

# Changes and Influential Factors of Chemotherapy Usage for Non-Small Cell Lung Cancer Patients in China: A Multicenter 10-Year (2005–2014) Retrospective Study

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**Background:** Chemotherapy has improved the survival of non-small cell lung cancer (NSCLC) patients over the past few decades. However, there have not been any epidemiological studies on chemotherapy for Chinese NSCLC patients.

**Patients and Methods:** The patients diagnosed as primary lung cancer between January 1, 2005, and December 31, 2014, in eight hospitals from eight provinces in China were retrospectively reviewed. Demographic and clinical data were extracted from medical history systems. Chi-square test and logistic regression were used to analyze the changes of chemotherapy usage and influential factors.

**Results:** A total of 7184 lung cancer cases were eligible, among which 6481 NSCLC cases were included in this analysis. Among stage I/II patients, the percentages of receiving adjuvant chemotherapy did not change significantly between the earlier (28.5%) and the latter five years (25.7%) ( $p = 0.1288$ ). Among stage IIIA patients, the percentages of chemotherapy usage did not change significantly between the earlier and the latter five years in neo-adjuvant (7.5% vs 5.6%,  $p = 0.1478$ ) and adjuvant (23.1% vs 26.8%,  $p = 0.1129$ ) treatment. The proportions of first-line platinum-based doublets for stage IIIB/IV patients changed significantly over the 10 years ( $p < 0.0001$ ). Patients from provinces with inferior gross domestic product, with lower medical reimbursement rates and without smoking history were more likely to use the docetaxel/paclitaxel doublets, comparing with the gemcitabine doublets.

**Conclusion:** From 2005 to 2014, there was no significant change in the chemotherapy pattern of early NSCLC. Economic factors mainly contributed to the significant changes in the first-line chemotherapy regimen selection for advanced patients.

**Keywords:** non-small cell lung cancer, chemotherapy, neo-adjuvant chemotherapy, adjuvant chemotherapy, epidemiology

## Introduction

Lung cancer has been the leading cause of cancer-related mortality both worldwide and in China.<sup>1–3</sup> The estimated age-standardized incidence rates of lung cancer flattened out among the whole population from 2005 to 2014 in China, fluctuating around 47 per 100,000 in males and 21 per 100,000 in females.<sup>4,5</sup> Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, most of which are squamous carcinoma and adenocarcinoma.<sup>6</sup>

Over the past two decades, surgical resection has remained the primary and recommended treatment for early stage NSCLC patients, particularly for those with good performance status (PS).<sup>7</sup> However, it's important to note that for these patients, adjuvant chemotherapy has been shown to improve survival in patients with completely resected NSCLC,<sup>8,9</sup> as well as neo-adjuvant chemotherapy.<sup>10</sup>

Unfortunately, the majority of patients have been at advanced stage (stage IIIB/IV) when diagnosed as NSCLC and the prognosis of untreated advanced patients was pretty poor, with a median survival of only 4–5 months.<sup>11,12</sup> However, the treatment efficacy for these patients has been improved since the introduction of platinum-based chemotherapy in the mid-1990s.<sup>13,14</sup> As the development of the third-generation platinum-based regimens, consisting of platinum plus docetaxel/paclitaxel or gemcitabine or pemetrexed or vinorelbine, the platinum-based doublets chemotherapy have been established as the standard first-line treatment for patients without driver mutations, with 1-year survival rates ranging from 31% to 36%.<sup>14</sup> Except for the pemetrexed and cisplatin combination that has demonstrated selectively superior efficacy in non-squamous NSCLC in the first-line treatment,<sup>15</sup> platinum-based doublets regimens have demonstrated similar response rates and survival benefits.<sup>14</sup>

Hitherto, some studies conducted in developed countries have described trends of the usage of chemotherapy for lung cancers and revealed that several epidemiological factors could influence its usage.<sup>12,16–18</sup> A comprehensive understanding of the trends of treatment patterns and their potential influential factors, especially the impact of epidemiological characteristics among NSCLC patients, could lead to more equitable evidence-based care. However, there have not been any analogous large-sample studies in China yet. Herein, we conducted a hospital-based, multicenter, retrospective clinical epidemiological survey in various geographic and socio-economic areas in China to illustrate the trends of chemotherapy usage among NSCLC patients and explore the correlations between demographic, tumor or economic characteristics and the usage of chemotherapy.

## Patients and Methods

### Study Design and Sampling Methods

This study was a hospital-based, multicenter, retrospective, clinical epidemiological survey of randomly selected primary lung cancer cases over a 10-year (2005–2014) interval in China via medical chart review.

The hospital selection and case sampling methods have been previously described in detail.<sup>19,20</sup> To obtain the study population, China was stratified into seven geographic regions (north, northeast, central, south, east, northwest and southwest) according to the traditional administrative district definition by the National Bureau of Statistics. One or two cancer hospitals of the highest level in each region were selected by means of convenience sampling, and a total of eight hospitals from eight provinces across China were finally included. One month was randomly selected from each year between 2005 and 2014 for each province, and all inpatient primary lung cancer cases were reviewed in each hospital. January and February were excluded from selection due to the potential confounding effects of the Chinese New Year vacation. A minimum of 100 inpatient primary lung cancer cases were collected in each hospital each year. If there were not enough eligible cases in the selected month, cases from the next month would be reviewed for supplement and the total sample was no less than 8000 cases.

