RESEARCH ARTICLE

Screening for Patients with Non-small Cell Lung Cancer Who Could Survive Long Term Chemotherapy

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Abstract

Background: Lung cancer was one of the most common cancers in both men and women all over the world. In this study, we aimed to clarify who could survive after long term chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Methods: We enrolled 186 patients with stage IV NSCLC after long term chemotherapy from Jun 2006 to Nov 2014 diagnosed in Jiangsu Cancer Hospital. Multiple variables like age, gender, smoking, histology of adenocarcinoma and squamous-cell cancer, number of metastatic sites, metastatic sites (e.g. lung, brain, bone, liver and pleura), hemoglobin, lymphocyte rate (LYR), Change of LYR during multiple therapies, hypertension, diabetes, chronic bronchitis, treatments (e.g.radiotherapy and targeted therapy) were selected. For consideration of factors influencing survival and response for patients with advanced NSCLC, logistic regression analysis and Cox regression analysis were used in an attempt to develop a screening module for patients with elevated survival after long term chemotherapy become possible. Results: Of the total of 186 patients enrolled, 69 survived less than 1 year (short-term group), 45 one to two years, and 72 longer than 3 years (long-term group). For logistic regression analysis, the short-term group was taken as control group and the long-term group as the case group. We found that age, histology of adenocarcinoma, metastatic site (e.g. lung and liver), treatments (e.g. targeted therapy and radiotherapy), LYR, a decreasing tendency of LYR and chronic bronchitis were individually associated with overall survival by Cox regression analysis. A multivariable Cox regression model showed that metastatic site (e.g. lung and liver), histology of adenocarcinoma, treatments (e.g. targeted therapy and radiotherapy) and chronic bronchitis were associated with overall survival. Thus metastatic site (e.g. lung and liver) and chronic bronchitis may be important risk factors for patients with advanced NSCLC. Gender, metastatic site (e.g. lung and liver), LYR and the decreasing tendency of LYR were significantly associated with long-term survival in the individual-variable logistic regression model ($P<0.05$). On multivariate logistic regression analysis, gender, metastatic site (e.g. lung and liver) and the decreasing tendency of LYR associated with long-term survival. Conclusions: In conclusion, female patients with stage IV adenocarcinoma of NSCLC who had decreasing tendency of LYR during the course therapy and had accepted multiple therapies e.g. more than third-line chemotherapy, radiotherapy and/or targeted therapy might be expected to live longer.

Keywords: Survival - NSCLC - prognosis - long term chemotherapy - gender - histology - metastases

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Introduction

Lung cancer is one of most common cancer in both man and women all over the word. Non-small cell lung cancer (NSCLC) represents about 80% of all lung cancer cases. And in China, more than 75% of patients with NSCLC are diagnosed at locally advanced (stage IIIB) or metastatic (stage IV) stage for which curative treatments are not available (Zhou et al., 2011). Although currently no standard regimen is established, first-line treatment for advanced NSCLC is a regimen containing cisplatin on the basis of its favourable efficacy and tolerability profile (Smit et al., 2003, Le et al., 2005). Docetaxel and pemetrexed are approved by the Food and Drug Administration (FDA) for use as the second-line chemotherapy. Some studys showed non-inferior efficacy and better tolerability for pemetrexed plus cisplatin than for cisplatin plus other chemotherapy agents e.g., gemcitabine or docetaxel especially, for patients with adenocarcinoma (Reck et al., 2009; Scagliotti et al., 2009; Klein et al., 2010). In recent years, Erlotinib has been approved in more than 80 countries for the treatment of NSCLC patients who have received at least one prior chemotherapy (Mok et al., 2010; Reck et al., 2010). Although these efforts for treating NSCLC, expected 1-year survival for patients with advanced NSCLC is still low.

