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Potential role of anti-p53 antibody in diagnosis of lung cancer: evidence from a bivariate meta-analysis

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Abstract. – OBJECTIVES: The diagnosis of lung cancer remains a clinical challenge. Many studies have assessed the diagnostic potential of anti-p53 antibody in lung cancer patients but with controversial results. This study aims to summarize the overall diagnostic performance of anti-p53 antibody in lung cancer.

MATERIALS AND METHODS: Based on a comprehensive search of the Pubmed and Embase, we identified outcome data from all articles estimating diagnostic accuracy of anti-p53 antibody for lung cancer. A summary estimation for sensitivity, specificity, and other diagnostic indexes were pooled using a bivariate model. The overall measure of accuracy was calculated using summary receiver operating characteristic curve and the area under curve (AUC) was calculated.

RESULTS: According to our inclusion criteria, 16 studies with 4414 subjects (2249 lung cancers, 2165 controls) were included. The summary estimates were: sensitivity 0.20 (95% CI 0.15-0.27), specificity 0.97 (95% CI 0.95-0.98), positive likelihood ratio 6.64 (95% CI 4.34-10.17), negative likelihood ratio 0.83 (95% CI 0.77-0.89), diagnostic odds ratio 8.04 (95% CI 5.05-12.79), the AUC was 0.84. Subgroup analysis suggested that anti-p53 antibody had a better diagnostic performance for small cell lung cancer than non-small cell lung cancer.

CONCLUSIONS: anti-p53 antibody can be an assistant marker in diagnosing lung cancer, but the low sensitivity limits its use as a screening tool for lung cancer. Further studies should be performed to confirm our findings.

Key Words:
Anti-p53 antibody, Lung cancer, Diagnosis, Meta-analysis.

Introduction

Lung cancer is one of the most common cancers worldwide, which is second in both male and female cancer incidence[1,2]. The American Cancer Society estimates that lung cancer will account for 160, 340 deaths, which is approximately 28% of all deaths in 2012, and will be the leading cause of death from cancer in 2013[3]. The high mortality of lung cancer is due mainly to the fact that this disease usually becomes clinically apparent after it has reached an advanced stage: about three-quarter of lung cancer patients were diagnosed after the disease has already advanced locally or metastasized[4]. Thus, early detection of lung cancer at the resectable and potentially curable stages may reduce overall mortality, which will be of great importance for the management of lung cancer patients.

The immune dysregulation exists in cancer patients, and growing studies described the presence of a humoral immune response, in the form of autoantibodies, to tumor-associated antigens in lung cancer[5]. The p53 tumor suppressor gene is the site identified most frequently for mutations in human cancers, and it's reported that p53 mutation are found in 90% of small cell lung cancer (SCLC) and 50% of non-small cell lung cancer (NSCLC), which can induce an immune response and occur early in the carcinogenic process[6]. Proteins produced from mutated p53 genes can lead to the accumulation of mutant proteins and to humoral immune responses producing anti-p53 antibody, and the prevalence of anti-p53 antibody was correlated with the degree of malignancy[7]. Consequently, this antibody can be detected in the sera of patients with lung cancer, thus, plays a role in the early diagnosis of lung cancer[7,8].

The diagnostic potential of anti-p53 antibody has been investigated in a number of studies, which have variable results. The aim of this meta-analysis is to establish the overall diagnos-

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tic performance of anti-p53 antibody, thus providing the important up-to-date information on anti-p53 antibody for lung cancer.

Materials and Methods

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and methods recommended by the Cochrane Diagnostic Test Accuracy Working Group[9].

Date Source and Search Strategy

Two investigators (Q. Lei and J. Liu) independently performed a systematic electronic search of the Pubmed and Embase databases until July 1, 2013 to identify potentially relevant articles. The Cochrane Library database was also searched for review and meta-analysis articles. The following search terms were used: "p53 autoantibody *or* tumor-associated antigens *or* anti-p53 antibody *or* p53" and "lung cancer" and "sensitivity *or* specificity *or* accuracy". In addition, we reviewed the bibliographies of all selection articles to identify additional relevant studies. The searches were limited to English-language publications on human subjects.