### Patient Selection

The patients first diagnosed by pathology as primary lung cancer between January 1, 2005, and December 31, 2014 were reviewed. The patient selection and inclusion criteria have been previously described in detail.<sup>19</sup> All the patients enrolled in this study were required to meet the following four inclusion criteria: (i) primary NSCLC was confirmed by pathology; (ii) the main treatment was received in the hospital where the survey was conducted (patients only receiving diagnosis or undergoing follow-up without any treatment were excluded); (iii) sociodemographic information was available; (iv) clinical characteristics including staging and pathology, and medical information including diagnosis and treatment were available.

### Data Collection and Quality Control

As described previously,<sup>19</sup> data were extracted using a questionnaire including demographic information, clinical characteristics and medical service usage. Local clerks with an educational background of clinical medicine or public health were responsible for the data extraction. They all had undergone training before screening cases according to the inclusion/exclusion criteria via the medical system in local hospitals and recording the results into a designed form according to the designated protocol.

Multilevel quality control was conducted to ensure the accuracy of the data. Local clerks checked on each other,

and data managers checked on the clerks. All variables were double-entered to computer-based database (EpiData 3.1) by two different data-input clerks, and then sent to the center team based at the National Cancer Center for the logic check.

## Data Analysis

As part of the whole epidemiological project, we extracted NSCLC cases from the database for analysis. According to the average gross domestic product (GDP) level over these 10 years, the provinces included were divided into a superior group (Zhejiang, Liaoning, Shanxi and Hunan) and an inferior group (Guangxi, Anhui, Gansu and Yunnan).<sup>19</sup> Descriptive analyses were used to demonstrate changes in the first-line chemotherapy regimens among the whole advanced NSCLC patients and subgroups. Changes in patient demographics, clinical characteristics and treatment selection over the 10-year period were analyzed using chi-square tests. Factors associated with administration of adjuvant chemotherapy among stage I/II patients, neo-adjuvant or adjuvant chemotherapy among stage IIIA patients and chemotherapy among stage IIIB/IV patients were analyzed using chi-square tests and binary unconditional logistic regression. Factors influencing the selection of first-line chemotherapy regimens among stage IIIB/IV patients were assessed using multinomial logistic regression. For all tests, two-sided  $p$  values  $< 0.05$  were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

From 2005 to 2014, a total of 7184 primary lung cancer cases were extracted into the database, among which 6481 cases (90.2%) were NSCLC patients. The changes in demographic and clinical characteristics of these cases between the former and the latter five years are summarized in Table 1. Except for patient distribution of provinces with different GDP level, all the other demographic and clinical characteristics included changed significantly over the 10 years.

### Stage I/II

A total of 645 (27.0%) patients in stage I/II received adjuvant chemotherapy. The percentage of patients receiving post-surgical adjuvant chemotherapy in the former five years

**Table 1** Characteristics of Non-Small Cell Lung Cancer Patients Over 10 Years (2005–2014)

Characteristics	2005–2009		2010–2014		p
	N	%	N	%	
Gender					
Male	2251	74.4	2429	70.3	0.0003
Female	776	25.6	1025	29.7	
Age distribution					
<45	324	10.7	300	8.7	<0.0001
45–59	1374	45.4	1433	41.5	
60–74	1201	39.7	1563	45.3	
≥75	128	4.2	158	4.6	
Marital status					
Married	2968	98.1	3388	98.1	0.0009
Not married	53	1.8	40	1.2	
Unknown	6	0.2	26	0.8	
Occupation					
Full-time employment	1244	41.1	839	24.3	<0.0001
Liberal profession/self-employment	57	1.9	77	2.2	
Farmer	1035	34.2	1581	45.8	
Unemployment	163	5.4	206	6.0	
Retirement	301	9.9	349	10.1	
Others	8	0.3	18	0.5	
Unknown	219	7.2	384	11.1	
Educational level					
Primary school or below	825	27.3	895	25.9	<0.0001
Middle/high school	997	32.9	796	23.0	
College or above	259	8.6	141	4.1	
Unknown	946	31.3	1622	47.0	
Medical insurance type					
UEBMI	477	15.8	684	19.8	<0.0001
URBMI	81	2.7	181	5.2	
NRCMI	544	18.0	1112	32.2	
Self-pay	1086	35.9	481	13.9	
Others	467	15.4	292	8.5	
Unknown	372	12.3	704	20.4	
GDP level					
Superior level	1491	49.3	1751	50.7	0.248
Inferior level	1536	50.7	1703	49.3	
Smoking					
Current/former	1798	59.4	1815	52.5	<0.0001
Never	1191	39.3	1597	46.2	
Unknown	38	1.3	42	1.2	
ECOG score					
0–2	1094	36.1	1504	43.5	<0.0001
3–4	19	0.6	25	0.7	
Unknown	1914	63.2	1925	55.7	

(Continued)

**Table 1** (Continued).

Characteristics	2005–2009		2010–2014		p
	N	%	N	%	
Chronic respiratory disease					
Yes	232	7.7	198	5.7	0.0018
No	2795	92.3	3256	94.3	
Stage <sup>a</sup>					0.0226
I/II	1110	36.7	1280	37.1	
III A	676	22.3	679	19.7	
III B/IV	1241	41.0	1495	43.3	
Histology					<0.0001
Adenocarcinoma	1197	39.5	1725	49.9	
Squamous	1450	47.9	1351	39.1	
Others	380	12.6	378	10.9	

**Notes:** <sup>a</sup>American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging system: 2005–2009: 6th edition; 2010–2014: 7th edition.

