

Improved Survival of Advanced Lung Cancer in Singapore Over the Past Decade

Chee Keong Toh, ¹MD, Whee Sze Ong, ²MAppStats, Daniel SW Tan, ¹MD, Quan Sing Ng, ¹MD, Ravindran Kanesvaran, ¹MD, Kam Weng Fong, ³MD, Mei Kim Ang, ¹MD, Eng Huat Tan, ¹MD, Wan Teck Lim, ¹MD

Abstract

Introduction: We reviewed changes in clinical characteristics, treatment and survival of lung cancer patients in Singapore over the past decade. **Materials and Methods:** We reviewed all primary lung cancer cases from January 2004 to December 2013. Basic demographic, clinical and treatment data were extracted from the database. Overall survival (OS) was calculated using Kaplan-Meier method; survival curves were compared using log-rank test. Linear regression trend lines were estimated using least squares approach, and Cox regression analyses were performed to identify prognostic factors. **Results:** Among 6006 lung cancer patients, the median age was 68 years old, 65% were males, 88% were Chinese, 92% had non-small-cell lung cancer and 76% had advanced stage IIIB/IV. There were proportionally more adenocarcinomas diagnosed over the years, while that of squamous cell carcinoma (SCC) and small-cell-lung cancer (SCLC) have remained stable. The median OS of all patients increased from 9.2 months in 2004 to 11.5 months in 2013. This survival improvement was statistically significant among patients with stage IIIB/IV (6.7 to 8.7 months; $P = 0.005$) and adenocarcinoma (12.7 to 15.4 months; $P = 0.041$). There was no improvement in median OS for SCC or SCLC. The use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) (hazard ratio [HR] 0.68; 95% CI, 0.63 to 0.73) and pemetrexed (HR, 0.69; 95% CI, 0.63 to 0.76) were significantly associated with improved OS. **Conclusion:** Survival of patients with advanced stage IIIB/IV lung adenocarcinoma has improved over the past decade, and is potentially associated with the use of EGFR TKI and pemetrexed.

Ann Acad Med Singapore 2017;46:333-8

Key words: Adenocarcinoma, Epidemiology, Southeast Asia

Introduction

Lung cancer remains the leading cause of cancer mortality in the world.¹ There is a changing landscape for lung cancer globally in the last decade as the incidence of adenocarcinoma has risen substantially, with a decrease in the incidence of small-cell lung cancer (SCLC) and other histological subtypes of non-small-cell lung cancer (NSCLC).² In addition, it is now recognised that NSCLC, in particular adenocarcinoma, comprises molecularly distinct subtypes with differential responses to various targeted therapies.³ These molecular subtypes involve genetic alterations that drive and maintain tumorigenesis, with epidermal growth factor receptor (EGFR) mutations being one of the first “driver mutations” to be discovered in NSCLC in 2002.⁴

Unlike the treatment of SCLC which has not changed over

the past decade, advances in the understanding and treatment of NSCLC have progressed remarkably. Concordant with the discovery of EGFR mutations more than a decade ago, lung cancer treatment has also evolved with the introduction of EGFR tyrosine kinase inhibitor (TKI) in 2003. In clinical trials, EGFR TKIs have led to improvements in progression-free survival, but not in overall survival (OS).⁵ While this has been attributed to treatment crossover, the selected nature of the patients who participate in these studies often raises the question whether these results could be extrapolated to the general population. Pemetrexed, the latest class of cytotoxics to show efficacy in NSCLC, was approved by the United States Food and Drug Administration (US FDA) for second-line treatment in 2004, first-line treatment in 2008 and maintenance therapy in 2009. Whether the use of these newer agents has truly benefited the “real world” population

¹Division of Medical Oncology, National Cancer Centre, Singapore, Singapore

²Division of Clinical Trials and Epidemiological Sciences, National Cancer Centre, Singapore, Singapore

³Division of Radiation Oncology, National Cancer Centre, Singapore, Singapore

Address for Correspondence: Dr Toh Chee Keong, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: toh.chee.keong@nccs.com.sg

is not known as many patients are either ineligible or do not have access to clinical trials.