It is hypothesized that a set of basic demographic features (e.g., performance status, age, gender and

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Table 1. Demographic and Clinical Characteristics of 186 Patients with Stage IV NSCLC

Patient Characteristic	Patients Survived More than 3 Years Long-term Group N=72 (%)	Patients Survived Less than 1 Year Short-term Group N=69 (%)	Patients Survived in 1 and 2 Years N=45 (%)
Gender			
Male	45 (62.5)	56 (81.2)	32 (71.1)
Female	27 (37.5)	13 (18.8)	13 (28.9)
Smoking			
Yes	22 (30.6)	27 (39.1)	20 (44.4)
No	50 (68.4)	42 (60.9)	25 (55.6)
Histology			
Squamous-cell cancer	23 (31.9)	44 (63.8)	12 (26.7)
Adenocarcinoma	49 (68.1)	25 (36.2)	33 (73.3)
Radiotherapy			
Yes	38 (52.8)	17 (24.6)	20 (44.4)
No	34 (47.2)	52 (75.4)	25 (55.6)
Targeted therapy			
Yes	42 (58.3)	18 (26.1)	19 (42.2)
No	30 (41.7)	51 (73.9)	26 (57.8)
Number of Metastatic sites			
<4	49 (68.1)	44 (63.8)	21 (46.7)
≥4	23 (31.9)	25 (36.2)	24 (53.3)
Metastatic sites			
Lung	47 (65.3)	56 (81.2)	42 (93.3)
Pleura	39 (54.2)	34 (49.3)	20 (44.4)
Bone	36 (50.0)	31 (44.9)	25 (55.6)
Brain	25 (34.7)	14 (20.3)	23 (51.1)
Liver	11 (15.3)	21 (30.4)	14 (31.1)
LYR			
<20%	21 (29.2)	32 (46.4)	14 (31.1)
<40%&≥20%	48 (66.7)	37 (53.6)	31 (68.9)
>40%	3 (4.1)	0 (0.0)	0 (0.00)
Change of LYR			
Raise	29 (40.3)	45 (65.2)	34 (75.6)
Decrease	43 (59.7)	24 (34.8)	11 (24.4)
Hemoglobin			
≥120 (g/L)	53 (73.6)	49 (71.0)	37 (82.2)
<120 (g/L)	19 (26.4)	20 (29.0)	8 (17.8)
Hypertension	8 (11.1)	12 (17.4)	5 (11.1)
Chronic bronchitis	4 (5.6)	11 (15.9)	2 (4.4)

LYR, lymphocyte rate

ethnicity), histopathological information (e.g., tumor stage and grade) and life style information (e.g., tobacco use and alcohol use) could be used to make therapeutic decisions and prognostic predictions (Kankesan et al., 2013; van et al., 2010; Dehing-Oberije et al., 2011). And further hypothesized that these decisions and predictions could be more presice after incorporated various genetic and molecular biomarkers to develop new prognostic models for lung cancer (Lee et al., 2008; Donovan et al., 2009; Kawaguchi et al., 2010).

In this study, regression analysis were used to analyze the relationships between these variables and survival time of patients with advanced NSCLC who had received long term chemotherapy. We also contrast the long-term survival and short-term survival cohort in order to screening out stage IV patients who could survival longer after long term chemotherapy. Survival analysis went on simultaneously.

Patients and Methods

Patients

Stage IV NSCLC patients who underwent comprehensive treatment including long-term chemotherapy with or without radiotherapy/targeted therapy between Jun 2006 to Nov 2014 in Jiangsu Cancer Hospital were enrolled in this study. Eligible patients had histologically or cytologically documented, advanced or recurrent NSCLC. Information on clinical parameters was obtained from the complete medical records, and the overall survival time was verified by call visits and the local police registration data. Further inclusion criteria were: Chinese; aged at least 18 years; life expectancy for more than 9 weeks; no less than one detectable metastatic lesion; adequate hematological, hepatic and renal functions. Exclusion criteria included: pregnant or breast-feeding women; patients with small-cell tumor. Patient characteristics are given in Table 1.