Selection of Studies

Two investigators (Q. Lei and J. Liu) independently screened titles and abstracts of all studies for relevance. Disagreements were resolved by a third opinion. The strength of the individual studies was weighed for relevance, based on following items: (1) the study should be a diagnostic study on human subjects and contain a control group; (2) the reference diagnostic standards were clearly described; (3) completeness of data (numbers of true-positive, false-positive, true-negative, false negative) were reported, to allow reconstruction of the diagnostic 2 by 2 tables; (4) the articles should be written in English. Studies with fewer than 20 patients or without a control group were excluded to avoid selection bias. Conference abstracts or review articles were excluded because of the limited data provided.

Data Extraction and Methods Appraisal

The final set of articles was assessed independently by two investigators (Q. Lei and J. Liu). The retrieved data included author, publication year, the number of included subjects (true-positive, false-positive, true-negative, false negative), the referenced standard for the diagnosis of lung cancer, anti-p53 antibody assay method. The methodological quality of included studies was evaluated with the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) Tool[10]. It is an evidence-based approach to quality assessment intended for use in systematic reviews of diagnostic accuracy studies. A quality index is generated, with a maximum value of 14.

Statistical Analysis

By using a bivariate regression method[11], we calculated the pooled sensitivity and specificity, positive likelihood ratio (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR) with their 95% confidence interval (95% CI). In addition, we constructed summary receiver operating characteristic (SROC) curve to summarize the overall diagnostic accuracy, and the area under the SROC curve (AUC) was determined.

Q test was used to determine whether there was heterogeneity and I^2 to estimate the degree of heterogeneity. The Fagan's nomogram was used to calculate the posttest probability. Since publication bias is a concern in meta-analyses of diagnostic studies, we tested for it using Deeks' funnel plots as described by Wang et al[12]. All analyses were performed using software Stata (version 12, Stata Corporation, College Station, TX, USA). All statistical tests were two-sided, and significance was set at $p < 0.05$.

Results

After we evaluated these citations and the bibliographies of the potential studies, 16 unique studies were eventually included in our meta-analysis[13-28]. The main reasons of excluding studies were as follows: the study was a duplicate between the Pubmed and Embase database, the study was not a diagnostic study, the study didn't contain a control group, or the study could not reconstruct the diagnostic 2 by 2 tables.

Study Characteristics and Quality Assessment

Overall, the selected 16 studies include 4414 patients, in which 2249 patients were lung cancer, 2165 patients were non-malignant lung diseases controls. Lung cancer was diagnosed based on histopathology, which is considered as the

gold standard for lung cancer diagnosis. Except for one study used plasma as analysis matrix[17], the other studies all used serum as the specimen. All the studies determined anti-p53 antibody with enzyme linked immunosorbent assay (ELISA) except one study used iummunoblot[25]. The quality of the 16 studies was generally high, with fourteen studies QUADAS scores ≥8, satisfying the majority of the criteria. The clinical characteristics and quality assessment of included studies were shown in Table I.

Data Synthesis and Meta-Analysis

The heterogeneity analysis showed I^2 of 92.44% for sensitivity, 72.39% for specificity and 100% for DOR, all represented a significant heterogeneity; thus, the random effects model approach was selected in this study. The forest plot of sensitivity and specificity for anti-p53 antibody in diagnosing lung cancer was shown in Figure 1. The overall pooled sensitivity of 16 studies was 0.20 (95% CI 0.15-0.27), pooled specificity was 0.97 (95% CI 0.95-0.98). The PLR was 6.64 (95% CI 4.34-10.17) and NLR was 0.83 (95% CI 0.77-0.89) (Figure 2), and the DOR was 8.04 (95% CI 5.05-12.79).

The SROC curve shows an overall summary of studies, which illustrates the relationship between sensitivity and specificity. As shown in Figure 3, the area under the SROC curve was 0.84 (95% CI, 0.80-0.87), indicating a potential role of anti-p53 antibody in the diagnosis of lung cancer. The Fagan's nomogram for likelihood ratios was shown in Figure 4, the results indicated that the anti-p53 antibody for detection lung cancer increased the post-probability to 62% when the results were positive and reduced the post-probability to 17% when the results were negative.