Situated in Southeast Asia, we have previously described the epidemiology of our lung cancer patients to be different from those in the West.⁶ There is sufficient data to show that a larger proportion of NSCLC patients in Asia have the clinical phenotypes and molecular genotypes that derive greatest benefit from the use of EGFR TKIs.⁷ Following the approval by US FDA, the EGFR TKIs and pemetrexed were also approved by the Health Sciences Authority of Singapore in 2003 and 2004, respectively. The approval marked 2 pivotal changes in advanced NSCLC management at the start of the new millennium in Singapore as the use of these newer therapeutics has increased substantially over the past decade. Thus, we aim to review our data to examine if there are changes in the trend of lung cancer patients presenting at the National Cancer Centre Singapore (NCCS) over the past decade and to review the impact of the newer therapeutics, EGFR TKIs and pemetrexed, on the survival of NSCLC patients in a real-world situation. The NCCS is a tertiary referral centre and treats the majority of cancer patients in Singapore.

Materials and Methods

This study was approved by the Singhealth Centralised Institutional Review Board. All primary invasive lung cancer diagnoses seen at the NCCS between 1 January 2004 and 31 December 2013 were extracted from the institution's Oncology Practice Management System. Lung cancer diagnoses were identified based on code 162 under the 9th revision of the International Classification of Disease (ICD) before 2012, and code C34 under the 10th revision of the ICD (Australian Modification version) from 2012 onwards. Invasive cancers were identified based on the morphological code 3 under the ICD for Oncology, 3rd edition (ICD-O-3). Recurrent diagnoses and diagnoses of non-Singaporean were excluded. The latter was excluded due to lack of long-term follow-up data. For patients with multiple primary lung cancer diagnoses during the study period, their earliest diagnosis was included in the analyses.

Basic demographic and clinical data of each patient was available from the Oncology Practice Management System, including age at diagnosis, gender, race, stage at diagnosis, histology and year of diagnosis. Disease stage was classified based on the 6th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging before July 2010, and the 7th edition from July 2010 onwards. ICD-O-3 histologic types were collapsed into broad categories: small cell carcinoma (SCLC), adenocarcinoma, squamous cell carcinoma (SCC) and non-small cell carcinoma-others (NSCLC-others).

Treatment information such as the receipt of specific chemotherapy agents and dates of treatment were extracted from the institution's Maxcare Pharmacy and Outpatient Administrative systems and merged with the Oncology Practice Management System data for analyses. Chemotherapy agents included in the extracted data were EGFR TKIs (erlotinib, gefitinib, afatinib) and pemetrexed. All patients who had consumed these agents following their diagnosis, including those who had consumed these drugs as part of clinical trial participation at NCCS, were identified based on the merged data.

Survival status was checked against the Singapore Registry of Births and Deaths as at 27 August 2014. OS was defined from the time of diagnosis till death from any cause. Patients who were alive were censored as at 27 August 2014. Overall survival was calculated using the Kaplan-Meier method, and survival curves were compared using log-rank test. Linear regression trend lines estimated using the least squares approach was used for trend analyses of median OS. Univariate and multivariate Cox regression models were fitted to the data to estimate hazard ratio (HR) to assess the association of various variables with OS. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using statistical analysis systems version 9.4 (Statistical Analysis Systems Institute, Cary, NC).

Results

A total of 6006 patients were diagnosed with primary lung cancers from the year 2004 to 2013. The median age at diagnosis was 68 years. The patients were predominantly males (65%) and Chinese (88%). Median age at diagnosis, gender and ethnic distribution among the patients diagnosed in each year remained stable over time (Fig. 1).