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; GDP, gross domestic product; NRCMI, new rural cooperative medical insurance; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance.

was not significantly different from that of the latter five years ( $p = 0.1288$ ). Chi-square tests indicated that the usage of adjuvant chemotherapy was found to be associated with age of diagnosis, occupation, educational level, medical insurance type, GDP level of the province, Eastern Cooperative Oncology Group (ECOG) score and stage of disease (Table 2). When included in logistic regression analyses, patients at age 60 years or older [60–74 and  $\geq 75$  vs <45: odds ratio (OR): 0.568, 95% confidence interval (CI): 0.403–0.800 and OR: 0.131, 95% CI: 0.057–0.301, respectively], without job or working as a farmer (farmer, unemployment and retirement vs full-time employment: OR: 0.735, 95% CI: 0.592–0.912, OR: 0.504, 95% CI: 0.304–0.834 and OR: 0.666, 95% CI: 0.476–0.932, respectively), with insurance type of urban resident basic medical insurance (URBMI), new rural cooperative medical insurance (NRCMI) or self-pay [URBMI, NRCMI and self-pay vs urban employee basic medical insurance (UEBMI): OR: 0.573, 95% CI: 0.344–0.955, OR: 0.741, 95% CI: 0.569–0.965 and OR: 0.576, 95% CI: 0.439–0.755, respectively], from inferior GDP level provinces (inferior vs superior: OR: 0.319, 95% CI: 0.258–0.395) and with ECOG score of 3–4 points (3–4 vs 0–2: OR: 0) were less likely to receive post-surgical chemotherapy, while administration of adjuvant chemotherapy was significantly more common among patients at stage IIB (stage IIB vs stage I: OR: 1.348, 95% CI: 1.083–1.678).

**Table 2** Factors Associated with Receipt of Adjuvant Chemotherapy in Stage I/II Non-Small Cell Lung Cancer Patients

Characteristics	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>	
Years					
2005–2009	316	28.5	0.1288		
2010–2014	329	25.7			
Gender					
Male	478	27.6	0.2519		
Female	167	25.3			
Age distribution					
<45	61	35.7	<0.0001	1.000	
45–59	314	30.8		0.804(0.572, 1.130)	
60–74	263	24.0		0.568(0.403, 0.800)	
$\geq 75$	7	6.8		0.131(0.057, 0.301)	
Marital status					
Married	634	27.2	0.2930		
Not married	10	23.3			
Unknown	1	8.3			
Occupation					
Full-time employment	246	29.3	<0.0001	1.000	
Liberal profession/self-employment	11	31.4		1.109(0.535, 2.298)	
Farmer	203	23.3		0.735(0.592, 0.912)	
Unemployment	20	17.2		0.504(0.304, 0.834)	
Retirement	54	21.6		0.666(0.476, 0.932)	
Others	2	22.2		0.691(0.143, 3.350)	
Unknown	109	40.7		1.658(1.246, 2.206)	
Educational level					
Primary school or below	129	22.3		<0.0001	1.000
Middle/high school	127	19.3	0.834(0.634, 1.099)		
College or above	39	27.5	1.321(0.870, 2.005)		
Unknown	350	34.6	1.847(1.461, 2.336)		
Medical insurance type					
UEBMI	158	33.3	<0.0001	1.000	
URBMI	22	22.2		0.573(0.344, 0.955)	
NRCMI	157	27.0		0.741(0.569, 0.965)	
Self-pay	134	22.3		0.576(0.439, 0.755)	
Others	102	34.2		1.044(0.769, 1.418)	
Unknown	72	21.5		0.549(0.398, 0.759)	
GDP level					
Superior level	514	34.6	<0.0001	1.000	
Inferior level	131	14.5		0.319(0.258, 0.395)	
Smoking					
Current/former	388	27.6	0.5032		
Never	245	25.9			
Unknown	12	32.4			
ECOG score					
0–2	319	34.6	<0.0001	1.000	
3–4	0	0.0		0(0, N/A) <sup>e</sup>	
Unknown	326	22.2		0.539(0.449, 0.648)	

(Continued)

**Table 2** (Continued).

Characteristics	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>
Chronic respiratory disease				
Yes	48	27.7	0.8156	
No	597	26.9		
Stage <sup>f</sup>			0.0204	1.000 1.202(0.959, 1.508) 1.348(1.083, 1.678)
I	319	24.8		
IIA	152	28.4		
IIB	174	30.7		
Histology			0.6627	
Adenocarcinoma	290	26.7		
Squamous	286	26.7		
Others	69	29.5		

**Notes:** <sup>a</sup>Number of stage I/II patients receiving adjuvant chemotherapy. <sup>b</sup>Percentage of stage I/II patients receiving adjuvant chemotherapy. <sup>c</sup>Bivariate  $\chi^2$ . <sup>d</sup>Estimated odds ratio of receiving adjuvant chemotherapy, adjusted for variables found to be significant during bivariate analyses. <sup>e</sup>Unbalanced result due to no patients with ECOG score 2–4. <sup>f</sup>American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging system: 2005–2009: 6th edition; 2010–2014: 7th edition.

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GDP, gross domestic product; NRCMI, new rural cooperative medical insurance; OR, odds ratio; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance.