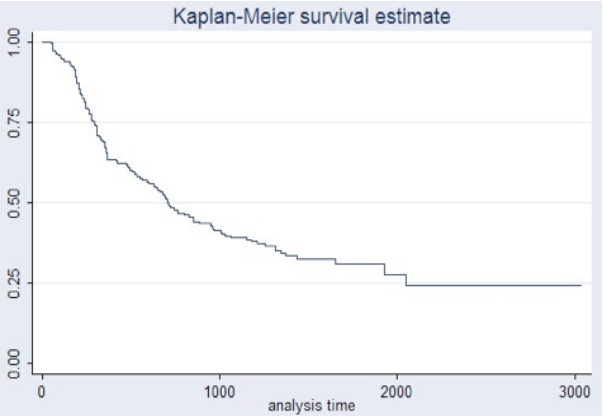

Figure 1. Survival Function from Advanced NSCLC Patients after Long Term Chemotherapy

Outcome Assessment

Patients were followed through call visits and the local police registration data and any deaths were recorded. Final survival status was confirmed on 30 November 2014, so that all patients had at least 3 years and up to 4 years of follow up.

Statistical Analysis

Survival times were censored at 30 November 2014, providing a minimum follow-up of 36 months. Survival analysis and calculation of survival rates used the Kaplan-Meier method. Hazard ratios were calculated using Cox regression. Initially, all variables were considered individually, with those variables with a likelihood ratio test $p<0.05$ considered for inclusion in a multiple-variable model. Forward selection was used until inclusion of further variables did not significantly improve the fit of the model. Logistic regression analysis and Cox regression analysis were used to analyze the relationships between these variables and survival time. Analysis was performed using Statistica version 8.0 software (StatSoft Inc., Tulsa, OK) with $p<0.05$ described as statistically significant. We have enough experience in conducting medical researches, and have published some results elsewhere (Qian et al., 2014; Ji et al., 2014; Huang et al., 2014; Wu et al., 2014; Xiao et al., 2014; Lu et al., 2014; Xu et al., 2014; Gong et al., 2014; Wu et al., 2013; Huang et al., 2013;Huang et al., 2013).

Table 2. Odds Ratios in Individual Variate Logistic Regression Analysis of Long-term Group and Short-term Group

Covariate	Odds Ratio (95% CI)	*P* Value
Gender		
Male	Reference	
Female	0.39 (0.18, 0.83)	0.016*
Age (years)		
<60	Reference	
≥60	1.84 (0.94, 3.59)	0.075
Number of metastatic sites		
<4	Reference	
≥4	1.21 (0.60, 2.43)	0.591
Lung Metastasis		
Yes	Reference	
No	0.44 (0.20, 0.95)	0.036*
Brain Metastasis		
Yes	Reference	
No	2.09 (0.98, 4.47)	0.058
Bone Metastasis		
Yes	Reference	
No	1.23 (0.63, 2.37)	0.547
Liver Metastasis		
Yes	Reference	
No	0.412 (0.18, 0.94)	0.035*
Pleural Metastasis		
Yes	Reference	
No	1.22 (0.63, 2.36)	0.561
LYR		
<20%	Reference	
≥20%	0.48 (0.24, 0.95)	0.036*
Change of LYR		
Decrease	Reference	
Raise	2.78 (1.40, 5.51)	0.003*
Hemoglobin (g/L)		
<120	Reference	
≥120	0.88 (0.42, 1.84)	0.730
Smoking history		
Yes	Reference	
No	0.68 (0.34, 1.37)	0.286
Hypertension		
Yes	Reference	
No	0.59 (0.23, 1.56)	0.289
Diabetes		
Yes	Reference	
No	1.97 (0.35, 11.12)	0.442
Chronic bronchitis		
Yes	Reference	
No	0.31 (0.09, 1.03)	0.055

CI, confidence interval; LYR, lymphocyte rate; *p<0.05

Results

Baseline characteristics of patients

Summaries of baseline patient characteristics are shown in Table 1. Overall, 69 patients survived less than 1 year (short-term group), 45 in one to two years, and 72 survived longer than 3 years (long-term group). In logistic regression analysis, the short-term group was taken as control group and the long-term group as case group. Kaplan-Meier survival estimates of survival rate was shown in Figure 1. In long-term group, 61 patients still alive. Odds ratios for baseline variables assessed for their association with long-term group are given in Table 2&3, and hazard ratios for overall survival in Table 4.