Most of the patients were diagnosed at advanced stage IIIB/IV (76%) and this has been consistent over the past 10 years (Fig. 2A). The majority (92%) had NSCLC and the histological subtypes were adenocarcinoma (53%), SCC (16%) and others (23%) (Fig. 2B). There was a noticeable increase in the diagnosis of adenocarcinomas from 44% in 2004 to 63% in 2013. In comparison, the proportion of SCLC and SCC diagnosed in each year were relatively stable over the past decade.

A total of 641 (11%) and 1558 (25%) patients in our study cohort had received surgery and radiotherapy to the thorax region, respectively. About 1 in every 5 patients were treated with EGFR TKI, and about 1 in every 10 patients were treated with pemetrexed across all stages. The use of EGFR TKI and pemetrexed had increased from 2006 to 2013 (Fig. 3). There was an increasing proportion of stage IIIB/IV patients and adenocarcinomas who were treated with EGFR TKI and/or pemetrexed between 2004

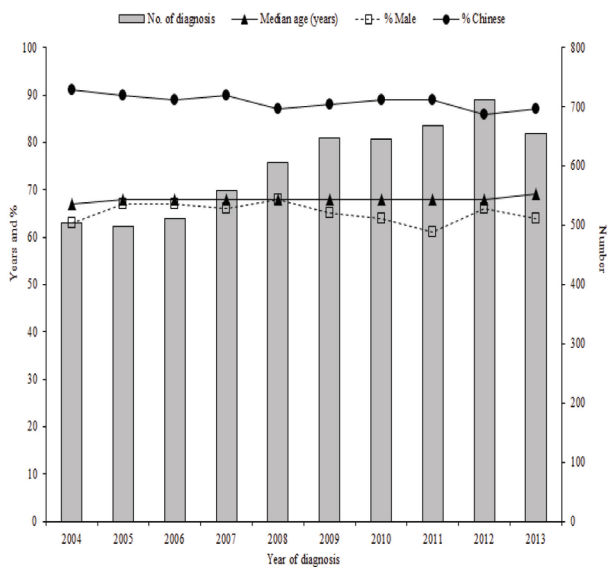


Fig. 1. Demographic characteristics by year of diagnosis.

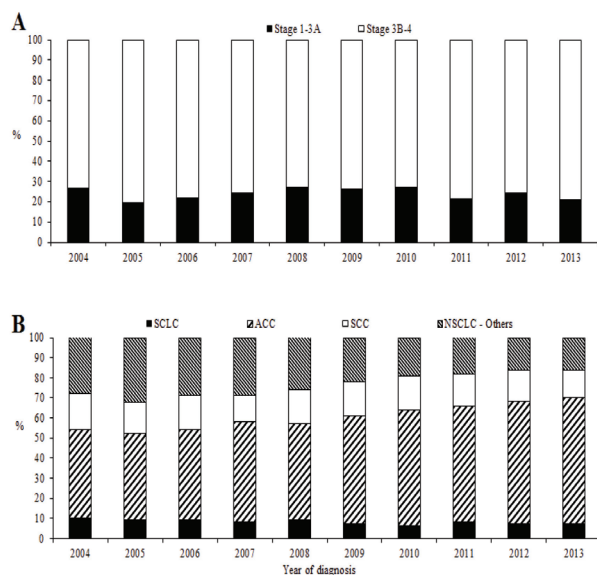


Fig. 2. (A) Stage at diagnosis and (B) histology distribution by year of diagnosis. ACC: Adenocarcinoma; NSCLC: Non-small cell carcinoma; SCC: Squamous cell carcinoma; SCLC: Small cell carcinoma.

and 2013 (Fig. 4).