Sub-group Analysis: Diagnostic Accuracy in NSCLC and SCLC

It's reported that the incidence of p53 mutation in NSCLC and SCLC was different, which was 90% in SCLC and 50% in NSCLC[7] thus, we conducted a subgroup analysis to identify whether anti-p53 antibody gave better diagnostic accuracy in SCLC than NSCLC. The data focused on NSCLC was available in nine studies with 1006 NSCLC patients, and focused on SCLC was available in nine studies with 448 SCLC patients. The pooled sensitivity, specificity, PLR, NLR, DOR and AUC of anti-p53 antibody for NSCLC were: 0.16 (95% CI 0.12-0.22), 0.97 (95% CI

Table I. Summary of the studies included in the meta-analysis.

Author	Year	Country	LC	Control	Gold standard	Specimen	Assay method	TP	FP	FN	TN	QUADAS
Chapman et al	2012	UK	235	266	Histopathology	Serum	ELISA	31	8	204	258	12
Park et al	2011	Korea	82	79	Histopathology	Serum	ELISA	28	4	54	75	11
Chapman et al	2011	UK	243	247	Histopathology	Serum	ELISA	39	5	204	242	11
Yu et al	2011	China	349	400	Histopathology	Serum	ELISA	92	20	257	380	10
Chapman et al	2008	UK	104	50	Histopathology	Plasma	ELISA	12	1	92	49	10
Megliorino et al	2005	USA	189	82	Histopathology	Serum	ELISA	20	2	169	80	11
Neri et al	2003	Italy	48	106	Histopathology	Serum	ELISA	8	2	40	104	10
Zhang et al	2003	China	56	346	Histopathology	Serum	ELISA	9	5	47	341	9
Cioffi et al	2001	Italy	109	50	Histopathology	Serum	ELISA	35	0	74	50	10
Mack et al	2000	Germany	134	46	Histopathology	Serum	ELISA	17	1	117	45	9
Oshikawa et al	2000	Japan	98	93	Histopathology	Serum	ELISA	60	5	38	88	10
Schneider et al	1999	Germany	101	179	Histopathology	Serum	ELISA	21	21	80	158	9
Lai et al	1998	China	125	24	Histopathology	Serum	Immunoblot	10	0	115	24	9
Segawal et al	1998	Japan	52	63	Histopathology	Serum	ELISA	24	3	28	60	10
Mitsudomi et al	1998	Japan	188	84	Histopathology	Serum	ELISA	38	4	150	80	7
Wild et al	1995	France	136	50	Histopathology	Serum	ELISA	16	0	120	50	8

LC: lung cancer; ELISA: enzyme linked immunosorbent assay; TP: true positive; FP: false positive; FN: false negative; TN: true negative; QUADAS: quality assessment of diagnostic accuracy studies.

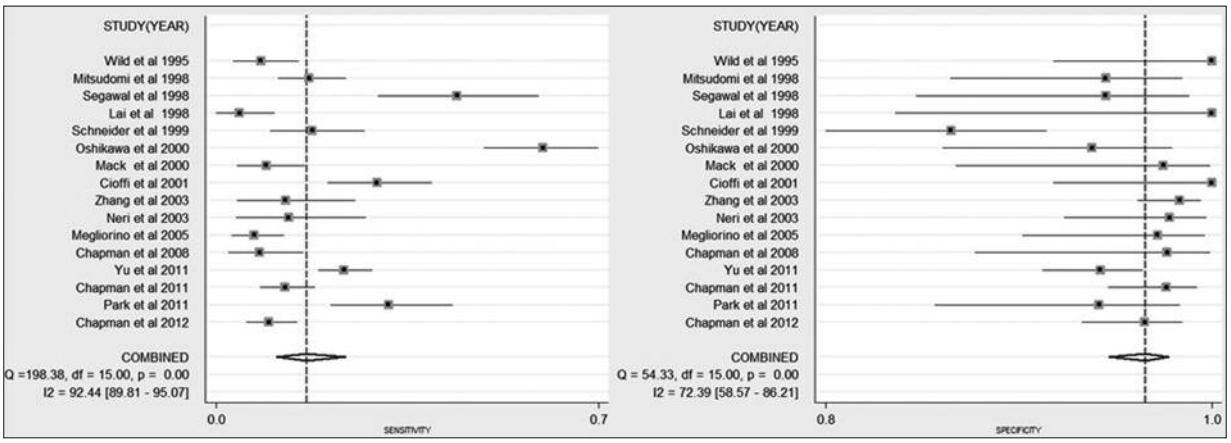

Figure 1. Forest plot of the sensitivity (Left) and specificity (Right) of anti-p53 antibody in the diagnosis of lung cancer.