Table 3. Odds Ratios in Multivariate Logistic Regression Analysis of Long-term Group and Short-term Group

Covariate	Odds Ratio in Multivariate Analysis (95% CI)	*P* Value
Gender		
Male	Reference	
Female	0.64 (0.15, 0.95)	0.015*
Lung Metastasis		
Yes	Reference	
No	0.40 (0.17, 0.93)	0.034*
Liver Metastasis		
Yes	Reference	
No	0.38 (0.15, 0.95)	0.038*
LYR		
<20%	Reference	
≥20%	0.64 (0.30, 1.40)	0.270
Change of LYR		
Decrease	Reference	
Raise	2.57 (1.23, 5.38)	0.012*

CI, confidence interval; LYR, lymphocyte rate; *p<0.05

Age and gender

The mean age of the patients in long-term group was 58 years (range=38-78), and in short-term group was 62 years (range=34-79). Patients with age less than 60 years were significantly associated with overall survival (P<0.05) in univariate cox regression analysis. 45 patients (62.5%) were male in long-term group and 56 patients (81.2%) were male in another group, and gender was associated with long-term survival (P<0.05) in logistic regression analysis. A tentative inference on this result is that female patients with stage IV NSCLC might survive longer than male patients.

Histology and Metastatic sites

Fifty-eight percents (107/186) of patients had adenocarcinoma and 42% (79/186) had squamous cell carcinoma. Adenocarcinoma was significantly associated with overall survival. In long-term group, 49 patients (68.1%) had less than 4 metastases and 23 patients (31.9%) had 4 or more than 4 metastases. In short-term group, 44 patients (63.8%) had less than 4 metastases and 25 patients (36.2%) had 4 or more than 4 metastases. In all metastatic sites, only lung and liver were associated with overall survival (P<0.05) which reached statistical significance. Both of lung and liver metastases were risk factors for patients with advanced NSCLC who had suffered long term chemotherapy, and these two metastatic sites may reduce survival of patients with advanced NSCLC.

Radiotherapy and targeted therapy

75 of 186 (40.32%) patients received radiotherapy during the long term chemotherapy, and 79 of 186 (42.47%) received targeted therapy. There was evidence that both of these two treatments were associated with overall survival (P<0.05). But it showed weak relationship with long-term survival.

Smoking history

Smoking status was available in 22/72 (30.56%)

Table 4. Cox Regression Analysis for Overall Survival

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Gender				
Male/Female	1.45 (0.97, 2.17)	0.072	Excluded	
Age (years)				
<60/≥60	0.68 (0.48, 0.98)	0.036*	0.87 (0.59, 1.28)	0.468
Histology				
Ad/non-Ad	0.55 (0.39, 0.79)	0.001*	0.58 (0.40, 0.86)	0.006*
Number of metastatic sites				
<4/≥4	0.86 (0.60, 1.22)	0.392	Excluded	
Lung Metastasis				
Yes/No	1.96 (1.20, 3.20)	0.007*	2.56 (1.51, 4.34)	0.000*
Brain Metastasis				
Yes/No	0.88 (0.61, 1.28)	0.508	Excluded	
Bone Metastasis				
Yes/No	0.86 (0.60, 1.22)	0.392	Excluded	
Liver Metastasis				
Yes/No	1.49 (1.01, 2.20)	0.046*	1.93 (1.28, 2.92)	0.002*
Pleural Metastasis				
Yes/No	0.88 (0.62, 1.26)	0.492	Excluded	
LYR				
<20%/≥20%	1.45 (1.01, 2.08)	0.045*	1.35 (0.93, 1.97)	0.118
Change of LYR				
Decrease/Raise	0.53 (0.36, 0.77)	0.001*	0.70 (0.46, 1.04)	0.077
Hemoglobin (g/L)				
<120/≥120	1.04 (0.69, 1.56)	0.864	Excluded	
Radiotherapy				
Yes/No	0.49 (0.34, 0.71)	0.0001*	0.58 (0.39, 0.86)	0.006*
Targeted therapy				
Yes/No	0.57 (0.39, 0.83)	0.003*	0.60 (0.40, 0.89)	0.012*
Smoking history				
Yes/No	1.21 (0.85, 1.74)	0.295	Excluded	
Hypertension				
Yes/No	1.37 (0.84, 2.24)	0.206	Excluded	
Diabetes				
Yes/No	0.70 (0.29, 1.72)	0.443	Excluded	
Chronic bronchitis				
Yes/No	1.83 (1.03, 3.27)	0.039*	2.78 (1.46, 5.29)	0.002*