### Stage IIIA

There were 1355 stage IIIA patients included. Factors associated with administration of neo-adjuvant or adjuvant chemotherapy in stage IIIA NSCLC patients are summarized in Table 3. Chi-square tests revealed that gender, educational level, GDP level of the province, smoking history, ECOG score and histology were associated with both neo-adjuvant and adjuvant chemotherapy in stage IIIA NSCLC patients.

Patient age, occupation, medical insurance type and stage of disease were only associated with adjuvant chemotherapy. When included in logistic regression analyses, female patients (female vs male: OR: 0.493, 95% CI: 0.270–0.900), patients without smoking history (non-smoker vs smoker: OR: 0.591, 95% CI: 0.364–0.959) and patients with ECOG score 3–4 (3–4 vs 0–2: OR: 0) were less likely to receive neo-adjuvant chemotherapy, while patients from inferior GDP level provinces (inferior vs superior: OR: 2.291, 95% CI: 1.472–3.564) and patients with squamous carcinoma (squamous vs adenocarcinoma: OR: 2.504, 95% CI: 1.475–4.251) were more likely to receive neo-adjuvant chemotherapy.

The usage of adjuvant treatment was significantly less common among patients at age 75 years or older ( $\geq 75$  vs  $< 45$ : OR: 0.168, 95% CI: 0.048–0.582), working as a farmer (farmer vs full-time employment: OR: 0.708, 95% CI:

0.522–0.959), with insurance type of URBMI or self-pay (URBMI and self-pay vs UEBMI: OR: 0.318, 95% CI: 0.120–0.845, OR: 0.639, 95% CI: 0.438–0.933, respectively), from inferior GDP level provinces (inferior vs superior: OR: 0.290, 95% CI: 0.218–0.386), with ECOG score 3–4 (3–4 vs 0–2: OR: 0), with N1 or N0 disease (N1 and N0 vs N2: OR: 0.487, 95% CI: 0.322–0.737, OR: 0.292, 95% CI: 0.124–0.687, respectively) and with squamous carcinoma (squamous vs adenocarcinoma: OR: 0.535, 95% CI: 0.412–0.696).

### Stage IIIB/IV

A total of 2736 stage IIIB/IV NSCLC patients were included into the analysis. In this group, the percentage of patients receiving chemotherapy did not change significantly over the 10 years ( $p = 0.1566$ ) (Table 4). Factors associated with the usage of chemotherapy among stage IIIB/IV patients included patient age, marital status, occupation, educational level, medical insurance type, GDP level of provinces, smoking history, ECOG score and stage of disease. When included in logistic regression analyses, patients at age 75 years or older ( $\geq 75$  vs  $< 45$ : OR: 0.468, 95% CI: 0.305–0.718), not married (not married vs married: OR: 0.392, 95% CI: 0.197–0.779), from inferior GDP level provinces (inferior vs superior: OR: 0.723, 95% CI: 0.607–0.861), without smoking history (non-smoker vs smoker: OR: 0.843, 95% CI: 0.715–0.994) and with ECOG score 3–4 (3–4 vs 0–2: OR: 0.515, 95% CI: 0.271–0.978) were less likely to receive chemotherapy. The usage of chemotherapy was more common among patients working as a farmer (farmer vs full-time employment: OR: 1.607, 95% CI: 1.321–1.954), with insurance type of NRCMI (NRCMI vs UEBMI: OR: 1.640, 95% CI: 1.264–2.128) and with stage IV disease (IV vs IIIB: OR: 1.640, 95% CI: 1.382–1.948).

### Changes in the Usage of First-Line Chemotherapy for Stage IIIB/IV Patients

The proportions of the usage of four main first-line platinum-based doublets regimens each year are displayed in Figure 1, including platinum plus docetaxel/paclitaxel or gemcitabine or pemetrexed or vinorelbine/vincristine. The proportion of the vinorelbine/vincristine doublets continuously reduced from 40.12% in 2005 to 5.80% in 2014, while the proportion of the pemetrexed doublets increased from 0.60% in 2005 to 22.22% in 2014. Subgroup analyses further illustrated that the usage of the pemetrexed doublets