Median OS improved significantly from 9.2 months in 2004 to 11.5 months in 2013 (Fig. 5A). This survival benefit was mainly accounted for by the improvements among stage IIIB/IV patients and those with adenocarcinomas over this period. The median OS of stage IIIB/IV patients increased significantly from 6.7 months in 2004 to 8.7 months in 2013 ($P = 0.005$; Fig. 5A), while the median OS of adenocarcinomas increased significantly from 12.7 months in 2004 to 15.4 months in 2013 ($P = 0.041$; Fig. 5B). The univariate and multivariate Cox analyses found that

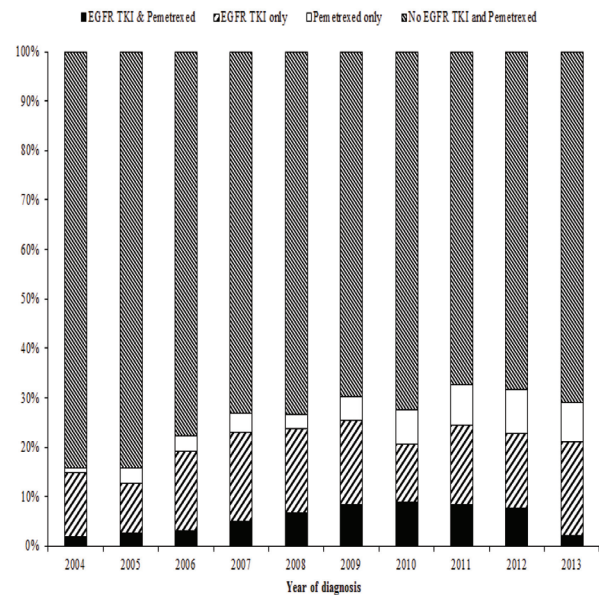


Fig. 3. Treatment with EGFR TKI and pemetrexed by year of diagnosis. EGFR TKI: Epidermal growth factor receptor tyrosine kinase inhibitor.

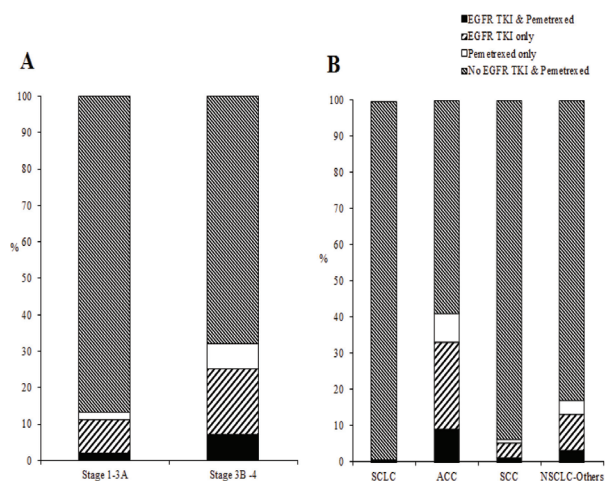


Fig. 4. Treatment with EGFR TKI and pemetrexed between 2004 and 2013 by (A) stage at diagnosis and (B) histology. ACC: Adenocarcinoma; EGFR TKI: Epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC: Non-small cell carcinoma; SCC: Squamous cell carcinoma; SCLC: Small cell carcinoma.

treatment with EGFR TKI and pemetrexed were significantly associated with improved OS (Table 1). On multivariate analysis, patients treated with EGFR TKI (HR, 0.68; 95% CI, 0.63 to 0.73) and pemetrexed (HR, 0.69; 95% CI, 0.63 to 0.76) had lower risk of death than patients who were not treated with these drugs.