HR, hazard ratio; CI, confidence interval; Ad, adenocarcinoma; LYR, lymphocyte rate; *p<0.05

patients in long-term group and 27/69 (39.13%) patients in short-term group. The patient-reported smoking history was not significantly associated with survival.

Comorbidity

Eight of 72 (11.11%) patients had hypertension in long-term group and 12 of 69 (17.39%) patients in short-term group. 4/72 (5.56%) patients had diabetes in long-term group and 2/69 (2.90%) patients in short-term group. The presence of both hypertension and diabetes were not significantly associated with survival. 4 of 72 (5.56%) patients had chronic bronchitis in long-term group and 11 of 69 (15.94%) patients in short-term survival group, and chronic bronchitis was significantly associated with overall survival which means the clinical history of chronic bronchitis could raise the risk of death.

Physiologic Testing

Baseline functional variable assessed for their association with long term survival after long term chemotherapy and the odds ratios from logistic regression are summarized in Table 2. There was evidence that LYR and the decreasing tendency of LYR were associated with overall survival significantly. And patients with advanced NSCLC who had a decreasing tendency of LYR might live longer.

Discussion

In this paper, comprehensively evaluation of a range of different factors in a reasonably sized population of advanced NSCLC patients from Jiangsu Cancer Hospital has been made to determine their effects on long-term survival after long term chemotherapy. All patients received long term chemotherapy, more than third-line chemotherapy. 40.32% (75/186) of patients underwent radiotherapy, and 42.47% (79/186) of patients received targeted therapy.

Acquiring consecutive prospective data from a single center has aided the consistency of investigation and thus made it easier to compare the effects of the different factors assessed. Using multiple-variable models, it was possible to identify the strongest prognostic factors over 3-4 years of follow-up. Assessing prognostic factors is very important because it can help screen out who can survival longer and what make this happen. In univariate cox regression analysis, age, histology of adenocarcinoma, metastatic site (e.g. lung and liver), treatments (e.g. targeted therapy and radiotherapy), LYR, the decreasing tendency of LYR and chronic bronchitis were significantly associated with overall survival. After multivariate cox regression analysis of these factors, histology of adenocarcinoma, metastatic site (lung and liver), treatments (targeted therapy and radiotherapy) and chronic bronchitis showed more association with overall survival (P<0.05). Factors significantly (P<0.05) associated with long-term survival in individual-variable logistic regression model were gender, metastatic site (lung and liver), LYR and the decreasing tendency of LYR. And in multivariate logistic regression analysis, gender, metastatic site (lung and liver) and the decreasing tendency of LYR were associated with long-term survival. In conclusion, we found that female patients with stage IV adenocarcinoma NSCLC who had accepted multiple therapies more than third-line chemotherapy, radiotherapy and/or targeted therapy could live longer. Metastatic sites (e.g. lung and liver) and medical history of chronic bronchitis were risk factors for patients with advanced NSCLC. And when the LYR showed a downward trend during the therapy, patients could survive longer.

In addition to demographic and basic clinical information, this study identified the effects of other related factors. The fact that chronic bronchitis was associated with overall survival (P<0.05) should focus the attention of the clinician on these patients and careful management will be necessary. Through this, we speculate patients with stage IV NSCLC who had a history of chronic bronchitis simultaneously may survive shorter relatively.