**Table 3** Factors Associated with the Usage of Neo-Adjuvant and Adjuvant Chemotherapy in Stage IIIA Patients

Characteristics	Neo-Adjuvant				Adjuvant			
	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>
Years								
2005–2009	51	7.5	0.1478		156	23.1	0.1129	
2010–2014	38	5.6			182	26.8		
Gender								
Male	76	7.5	0.0190	1.000	225	22.1	<0.0001	1.000
Female	13	3.8		0.493 (0.270, 0.900)	113	33.3		1.758 (1.342, 2.303)
Age distribution								
<45	8	7.5	0.7159		25	23.6	0.0003	1.000
45–59	39	6.4			176	28.7		1.302 (0.805, 2.107)
60–74	36	6.3			134	23.3		0.987 (0.605, 1.608)
≥75	6	9.8			3	4.9		0.168 (0.048, 0.582)
Marital status								
Married	87	6.5	0.7893		333	25.0	0.7828	
Not married	1	5.9			3	17.6		
Unknown	1	12.5			2	25.0		
Occupation								
Full-time employment	27	6.7	0.4888		106	26.4	0.0001	1.000
Liberal profession/self-employment	3	9.7			10	32.3		1.330 (0.606, 2.915)
Farmer	37	6.7			111	20.2		0.708 (0.522, 0.959)
Unemployment	7	10.1			17	24.6		0.913 (0.506, 1.648)
Retirement	9	7.4			24	19.7		0.684 (0.415, 1.126)
Others	0	0.0			3	33.3		1.396 (0.343, 5.682)
Unknown	6	3.5			67	38.7		1.765 (1.210, 2.576)
Educational level								
Primary school or below	29	8.2	0.0121	1.000	56	15.9	<0.0001	1.000
Middle/high school	32	9.1		1.114 (0.658, 1.884)	64	18.2		1.175 (0.792, 1.741)
College or above	4	5.6		0.665 (0.226, 1.954)	13	18.3		1.185 (0.609, 2.306)
Unknown	24	4.1		0.481 (0.275, 0.840)	205	35.3		2.890 (2.072, 4.029)
Medical insurance type								
UEBMI	16	7.0	0.4088		71	31.0	0.0290	1.000
URBMI	3	7.5			5	12.5		0.318 (0.120, 0.845)
NRCMI	20	5.7			91	25.9		0.776 (0.537, 1.121)
Self-pay	18	5.2			77	22.3		0.639 (0.438, 0.933)
Others	18	10.0			51	28.3		0.880 (0.573, 1.350)
Unknown	14	6.7			43	20.6		0.576 (0.372, 0.892)
GDP level								
Superior level	34	4.4	0.0002	1.000	263	33.9	<0.0001	1.000
Inferior level	55	9.5		2.291 (1.472, 3.564)	75	13.0		0.290 (0.218, 0.386)
Smoking								
Current/former	62	7.6	0.0147	1.000	188	23.0	0.0375	1.000
Never	24	4.6		0.591 (0.364, 0.959)	143	27.5		1.273 (0.989, 1.638)
Unknown	3	18.8		2.818 (0.782, 10.152)	7	43.8		2.613 (0.960, 7.110)
ECOG score								
0–2	55	8.8	0.0090	1.000	195	31.2	<0.0001	1.000
3–4	0	0.0		0 (0, N/A) <sup>e</sup>	0	0.0		0 (0, N/A) <sup>e</sup>
Unknown	34	4.7		0.510 (0.328, 0.793)	143	19.7		0.542 (0.423, 0.696)

(Continued)

**Table 3** (Continued).

Characteristics	Neo-Adjuvant				Adjuvant			
	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>
Chronic respiratory disease								
Yes	4	3.9	0.2618		18	17.6	0.0765	
No	85	6.8			320	25.5		
Stage <sup>f</sup>								
N2	74	7.4	0.1069		279	27.9	0.0001	1.000
N1	5	2.6			30	15.9		0.487 (0.322, 0.737)
N0	3	5.1			6	10.2		0.292 (0.124, 0.687)
Unknown	7	6.5			23	21.3		0.698 (0.432, 1.130)
Histology								
Adenocarcinoma	19	3.7	0.0022	1.000	166	32.1	<0.0001	1.000
Squamous	60	8.7		2.504 (1.475, 4.251)	139	20.2		0.535 (0.412, 0.696)
Others	10	6.7		1.872 (0.851, 4.118)	33	22.0		0.596 (0.389, 0.915)

**Notes:** <sup>a</sup>Number of stage IIIA patients receiving neo-adjuvant or adjuvant chemotherapy. <sup>b</sup>Percentage of stage IIIA patients receiving neo-adjuvant or adjuvant chemotherapy. <sup>c</sup>Bivariate  $\chi^2$ . <sup>d</sup>Estimated odds ratio of receiving neo-adjuvant or adjuvant chemotherapy, adjusted for variables found to be significant during bivariate analyses. <sup>e</sup>Unbalanced result due to no patients with ECOG score 2–4. <sup>f</sup>American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging system: 2005–2009: 6th edition; 2010–2014: 7th edition.

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GDP, gross domestic product; NRCMI, new rural cooperative medical insurance; OR, odds ratio; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance.

mainly increased among non-squamous cases, rising dramatically from 1.72% in 2008 to 12.12% in 2009, and gradually ascended to 32.61% in 2014 (Figure 2A), while remained relatively low among squamous carcinoma cases (Figure 2B). The proportions of each regimen varied significantly in the latter five years compared with the former five years ( $p < 0.0001$ ) (Supplemental Table 1).

### Factors Affecting the Selection of the Four First-Line Platinum-Based Doublets

Except the platinum plus gemcitabine regimen, the other three platinum-based doublets regimens all experienced significant changes in usage between the former and the latter five years (Supplemental Table 2). The usage of docetaxel/paclitaxel doublets and gemcitabine doublets increased significantly, while the usage of the vinorelbine/vincristine doublets decreased significantly. In bivariate analyses, the usage of these four regimens was found to be significantly associated with gender, occupation, educational level, medical insurance types, GDP level of the province, smoking history, disease stage and histology types.

