Original Article

The role of SOX-2 on the survival of patients with non-small cell lung cancer

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Background: Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death worldwide. Observational studies on the prognostic role of SOX-2 in non-small-cell lung cancer (NSCLC) are controversial.

Methods: To clarify the impact of SOX-2 in NSCLC survival, we performed this meta-analysis that included eligible studies. The combined hazard ratios and their corresponding 95% confidence intervals (95% CI) were calculated in terms of overall survival.

Results: A total of seven studies with 1,944 patients were evaluable for this meta-analysis. The studies were categorized by histology, disease stage and patient race. Our results suggested that SOX-2 overexpression had a favorable impact on survival of patients with NSCLC, the HR (95% CI) was 0.57 (0.48 to 0.65). However, highly significant heterogeneity was detected among these studies (I^2=76.7%, P=0.000).

Conclusions: SOX-2 overexpression indicates a favorable prognosis for patients with NSCLC.

Keywords: SOX-2; prognosis; lung cancer; meta-analysis

Submitted May 07, 2015. Accepted for publication Jul 05, 2015.
doi: 10.3978/j.issn.2072-1439.2015.07.14
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.07.14

Introduction

Lung cancer remains the most lethal cancer worldwide, despite improvements in diagnostic and therapeutic techniques. Its incidence has not peaked in many parts of world, particularly in China, which has become a major public health challenge all the world (1). The prognosis for lung cancer patients is generally poor, with an overall 5-year survival rate of approximately 15%, and it has shown little improvement in recent decades (2,3). Several independent prognostic factors for survival have been identified: performance status (PS), disease stage, age, sex and amount of weight lost (4). Some of these factors are useful when choosing treatment options for an individual, principally disease stage and PS. However, the discriminant value of most potential prognostic biological markers is insufficient to predict the optimal therapeutic course for an individual (5,6).

SRY (sex determining region Y)-box 2, also known as SOX-2, is one of the key transcriptional factors that control the unique properties of stem cells self-renewal and pluripotency (7,8) and play a critical role inmaintaining the stem cell-like phenotype in cancer cells (9-12). Over-expression of SOX2 in NSCLC cells stimulates cellular migration and anchorage-independent growth while SOX-2 knockdown impairs cell growth (13,14).

Recently, a number of studies have reported the contribution of SOX-2 to tumorigenesis and its correlation with clinical progression of various types of tumors, including lung cancer. However, no consensus has been reached; conflicting results have been reported from different laboratories. We therefore carried out a meta-

Table 1 Main characteristics and results of the eligible studies

First author-year	Patients source	Histology	stage	N pts	Method	Positive (%)	HR estimation	Survival results
Lu-2010	USA	SCC	I-III	89	IHC	19/89	Survival curves 0.35 (0.17-0.73)	Favorable
Sholl-2010	USA	AC	I	104	IHC	50%	HR and 95% CI 1.94 (0.97-3.90)	NS
Wilbertz-2011	Switzerland/USA	SCC	I-IV	758	IHC	225/758	Survival curves 0.66 (0.46-0.94)	Favorable
Sasaki-2012	Japan	NSCLC	I-IV	127	q-PCR	33.1	Survival curves 0.81 (0.42-1.59)	Favorable
Li-2012	China	NSCLC	I-IV	44	IHC	31/44	Survival curves 0.48 (0.19-1.24)	NS
Velcheti-2013	USA/Greece	NSCLC	I-IV	647	IHC	418/647	HR and 95% CI 0.46 (0.36-0.60) Training cohort	Favorable
							0.67 (0.49-0.90) Validation cohort	Favorable
Chou-2013	China	NSCLC	I-IV	175	IHC	NA	Survival curves	Poor

IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; AC, adenocarcinoma; Scc, squamous cell carcinoma; NS, not significant; HR, hazard ratio; N pts, number of patients.

analysis of data from published studies to quantitatively review the effect of SOX-2 overexpression in tumor tissue on survival in patients with non-small-cell lung cancer (NSCLC).

Materials and methods

Search strategy and study selection

The electronic databases PubMed, Embase, and CNKI (China National Knowledge Infrastructure) were searched for studies to include in our meta-analysis. An upper date limit of Nov 01, 2014 was applied; we used no lower date limit. Searches included the terms "lung cancer", "SOX-2", "SRY-box 2,", and "prognosis". We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search.

Studies eligible for inclusion in this meta-analysis met the following criteria: (I) measure SOX-2 expression in the primary lung cancer tissue with IHC (immunohistochemistry) or other methods; (II) provide information on survival (studies investigating response rates only were excluded); (III) have a follow-up time exceeding 5 years; and (IV) When the same author reported results obtained from the same patient population in more than one publication, only the most recent report, or the most complete one, was included in the analysis. Two reviewers independently determined study eligibility. Disagreements were resolved by consensus.