In our study, histology of adenocarcinoma was significantly associated with overall survival. Among all metastatic sites, only lung and liver were associated with overall survival (P<0.05) which reached statistical significance. Both of lung and liver metastases were risk factors for patients with advanced NSCLC who had suffered long term chemotherapy, and these two metastatic sites may reduce survival.

A positive link between smoking and unfavorable survival in lung cancer patients was noted in a large number of previous studies, (Ferketich et al., 2013; Kogure et al., 2013) although there is some controversy regarding this finding (Li et al., 2011). In our study, smoking history had weak association with long term survival for advanced NSCLC patients who suffered long term chemotherapy, but the results were not statistically significant (Supporting Information Table 2 and Table 4). This might because the present study was focused on advanced-stage patients in which the effect of smoking on survival was overshadowed by other more prominent factors. It might also be partly accounted for by the relatively large number of never-smokers in this study.

The main limitation of this study is the relatively small sample size, which allowed identification of major factors that are associated with long term survival but which may have missed more moderate risk factors. Thus, negative findings should be interpreted with caution.

In conclusion, female patients with stage IV adenocarcinoma of NSCLC who had decreasing tendency of LYR during the course therapy and had accepted multiple therapies e.g. more than third-line chemotherapy, radiotherapy and/or targeted therapy could live longer. Lung and liver metastases were risk factors for patients with advanced NSCLC who had suffered long term chemotherapy. Careful attention is required when managing patients with chronic bronchitis, which might reduce the survival time of patients with stage IV NSCLC. While considering the sample size of this study is not large enough to detect minor difference of these variables regarding the influence on the response, a further study containing sufficient number of cases is needed to re-confirm this result.

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References

Dehing-Oberije C, Aerts H, Yu S, et al (2011). Development and validation of a prognostic model using blood biomarker information for prediction of survival of non-small-cell lung cancer patients treated with combined chemotherapy and radiation or radiotherapy alone (NCT00181519, NCT00573040, and NCT00572325). *Int J Radiat Oncol Biol Phys*, **81**, 360-8.

Donovan MJ, Kotsianti A, Bayer-Zubek V, et al (2009). A systems pathology model for predicting overall survival in patients with refractory, advanced non-small-cell lung cancer treated with gefitinib. *Eur J Cancer*, **45**, 1518-26.

Ferketich AK, Niland JC, Mamet R, et al (2013). Smoking status and survival in the national comprehensive cancer network non-small cell lung cancer cohort. *Cancer*, **119**, 847-53.

Gong JP, Yang L, Huang XE, et al (2014). Outcomes based on risk assessment of anastomotic leakage after rectal cancer surgery.*Asian Pac J Cancer Prev*, **15**, 707-12.

Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev*, **14**, 2611-4.

Huang XE, Tian GY, **one more,** et al (2013). Pemetrexed as a component of first-, second- and third- line chemotherapy in treating patients with metastatic lung adenocarcinoma. *Asian Pac J Cancer Prev*, **14**, 6663-7.

Huang XE, Cao J, **one more,** et al (2014). Leucogen tablets at 60 mg three times per day are safe and effective to control febrile neutropenia.*Asian Pac J Cancer Prev*, **15**, 8495-7.

Ji ZQ, Huang XE, Wu XY, et al (2014). Safety of *Brucea javanica* and cantharidin combined with chemotherapy for treatment of NSCLC patients. *Asian Pac J Cancer Prev*, **15**, 8603-5.

Kankesan J, Shepherd FA, Peng Y, et al (2013). Factors associated with referral to medical oncology and subsequent use of adjuvant chemotherapy for non-small-cell lung cancer: a population-based study. *Curr Oncol*, **20**, 30-7.

Kawaguchi T, Takada M, Kubo A, et al (2010). Performance status and smoking status are independent favorable prognostic factors for survival in nonsmall cell lung cancer: a comprehensive analysis of 26, 957 patients with NSCLC. *J Thorac Oncol*, **5**, 620-30.