When included in logistic regression analyses, the platinum plus docetaxel/paclitaxel regimen was more likely to be used among patients with insurance type of NRCMI (NRCMI vs UEBMI: OR: 1.678, 95% CI: 1.205–2.337) and squamous carcinoma (squamous vs adenocarcinoma: OR: 1.308, 95%

CI: 1.049–1.630), and less likely among patients after retirement (retirement vs full-time employment: OR: 0.613, 95% CI: 0.398–0.944). The platinum plus gemcitabine regimen was more likely to be used among patients with squamous NSCLC (squamous vs adenocarcinoma: OR: 1.593, 95% CI: 1.293–1.961), and less likely among female patients (female vs male: OR: 0.780, 95% CI: 0.626–0.972), patients with an educational level of middle/high school (middle/high school vs primary school or below: OR: 0.650, 95% CI: 0.507–0.833), patients from inferior GDP level provinces (inferior vs superior: OR: 0.599, 95% CI: 0.492–0.730) and patients without smoking history (non-smoker vs smoker: OR: 0.754, 95% CI: 0.619–0.917). The platinum plus pemetrexed regimen was more likely to be used among female patients (female vs male: OR: 1.831, 95% CI: 1.350–2.485), patients with an educational level of middle/high school (middle/high school vs primary school or below: OR: 1.884, 95% CI: 1.262–2.813), patients from inferior GDP level provinces (inferior vs superior: OR: 1.469, 95% CI: 1.068–2.022), patients without smoking history (non-smoker vs smoker: OR: 2.032, 95% CI: 1.496–2.761) and patients with stage IV disease (stage IV vs stage IIIB: OR: 2.317, 95% CI: 1.557–3.449), and less likely among patients with insurance type of self-pay (self-pay vs UEBMI: OR: 0.489, 95% CI: 0.303–0.788) and patients with squamous disease (squamous vs adenocarcinoma: OR: 0.074, 95% CI: 0.040–0.137). The platinum plus vinorelbine/

**Table 4** Factors Associated with the Usage of Chemotherapy in Stage IIIB/IV Non-Small Cell Lung Cancer Patients

Characteristics	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>
Years				
2005–2009	854	68.8	0.1566	
2010–2014	1066	71.3		
Gender				
Male	1372	70.9	0.1740	
Female	548	68.3		
Age distribution				
<45	253	72.9	0.0001	1.000
45–59	860	73.2		1.014 (0.775, 1.328)
60–74	739	67.7		0.778 (0.595, 1.017)
≥75	68	55.7		0.468 (0.305, 0.718)
Marital status				
Married	1900	70.6	0.0004	1.000
Not married	16	48.5		0.392 (0.197, 0.779)
Unknown	4	33.3		0.208 (0.063, 0.693)
Occupation				
Full-time employment	559	66.5	<0.0001	1.000
Liberal profession/self-employment	46	67.6		1.051 (0.620, 1.782)
Farmer	911	76.2		1.607 (1.321, 1.954)
Unemployment	126	68.5		1.092 (0.775, 1.538)
Retirement	194	69.8		1.161 (0.866, 1.557)
Others	3	37.5		0.302 (0.072, 1.271)
Unknown	81	50.0		0.503 (0.358, 0.706)
Educational level				
Primary school or below	602	76.3	<0.0001	1.000
Middle/High school	566	72.3		0.810 (0.646, 1.017)
College or above	136	72.7		0.828 (0.577, 1.189)
Unknown	616	63.1		0.530 (0.430, 0.653)
Medical insurance type				
UEBMI	306	67.0	<0.0001	1.000
URBMI	91	74.0		1.403 (0.897, 2.195)
NRCMI	555	76.9		1.640 (1.264, 2.128)
Self-pay	435	70.0		1.154 (0.890, 1.496)
Others	201	71.5		1.240 (0.897, 1.715)
Unknown	332	62.4		0.819 (0.630, 1.065)
GDP level				
Superior level	731	74.4	0.0003	1.000
Inferior level	1189	67.8		0.723 (0.607, 0.861)
Smoking				
Current/former	1000	72.1	0.0144	1.000
Never	906	68.5		0.843 (0.715, 0.994)
Unknown	14	51.9		0.417 (0.194, 0.895)
ECOG score				
0–2	657	62.5	<0.0001	1.000
3–4	18	46.2		0.515 (0.271, 0.978)
Unknown	1245	75.6		1.862 (1.574, 2.203)

(Continued)

**Table 4** (Continued).

Characteristics	N <sup>a</sup>	% <sup>b</sup>	p <sup>c</sup>	OR (95% CI) <sup>d</sup>
Chronic respiratory disease				
Yes	105	67.7	0.4953	
No	1815	70.3		
Stage <sup>e</sup>				
IIIB	550	62.9	<0.0001	1.000
IV	1370	73.6		1.640 (1.382, 1.948)
Histology				
Adenocarcinoma	944	71.5	0.2746	
Squamous	723	69.4		
Others	253	67.6		

**Notes:** <sup>a</sup>Number of stage IIIB/IV patients receiving chemotherapy. <sup>b</sup>Percentage of stage IIIB/IV patients receiving chemotherapy. <sup>c</sup>Bivariate  $\chi^2$ . <sup>d</sup>Estimated odds ratio of receiving chemotherapy, adjusted for variables found to be significant during bivariate analyses. <sup>e</sup>American Joint Committee on Cancer (AJCC) tumor–nodemetastasis (TNM) staging system: 2005–2009: 6th edition; 2010–2014: 7th edition.

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GDP, gross domestic product; NRCMI, new rural cooperative medical insurance; OR, odds ratio; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance.

vincristine regimen was more likely to be used among patients with an educational level of middle/high school (middle/high school vs primary school or below: OR: 1.430, 95% CI: 1.073–1.906) and patients with insurance type of self-pay (self-pay vs UEBMI: OR: 1.895, 95% CI: 1.301–2.761), while less likely among patients with stage IV disease (stage IV vs stage IIIB: OR: 0.597, 95% CI: 0.470–0.760).