0.94-0.99), 5.62 (95% CI 2.61-12.08), 0.86 (95% CI 0.82-0.92), 6.50 (95% CI 2.93-14.39), 0.62 (95% CI 0.57-0.66), for SCLC, the corresponding values were: 0.21 (95% CI 0.14-0.30), 0.97 (95% CI 0.95-0.99), 7.45 (95% CI 4.41-12.57), 0.82 (95% CI 0.75-0.90), 9.12 (95% CI 5.32-15.65), 0.75 (95% CI 0.71-0.78). These results suggested that anti-p53 antibody is a better marker for diagnosing SCLC than NSCLC, but both with low diagnostic efficacy.

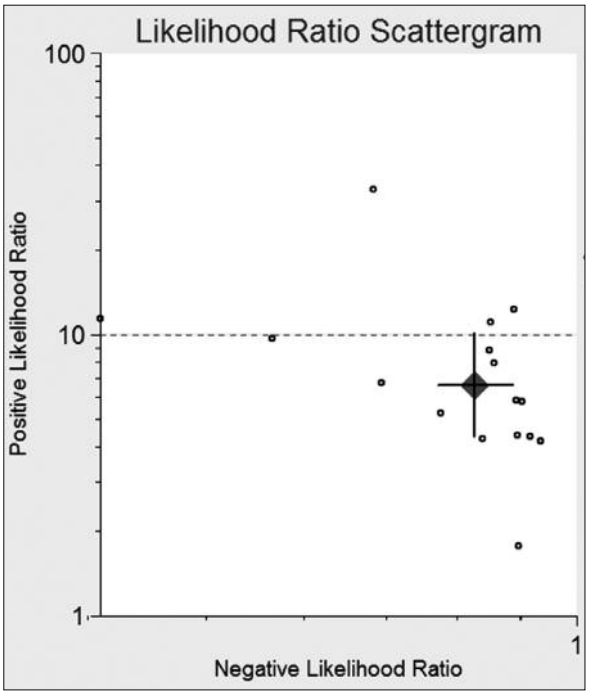

Figure 2. Scattergram of the positive likelihood ratio and negative likelihood ratio.

Publication Bias

Deeks' funnel plot asymmetry test was used to evaluate the final included studies for potential publication bias (Figure 5). The slope coefficient was associated with a *p* value of 0.23, suggesting symmetry in the data and a low likelihood of publication bias.

Discussion

Lung cancer remains a leading cause of cancer mortality worldwide, for often be found in late phase of the disease[1,2]. At present there is little to offer for early diagnosis, even in those at high

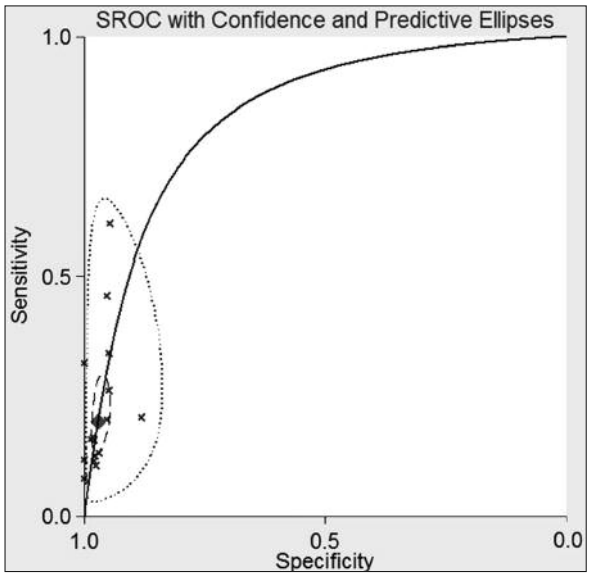

Figure 3. Summary receiver operating characteristic (SROC) curve for anti-p53 antibody assay.