Klein R, Wielage R, Muehlenbein C, et al (2010). Cost-effectiveness of pemetrexed as first-line maintenance therapy for advanced nonsquamous non-small cell lung cancer. *J Thorac Oncol*, **5**, 1263-72.

Kogure Y, Ando M, Saka H, et al (2013). Histology and smoking status predict survival of patients with advanced non-small-cell lung cancer. Results of West Japan Oncology Group (WJOG) Study 3906L. *J Thorac Oncol*, **8**, 753-8.

Le Chevalier T, Scagliotti G, Natale R et al (2005). Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. *Lung Cancer*, **47**, 69-80.

Lee ES, Son DS, Kim SH, et al (2008). Prediction of recurrence-free survival in postoperative nonsmall cell lung cancer patients by using an integrated model of clinical information and gene expression. *Clin Cancer Res*, **14**, 7397-404.

Li C-T, Marek M, Guclu SZ, et al (2011). Smoking and prognostic factors in an observational setting in patients with advanced non-small cell lung carcinoma.*J Cancer*, **2**, 52.

Lu YY, Huang XE, **one more,** et al (2014)Clinical observations on associations between the UGT1A1 genotype and severe toxicity of irinotecan.*Asian Pac J Cancer Prev*, **15**, 3335-41.

Mok T, Wu YL, Au JS et al (2010). Efficacy and safety of erlotinib in 1242 East/South-east Asian patients with advanced nonsmall cell lung cancer. *J Thorac Oncol*, **5**, 1609-15.

Qian YD, Xu X, **one more,** et al (2014). Clinical safety of chemotherapy for elderly cancer patients complicated with hypertension.*Asian Pac J Cancer Prev*, **15**, 9875-7.

Reck M, von Pawel J, Zatloukal P, et al (2009). Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer, *AVAil*. *J Clin Oncol*, **27**, 1227-34.

Reck M, van Zandwijk N, Gridelli C et al (2010). Erlotinib in advanced non-small cell lung cancer efficacy and safety findings of the global phase IV Tarceva lung cancer survival treatment study. *J Thorac Oncol*, **5**, 1616-22.

Scagliotti G, Hanna N, Fossella F, et al (2009). The differential efficacy of pemetrexed according to NSCLC histology, a review of two Phase III studies. *Oncologist*, **14**, 253-63.

Smit EF, van Meerbeeck JP, Lianes P et al (2003). Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced nonsmall- cell lung cancer: a phase III trial of the European Organization for

Research and Treatment of Cancer Lung Cancer Group—EORTC 08975. *J Clin Oncol*, **21**, 3909-17.

Van der Pijl LL, Birim O, van Gameren M, et al (2010). Validation of a prognostic model to predict survival after non-small-cell lung cancer surgery. *Eur J Cardiothorac Surg*, **38**, 615-9.

Wu XY, Huang XE, **one more,** et al (2014). A predictive model for evaluating responsiveness to pemetrexed treatment in patients with advanced colorectal cancer. *Asian Pac J Cancer Prev*, **15**, 5941-4.

Wu XY, Huang XE, You SX, et al (2013). Phase II study of pemetrexed as second or third line combined chemotherapy in patients with colorectal cancer. *Asian Pac J Cancer Prev*, **14**, 2019-22.

Xiao Y, Liu J, Liu YC, Huang XE, et al (2014). Phase II Study on EANI combined with hydrochloride palonosetron for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy.*Asian Pac J Cancer Prev*, **15**, 3951-4.

Xu C, Huang XE, **one more,** et al (2014). Drainage alone or combined with anti-tumor therapy for treatment of obstructive jaundice caused by recurrence and metastasis after primary tumor resection. *Asian Pac J Cancer Prev*, **15**, 2681-4.

Zhou Q, Shi Y, Chen J, et al (2011). Long-term survival of personalized surgical treatment of locally advanced non-small cell lung cancer based on molecular staging. *Zhongguo Fei Ai Za Zhi*, **14**, 86-106 (in Chinese).