In further multinomial logistic regression analyses (Supplemental Table 3), comparing with the gemcitabine doublets, patients diagnosed during the latter five years (2010–2014 vs 2005–2009,  $p = 0.0033$ ), with insurance type of NRCMI (NRCMI vs UEBMI,  $p = 0.0257$ ), from inferior GDP level provinces (inferior vs superior,  $p = 0.0072$ ) and without smoking history (non-smoker vs smoker:  $p = 0.0088$ ) tended to receive docetaxel/paclitaxel doublets treatment. Comparing with the gemcitabine doublets, the administration of the vinorelbine/vincristine doublets was less common among patients diagnosed during the latter five years (2010–2014 vs 2005–2009,  $p < 0.0001$ ), patients with stage IV disease (stage IV vs stage IIIB,  $p < 0.0001$ ) and patients with squamous disease (squamous vs adenocarcinoma,  $p = 0.0123$ ), while more common among female patients (female vs male,  $p = 0.0249$ ), patients with an educational level of middle/high school (middle/high school vs primary school or below,  $p = 0.0067$ ) and patients from inferior GDP level provinces (inferior vs superior,  $p < 0.0001$ ).



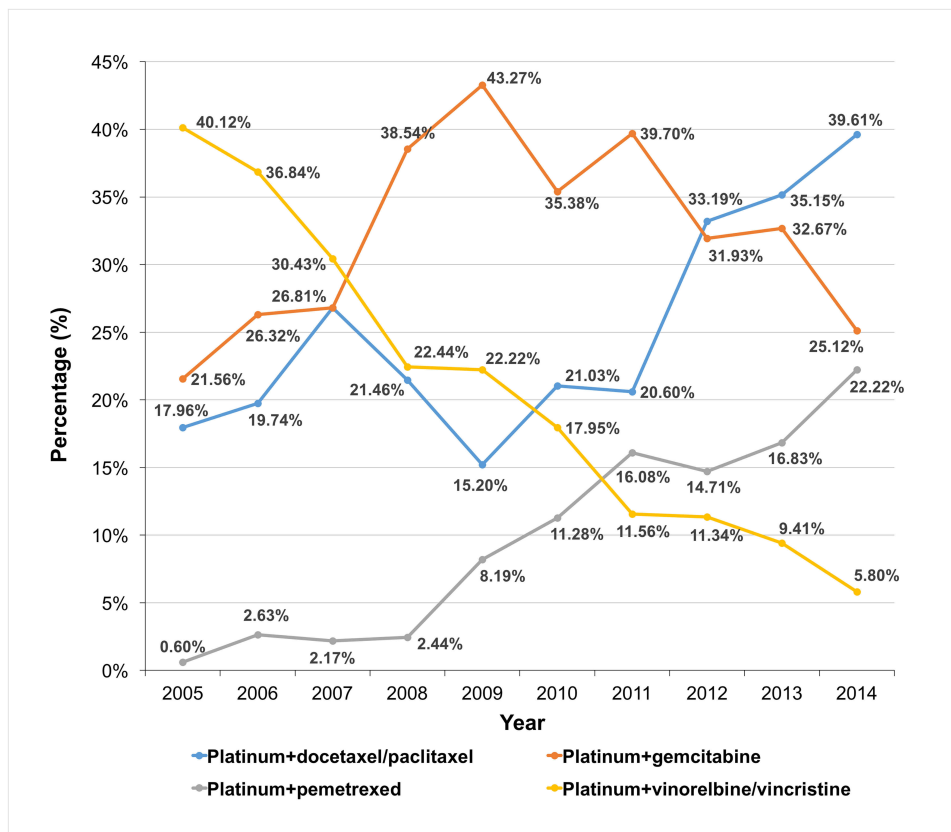


Figure 1 Trends of the usage of four main first-line platinum-based doublets regimens over the 10 years.

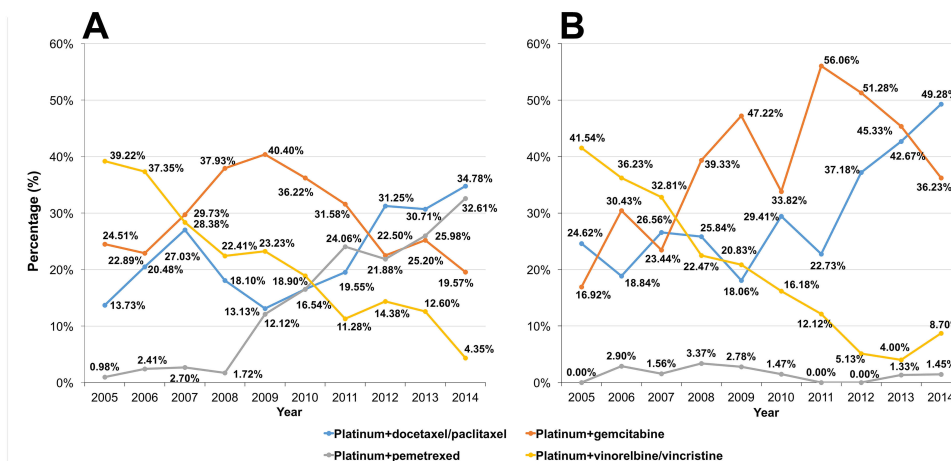


Figure 2 Trends of the usage of four main first-line platinum-based doublets regimens over the 10 years stratified by histological types. (A) Non-squamous NSCLC; (B) squamous NSCLC.