Discussion

Our study is probably the largest dataset of lung cancer patients in East Asia to demonstrate the impact of novel therapies introduced as routine management at the start of

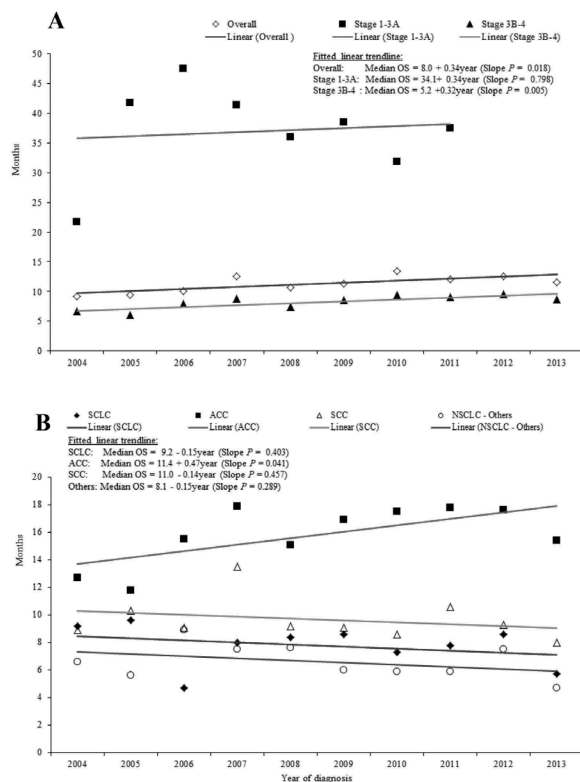


Fig. 5. Median overall survival by year of diagnosis and (A) stage at diagnosis; and (B) histology with best-fit linear trend line. Median survival for Stage 1-3A was not reached for 2012 and 2013. ACC: Adenocarcinoma; NSCLC: Non-small cell-lung carcinoma; SCC: Squamous cell carcinoma; SCLC: Small cell carcinoma.

the new millennium on survival outcome in a real-world setting.

The main changes over the past decade are seen among the adenocarcinoma subtype of NSCLC. This is not surprising as much progress has been made in this group of patients. Over the past 10 years, the proportion of adenocarcinoma has increased substantially in our dataset and this trend is similarly seen in other studies.² This may not be due to a true increase in numbers as the proportion of SCC and SCLC has remained stable, but to better classification of ‘NSCLC-others’ with the use of newer immunostaining and molecular subtyping techniques as well as cumulative experience of the dedicated thoracic pathologists. The use of EGFR TKI and pemetrexed has also increased over the past decade as data pertaining to these agents in adenocarcinoma of the lung evolved and matured. The EGFR TKIs were initially used in patients with the clinical phenotypes of never-smoker status, females and adenocarcinomas^{8,9} and administered in the second-line setting after progression of chemotherapy.¹⁰⁻¹¹ However, as more studies proved efficacy of EGFR TKIs in the first-line setting,¹²⁻¹⁴ the use of these agents shifted to front-line use and thus, more patients were treated with EGFR TKIs over the years. Similarly, pemetrexed was used in the second-line setting initially from 2004.¹⁵ Subsequently, it was approved for use in the first-line therapy for non-squamous NSCLC in 2008¹⁶ and maintenance treatment in 2009.¹⁷ With its favourable toxicity

Table 1. Cox Regression of Overall Survival

Variables	Categories	HR (95% CI)	P Value*	HR (95% CI)	P Value*
Age at diagnosis	Per year increase	1.02 (1.02 – 1.03)	<0.001	1.03 (1.02 – 1.03)	<0.001
Gender	Male	1	<0.001	1	<0.001
	Female	0.70 (0.66 – 0.74)		0.75 (0.70 – 0.80)	
Ethnic group	Chinese	1	0.002	1	<0.001
	Malays	1.22 (1.10 – 1.35)		1.29 (1.16 – 1.44)	
	Indians	0.93 (0.78 – 1.11)		0.96 (0.80 – 1.15)	
	Others	0.97 (0.77 – 1.24)		1.03 (0.81 – 1.32)	
Stage at diagnosis	1 – 3A	1	<0.001	1	<0.001
	3B – 4	3.42 (3.16 – 3.70)		4.23 (3.90 – 4.59)	
Histology	SCLC	1	<0.001	1	<0.001
	ACC	0.52 (0.47 – 0.57)		0.86 (0.77 – 0.96)	
	SCC	0.70 (0.63 – 0.79)		1.01 (0.90 – 1.15)	
	NSCLC-others	0.86 (0.77 – 0.95)		1.15 (1.03 – 1.29)	
Received EGFR TKI	No	1	<0.001	1	<0.001
	Yes	0.69 (0.64 – 0.74)		0.68 (0.63 – 0.73)	
Received pemetrexed	No	1	<0.001	1	<0.001
	Yes	0.70 (0.64 – 0.76)		0.69 (0.63 – 0.76)	