Data extraction and quality assessment

The final articles included were assessed independently by two reviewers. Data retrieved from the reports included first author, publication year, patient source, histology, disease stage, test method, SOX-2 positive and survival data (*Table 1*). If data from any of the above categories were not reported in the primary study, items were treated as "not applicable". We did not contact the author of the primary study to request the information.

Statistical methods

For the quantitative aggregation of the survival results, hazard ratios (HR) and their 95% confidence intervals (CIs) were combined to give the effective value. When these statistical variables were not given explicitly in an article,

they were calculated from available numerical data using methods reported by Parmar *et al.* (15).

Heterogeneity of the individual HRs was calculated with Chi-squared tests according to Peto's method (16). Meanwhile, Heterogeneity test with I^2 statistic and Q statistic was performed. All the studies included were categorized by patient race, histology, disease stage. Individual meta-analysis was conducted in each subgroup. If HRs were found to have fine homogeneity, a fixed effect model was used for secondary analysis; if not, a random-effect model was used. In this meta-analysis, DerSimonian-Laird random effects analysis (17) was used to estimate the effect of SOX-2 overexpression on survival. By convention, an observed HR >1 implies worse survival for the group with SOX-2 overexpression. The impact of TTF-1 on survival was considered to be statistically significant if the 95% CI did not overlap with 1. Horizontal lines represent 95% CIs. Each box represents the HR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI represented by its width. The unbroken vertical line is set at the null value (HR =1.0).

Evidence of publication bias was sought using the methods of Egger *et al.* (18) and of Begg *et al.* (19). Moreover, contour-enhanced funnel plot (20) was performed to aid in interpreting the funnel plot. If studies appear to be missing in areas of low statistical significance, then it is possible that the asymmetry is due to publication bias. If studies appear to be missing in areas of high statistical significance, then publication bias is a less likely cause of the funnel asymmetry. Intercept significance was determined by the *t*-test suggested by Egger ($P<0.05$ was considered representative of statistically significant publication bias). All calculations were performed using STATA version 11.0 (Stata Corporation, College Station, TX).

Results

Study selection and characteristics

Seven studies (21-27) published between 2010 and 2013 were eligible for this systematic review with meta-analysis. All reported the prognostic value of SOX-2 status for survival in NSCLC patients. The total number of patients included was 1,944, ranging from 44 to 758 patients per study (median 277). The major characteristics of the seven eligible publications are reported in *Table 1*.

These publications followed several different patient cohorts. Among the seven studies evaluating SOX-2 expression in NSCLC, three studies were performed in Asian populations, and the remaining four studies followed European or American patients. Only one of the 17 studies identified SOX-2 overexpression as an indicator of poor prognosis, two studies showed no statistically significant impact of SOX-2 overexpression on survival, and the other five studies showed for favorable significance.

Meta-analysis

The results of the meta-analysis are reported in *Figure 1*. Overall, the combined HR for all eligible studies evaluated SOX-2 expression in NSCLC was 0.57 (95% CI: 0.48 to 0.65), indicating that SOX-2 overexpression was an indicator of favorable prognosis for NSCLC patients. However, highly significant heterogeneity was detected among these studies (I^2=76.7%, P=0.000).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias in the literature. All seven eligible studies investigating NSCLC patients yielded a Begg's test score of P=0.654 and an Egger's test score of P=0.976, meanwhile according to the contour-enhanced funnel plot (*Figure 2*), the absence of publication bias was found in all seven studies. These results suggest that there is no publication bias at work.

Discussion

NSCLC is the leading cause of cancer death, with an overall fiveyear survival rate of less than 15% (1-3). New biological markers of NSCLC carcinogenesis may provide important progress in clinical decision making (3). Emerging evidences have suggested functional molecules involved in cell-cycle control, DNA repair, proliferation, apoptosis that may modulate response to platinum-based chemotherapy and serve as promising biomarkers for individualized chemotherapy and prognosis of NSCLC patients (28).

SOX2 expression plays a critical role incell cycle control, DNA damage response and long-term self-renewal in neural stem cells (29,30). Moreover, several studies have identified that SOX2 expression correlated with tumorigenesis, chemoresistance, and maintaining the stem cell-like phenotype in cancer cells (31). In the present meta-analysis, we have combined seven published studies