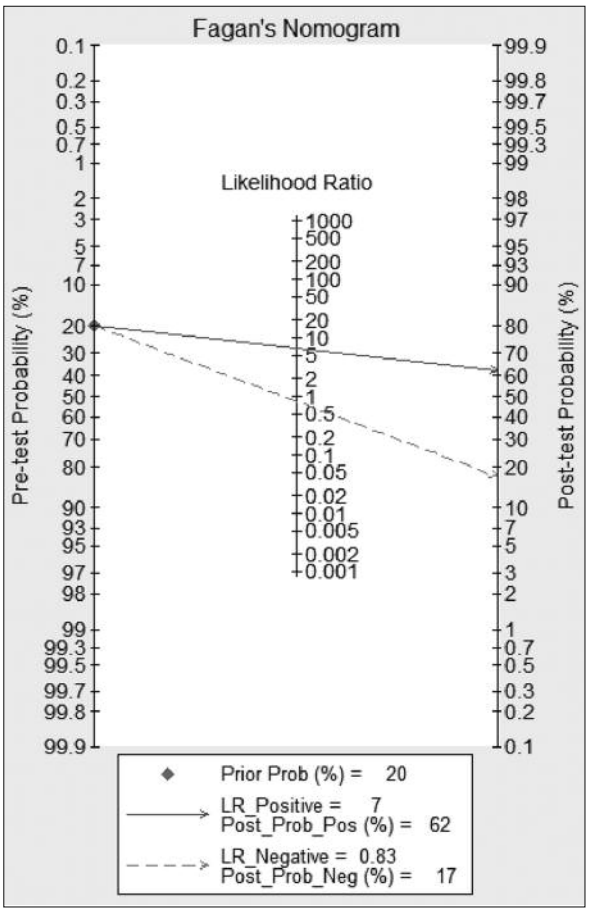

Figure 4. Fagan's nomogram for likelihood ratios and the probability for anti-p53 antibody assay in the diagnosis of lung cancer.

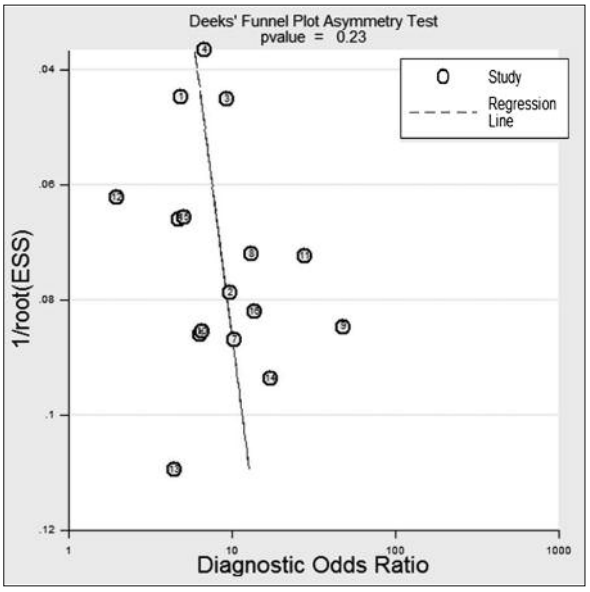

Figure 5. The Deek's funnel plot for the assessment of potential publication bias.

risk of developing the disease. Imaging is the most common method to screen lung cancer, but it was limited by the harm of radiation exposure. Meanwhile the CT change often appears in the late phase as well, in addition, the high rate of false positives requires follow-up examinations and a substantial proportion of individuals may undergo unnecessary thoracotomy[4]. The current available tumor markers, such as neuron-specific enolase, cytokeratin 19 fragment, carcino-embryonic antigen, and tissue polypeptide antigen, although play a role in diagnosing lung cancer, they are lack of specificity, and are mostly used in conjunction[5]. Therefore, it is of high clinical importance to develop an easy-to-perform diagnosing test that can identify lung cancer patients in early curable stage.