## Discussion

Our study was the first multicenter, large sample epidemiological study of the chemotherapy treatment for NSCLC patients in China over the past decades. Our study illustrated the trends of neo-adjuvant or adjuvant

chemotherapy treatment for early stage NSCLC patients and first-line chemotherapy treatment for advanced NSCLC patients from 2005 to 2014 in China and revealed the correlations between demographic, tumor or economic characteristics and the usage of chemotherapy.

During the study period, the usage of neo-adjuvant or adjuvant chemotherapy for stage I/II and IIIA patients remained stable between the former and the latter five years. However, several sociodemographic characteristics may still influence the usage of the adjuvant chemotherapy. According to the International Adjuvant Lung Cancer Trial (IALT), patients at age 70 years or older might ultimately reap less benefit from adjuvant chemotherapy (trend  $p$  value of 0.08),<sup>21</sup> while another observational cohort study demonstrated that postoperative chemotherapy could benefit patients up to 80 years old.<sup>22</sup> Our results revealed that during the clinical practice in the real world in China patients at age 60 years or older in stage I/II and patients at age 75 years or older in stage IIIA were significantly less likely to receive postoperative adjuvant chemotherapy, which indicated that the usage of adjuvant chemotherapy might be relatively conservative among elderly patients in China.

The treatment of patients at stage IIIA with N2 nodal involvement was the most controversial issue in the management of NSCLC. Several studies indicated that neo-adjuvant chemotherapy might benefit selected patients with N2 disease.<sup>23,24</sup> In our study, patients with N2 nodal involvement were more likely to take neo-adjuvant chemotherapy, but the result was not significant. This may result from the relatively small sample of the stage IIIA patients.

For stage IIIB/IV NSCLC patients, platinum-based chemotherapy has generated a plateau, with an overall response rate between 25% and 35% and a median survival of 8–10 months. However, platinum-based doublets are still established as first-line treatment among patients with good performance status (PS 0–1) and without driver mutations. These doublets can prolong survival, improve symptom control and yield superior quality of life in comparison to best supportive care.<sup>6</sup>

Except for pemetrexed doublets, which are only approved to be used in non-squamous NSCLC patients, the other three doublets are all approved to be used in both squamous and non-squamous NSCLC patients in the first line. Several studies indicated that there was no significant difference in overall survival between gemcitabine doublets, paclitaxel/docetaxel doublets and vinorelbine doublets.<sup>25–30</sup> However, during clinical practice in the real world, we found a tendency of unbalanced choices of these regimens.

One regimen that experienced a consecutive reduction during the study period was the vinorelbine/vincristine and

platinum combination. The amount of this combination in the latter five years was significantly lower than that of the former five years. Cost-effectiveness analysis may be able to explain this phenomenon. Measured by quality-adjusted life year, vinorelbine doublets do not cost least but benefit patients least. Thus vinorelbine doublets can neither be the optimal effective selection nor a cost-effective selection.<sup>31</sup>

Multinomial logistic regression analyses suggested that patients from inferior GDP provinces and patients with insurance type of NRCMI (insurance with lower medical reimbursement rate) were more likely to use the docetaxel/paclitaxel doublets compared with the gemcitabine doublets. Cost-effectiveness analysis may partly explain the results as well. For patients with squamous disease, the paclitaxel doublets were the minimum cost options and therefore represented the initial high cost-effective treatment, and paclitaxel's preferred alternative favored docetaxel over gemcitabine, as docetaxel's greater effectiveness seemed to outweigh the additional acquisition cost.<sup>31</sup> One single-center cost-effectiveness study on chemotherapy for advanced NSCLC conducted in China also suggested that the gemcitabine doublets became the most expensive regimen among the four third-generation platinum-based regimens after price cuts since 2006.<sup>32</sup>

Our study also revealed that the usage of pemetrexed doublets increased remarkably in 2009 in non-squamous NSCLC patients, which was in accordance with the development of pemetrexed and the approval of pemetrexed to be used in locally advanced or metastatic non-squamous NSCLC in 2008.<sup>33</sup> The significant survival advantage of pemetrexed doublets over gemcitabine doublets among non-squamous NSCLC patients contributed to its growing usage among these patients.<sup>15</sup>

There are several limitations in our study as well. First, although our study was conducted nationwide and selected patients using convenience sampling, there might be still bias in patient selection due to the relatively high hospital level. Second, target therapies have become increasingly important in the first-line treatment for advanced NSCLC patients. However, because we only enrolled inpatients, outpatients treated with oral target therapies were omitted. Third, data quality is partly dependent on the quality of the medical history documentation, which lacks a standard to assess. Finally, as a retrospective study without follow-up, we are not able to evaluate whether the changes in the treatment choices have led to different survival benefits.

## Conclusion

Our study demonstrated the changes of the usage of chemotherapy for NSCLC patients in China from 2005 to 2014. The usage of neo-adjuvant or adjuvant chemotherapy among early stage patients did not vary significantly over these ten years. Economic factors mainly contributed to the significant changes in the first-line chemotherapy regimen selection for advanced patients.

## Ethics and Consent Statements

This study was conducted as a part of a broader National Key Public Health Program of China–Cancer Screening Program in Urban China, which was approved by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences (Approval No. 15-071/998). Because it is a retrospective study that contained no identifiable data, informed consent was waived. This study was conducted in accordance with the Declaration of Helsinki. Patients' privacy and personal identity information were well protected.

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## Disclosure

The authors declare that they have no conflict of interest with respect to this research study and paper.

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