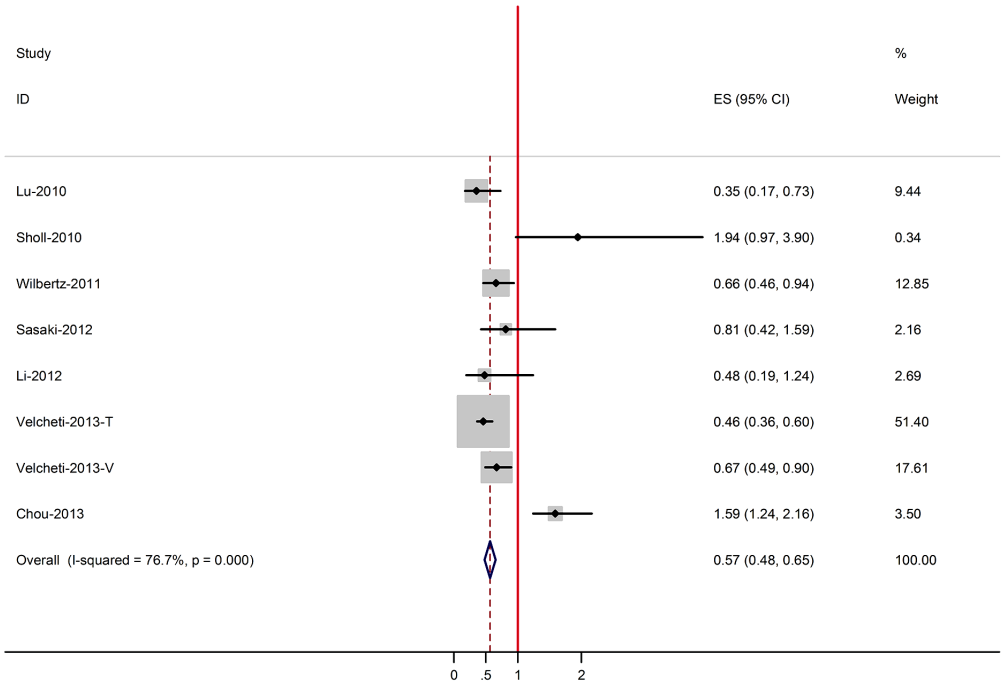

Figure 1 Meta-analysis (Forest plot) of the seven evaluable studies assessing SOX-2 in NSCLC. NSCLC, non-small-cell lung cancer.

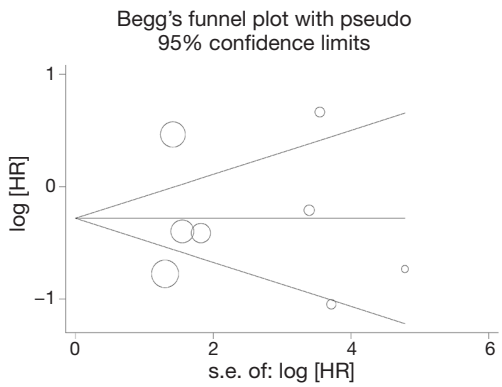

Figure 2 Funnel plot of the seven evaluable studies assessing SOX-2 in NSCLC. NSCLC, non-small-cell lung cancer.

including 1,944 patients with NSCLC to yield summary statistics that indicate that SOX-2 overexpression has a significant correlation with favorable survival in NSCLC. We observed a statistically significant effect of SOX-2 on favorable survival, suggesting that this good prognostic factor could be of importance not only in early-stage NSCLC but also in advanced staged NSCLC.

Recently, several systematic reviews (32-40) with meta-analyses on other biological prognostic factors for NSCLC had been reported. P53, microvessel density, HER-2, Ki-67 and RAS might be poor prognostic factors for survival in NSCLC, however, Bcl-2 might be better prognostic factor for survival in NSCLC. In order to clarify the prognostic impact of other biological factors in lung cancer, our group has performed several systematic reviews of the literature with meta-analyses. We found that VEGF (41), E-cadherin (42) and matrix metalloproteinase 2 (43) might be poor prognostic factor in NSCLC, COX-2 (44) might be poor prognostic factor for stage I NSCLC, the ground glass opacity (GGO) area (45) had a favorable prognostic value of overall survival and relapse-free survival in small lung adenocarcinoma.

Another potential source of bias is related to the method of HR and 95% CI extrapolation. If these statistics were not reported by the authors, we calculated them from the data available in the article. If this was not possible, we extrapolated them from the survival curves, necessarily making assumptions about the censoring process. Data for multivariate survival analysis reported in the article were included in the present systematic review with meta-analysis; if these data were not available, data calculated from survival curves by univariate analysis were included.

These results should be confirmed by an adequately designed prospective study. Furthermore, the exact value of SOX-2 overexpression status needs to be determined by appropriate multivariate analysis. Unfortunately, few prospectively designed prognostic studies concerning biomarkers have been reported; thus, our collection of many retrospective studies revealed more significance.

Publication bias (46) is a major concern for all forms of meta-analysis; positive results tend to be accepted by journals, while negative results are often rejected or not even submitted. The present analysis does not support publication bias; the obtained summary statistics likely approximate the actual average. However, it should be noted that our meta-analysis could not completely exclude biases. For example, the study was restricted to papers published in English and Chinese, which probably introduced bias.

In conclusion, SOX-2 overexpression is associated with a favorable prognosis in patients with NSCLC in present meta-analysis, but there is a high heterogeneity between the studies. These results should be confirmed by an adequately designed prospective study.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Shao W, Chen H, He J. The role of SOX-2 on the survival of patients with non-small cell lung cancer. J Thorac Dis 2015;7(7):1113-1118. doi: 10.3978/j.issn.2072-1439.2015.07.14