Recent studies suggest that to search for tumor antigens that induce specific immune responses in patients with lung cancer is a promising approach in this field. Evidence for a specific humoral response against a number of intracellular and surface tumoral antigens is now established in patients with lung cancer, and among them, the anti-p53 antibody is highlighted. anti-p53 antibody has been shown to be present in the circulation of people with lung cancer before cancer-associated antigens can be detected and symptoms appeared, thus, plays a role in the early diagnosis of lung cancer[29].

In this study, we clarified the diagnostic accuracy of anti-p53 antibody for lung cancer. Meanwhile we evaluated the diagnostic accuracy of anti-p53 antibody for SCLC and NSCLC, respectively. To our best knowledge, this is the first meta-analysis to estimate the diagnostic accuracy of anti-p53 antibody in lung cancer. The results of these 16 studies showed that anti-p53 antibody plays a role in diagnosing lung cancer. Using the bivariate random-effects approach, we found a summary AUC of 0.84, a summary estimate of 20% for sensitivity and 97% for specificity, which indicated that the assay may result in a 80% false-negative test result and a 3% false-positive test result. The DOR of a test is the ratio of the odds of positive test results in the patient with disease relative to the odds of positive test results in the patient without disease, with higher values indicating higher accuracy. In this meta-analysis we found that the mean DOR was 8.04, indicating a moderate level of overall accuracy. Likelihood ratios are considered to be more clinically meaningful, a value of pooled PLR greater than 10 and of pooled NLR less than 0.1 were

noted as providing convincing diagnostic evidence, The pooled PLR 6.64 suggests that patients with lung cancer have an approximately seven-fold higher chance of being anti-p53 antibody positive compared with patients without lung cancer. On the other hand, the pooled NLR 0.83 suggests that even the anti-p53 antibody was negative, the probability that this patient has lung cancer was 83 percent, which is not low enough to rule out lung cancer. These data suggest that a negative anti-p53 antibody result should not be used alone to diagnosis lung cancer. For clinical use of anti-p53 antibody in lung cancer diagnosis, the results should be interpreted with the combination of other test results and clinical findings

Besides diagnostic information, anti-p53 antibody assay can provide prognostic information about patients with lung cancer. The concentrations of serum levels anti-p53 antibody were significantly higher in patients with NSCLC and its levels increased according to the stage of disease[30]. Lai et al[25] reported that the anti-p53 antibody-positive lung cancer patients had a worse prognosis than the anti-p53 antibody-negative patients ($p < 0.02$; median survival, 20 versus 41 weeks). Laudanski et al[31] also pointed out that serum anti-p53 antibody may be an independent prognostic factor in NSCLC, especially in the squamous cell carcinoma patients and may be useful in identifying resected lung cancer patients at high risk for treatment failure. Since the prognostic role of anti-p53 antibody is debatable, more studies should be carried out. In addition, serum anti-p53 antibody level remarkably decreased after neoadjuvant chemotherapy treatment and pre-neoadjuvant chemotherapy low serum anti-p53 antibody level correlated with high objective chemoresponse rate[16]. Thus, anti-p53 antibody may turn out to be useful not only for diagnosing lung cancer but also for predicting chemosensitivity and prognosis, which will improve the comprehensive management of lung cancer patients[32].

For clinical application of anti-p53 antibody in the diagnosis of lung cancer, there are several points should be addressed. First, serum anti-p53 antibodies were detected only in a proportion of lung cancer cases, the precise mechanism of anti-p53 antibody in the pathogenesis of lung cancer is still unclear. Second, although most studies used ELISA to analyze serum anti-p53 antibody, the cut-off value in lung cancer patients has not been founded[7], which may contribute to the heterogeneity among include studies, further studies are needed to confirm the optimized cutoff value of anti-p53 antibody for lung cancer. Third, the sample sizes of several included studies were rather small and they may do not have adequate ability to assess the diagnostic accuracy. In addition, we included only English-language articles, this may be cause language bias, and this meta-analysis limited to published studies that may miss some of the gray literature. For further studies to investigate the role of anti-p53 antibody in lung cancer, more attention should be paid to the mechanism and the study design.

Conclusions

The evidence from current meta-analysis suggests that anti-p53 antibody has a potential diagnostic role for lung cancer, while the low sensitivity limited its use as a screen tool for lung cancer. To put a further work on the diagnostic and prognostic value of anti-p53 antibody will be of great importance for the management of lung cancer patients.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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