ACC: Adenocarcinoma; CI: Confidence interval; EGFR TKI: Epidermal growth factor receptor tyrosine kinase inhibitor; HR: Hazard ratio; NSCLC: Non-small cell carcinoma; SCC: Squamous cell carcinoma; SCLC: Small cell carcinoma
*Based on Wald’s test.

profile and convenience of administration, pemetrexed usage has increased over the years and this rise is seen in our data.

What is significant in our findings is that the survival of our lung cancer patients with adenocarcinoma subtype has improved over the past decade. This is mainly seen among the advanced stage IIIB/IV patients. There was no statistically significant improvement in OS for the earlier stage I-IIIa patients. In addition, we found that the survival is significantly associated with the use of EGFR TKI and pemetrexed. The findings are consistent as the use of EGFR TKI and pemetrexed are mainly limited to patients with advanced disease. Many clinical trials have found mainly progression-free survival benefit and no OS benefit with the use of the EGFR TKIs and this could be a result of cross-over of patients. Due to various reasons, many patients are not eligible for clinical trials, or even if eligible, may not get access to clinical trials. Comparing across clinical trials conducted in advanced cancer patients in different decades, the OS for adenocarcinoma has increased. However, it is not known if the data from trials can be extrapolated to the general population. The findings from our study suggest that the use of EGFR TKI and pemetrexed among our patients in the real world setting is associated with OS benefit, after adjusting for differences in patient demographics. Our study focused on EGFR TKI and pemetrexed as both groups of drugs are used frequently in the treatment of NSCLC in Singapore. The use of bevacizumab is limited in our population due mainly to cost constraints. Hence the use of bevacizumab was not reviewed here even though it has OS benefit in combination with paclitaxel/carboplatin chemotherapy in clinical trials of non-squamous NSCLC.

We found that the proportion of SCLC and SCC subtypes of lung cancer has remained stable over the past decade. This is consistent with several other studies where the incidence is either stable or decreasing.^{18,19} These 2 subtypes are known to be strongly associated with a history of chronic smoking.²⁰ Lowering the incidence rates of these highly preventable cancers can be achieved via aggressive smoking cessation campaigns. Unfortunately, despite governmental efforts to reduce smoking rates in Singapore, the proportion of smokers has increased slightly over the recent years after a previous long-term decline. What is sobering is that the survival of patients with these 2 subtypes has not improved due to the lack of progress in the realm of SCC and SCLC. However, the recent approval of the immune check point inhibitor, Nivolumab, for use in second-line therapy for SCC may improve upon this dismal prognosis.²¹ It is possible that we can see a progressive improvement in survival outcome for patients with SCC over the next 10 years when the use of such agents become more pervasive.

The strengths of our study are the large number of patients

prospectively collected over time in a computerised database and the fact that we limited our analysis to residents of Singapore with complete survival data outcome. Our study also spans across a decade, which provides sufficient time to chart improvements in the outcome in a disease with 5-year survival rates of 10%.²²

