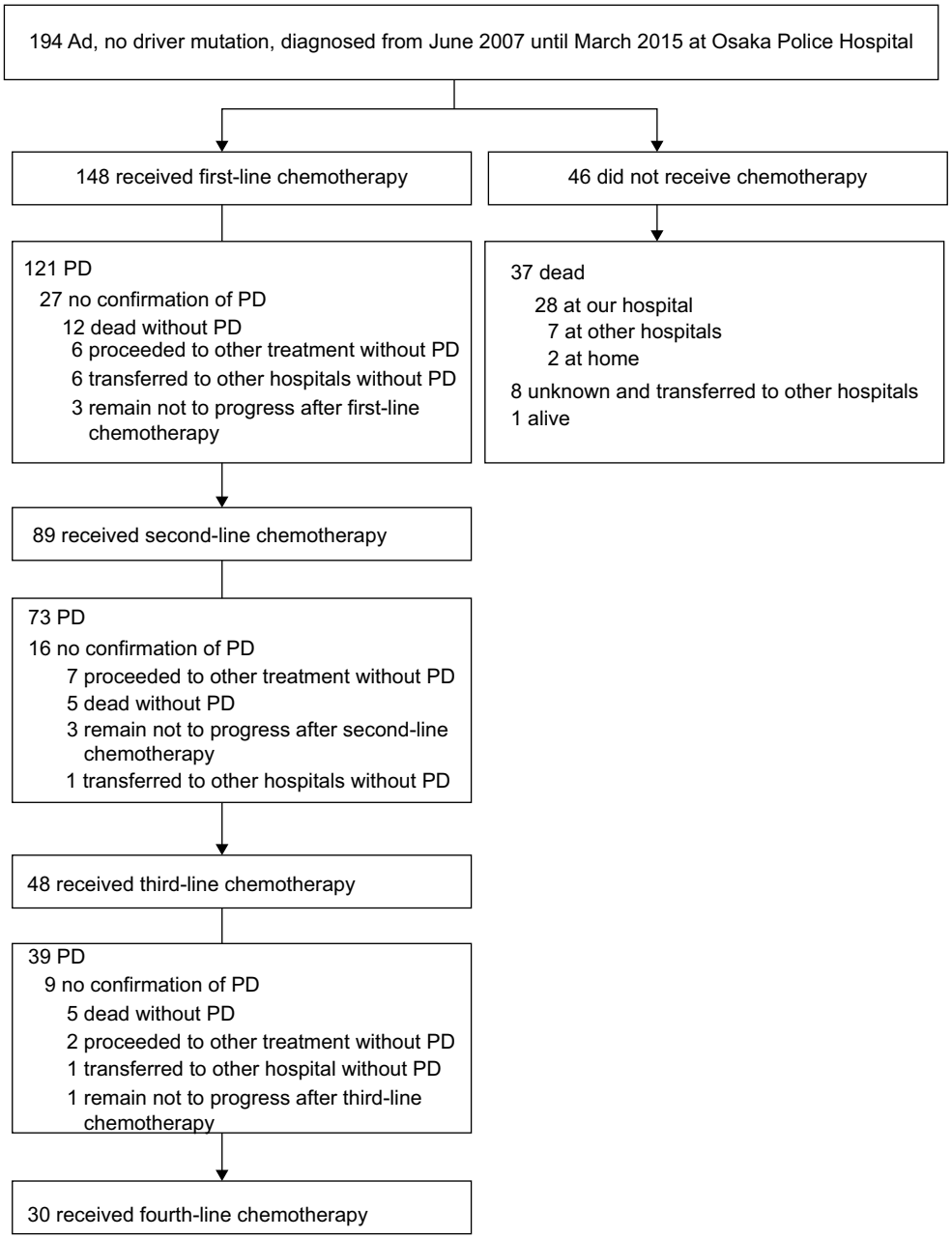

Figure S1 Patient flowchart.
Abbreviations: Ad, adenocarcinoma; PD, progressive disease.