We do appreciate the limitations of our study, one of which is the change in staging classification in the year 2010. There was a change in the AJCC classification from the 6th to the 7th editions and the concern is that this may impact our findings. We evaluated the impact of this change by reviewing a group of patients diagnosed after 2010 that had documentation of both the 6th and 7th editions of AJCC staging and found that only a small percentage of patients had stage migration when using the 7th edition as compared to using the 6th edition (data not shown). In recent years, staging modalities have changed with more widespread use of positron emission tomography (PET) imaging. PET imaging used in clinical staging has resulted in a different stage compared to those using conventional imaging, resulting in more frequent upstaging.²³ This has the potential to result in a misleading better survival statistics – the Will Rogers phenomenon.²⁴ We were unable to determine the proportion of our patients who had PET imaging as part of their initial staging. However, if the phenomenon was the reason for better survival in our study, we would see improvement in survival not just in the patients with advanced stage IIIB/IV, but also in those with earlier stages. This was not evident in our study as statistically significant improvement in survival was only seen in the advanced stages. Another limitation is that our study was confined to a limited number of variables for which complete data are available from the databases in our centre. Data on some of the known prognostic factors for lung cancer such as smoking history and molecular status were not routinely collected over the entire study period, and these variables were inadvertently excluded from our study. In addition, the effects of other treatment modalities, such as surgery or radiotherapy, were not analysed in further details as a significant proportion of these data were not available. Thus, careful interpretation of the survival outcomes in this study is needed in light of the potential bias which may arise from a lack of control for confounding variables in the analyses.

The landscape of treatment options now available for NSCLC is vastly different from a decade ago, and there is improved survival for lung adenocarcinomas over time. Unmet needs still remain for SCLC and SCC where smoking cessation is likely to be the best intervention. Further improvements in survival may continue to be seen with the advent of next generation EGFR TKI and immunotherapeutics.

Conclusion

We appeared to have done relatively well and have progressed in the right direction in the treatment of NSCLC. With our computerised database that allows for comprehensive capture of information of our patients, we are confident that we will be able to gather more data in the future that will better reflect the changes in the epidemiology and survival of our lung cancer patients.

Acknowledgement

The authors would like to thank the staff at the Department of Cancer Informatics, National Cancer Centre Singapore, for providing data.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86.
2. Houston KA, Henley SJ, Li J, White MC, Richards TB. Patterns in lung cancer incidence rates and trends by histologic type in the United States, 2004-2009. *Lung Cancer* 2014;86:22-8.
3. Devarakonda S, Morgensztern D, Govindan R. Genomic alterations in lung adenocarcinoma. *Lancet Oncol* 2015;16:e342-51.
4. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
5. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst* 2013;105:595-605.
6. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *J Clin Oncol* 2006;24:2245-51.
7. Tetsuya Mitsudomi. Molecular epidemiology of lung cancer and geographic variations with special reference to EGFR mutations. *Transl Lung Cancer Res* 2014;3:205-11.
8. Lim ST, Wong EH, Chuah KL, Leong SS, Lim WT, Tay MH, et al. Gefitinib is more effective in never-smokers with non-small-cell lung cancer: experience among Asian patients. *Br J Cancer* 2005;93:23-8.
9. Lee DH, Han JY, Yu SY, Kim HY, Nam BH, Hong EK, et al. The role of gefitinib treatment for Korean never-smokers with advanced or metastatic adenocarcinoma of the lung: a prospective study. *J Thorac Oncol* 2006;1:965-71.
10. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small cell lung cancer. *N Engl J Med* 2005;353:123-32.
11. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008;372:1809-18.
12. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
13. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
14. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121-8.
15. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomised phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-97.
16. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.
17. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247-55.
18. Meza R, Meernik C, Jeon J, Cote ML. Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010. *PLoS One* 2015;10:e0121323.
19. Au JS, Mang OW, Foo W, Law SC. Time trends of lung cancer incidence by histologic types and smoking prevalence in Hong Kong 1983-2000. *Lung Cancer* 2004;45:143-52.
20. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer* 2001;31:139-489.
21. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:123-35.
22. Rami-Porta R, Ball D, Crowley J, Giroux DJ, Jett J, Travis WD, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:593-602.
23. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koëter GH, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med* 2000;343:254-61.
24. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985;312:1604-8.