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Original Article

P53 status as a biomarker to predict the response to neoadjuvant therapy in esophageal cancer: a systematic review and meta-analysis

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Abstract: Background: Numerous studies published previously have reached inconsistent conclusions regarding the relationship between p53 status and the response to neoadjuvant therapy in patients with esophageal cancer. To acquire a more precise evaluation of such association, we performed this meta-analysis. Methods, findings: 25 eligible studies encompassing 1234 patients were identified and included in this meta-analysis. Significant association was found between wild-type form of p53 status (low expression of p53 protein and/or wild p53 gene) and improved response in esophageal cancer patients who received neoadjuvant therapy (good response: risk ratio [RR] = 1.306; 95% confidence intervals [CI] = 1.131-1.507; P<0.001). In further stratified analysis, wild-type form of p53 status was associated with improved response to neoadjuvant chemoradiotherapy (RR = 1.308, 95% CI = 1.104-1.551, P = 0.002) and neoadjuvant chemotherpay (RR = 1.436, 95% CI = 1.052-1.960, P = 0.023). Patients with wild-type form of p53 status had high complete response rate to neoadjuvant therapy (RR = 1.844, 95% CI = 1.262-2.694, P = 0.002). Additionally, association with good response remained in the Asian population (RR = 1.268; 95% CI = 1.074-1.499; P = 0.005), while in the European subgroup, patients with wild-type form of p53 status tended to have a good response to neoadjuvant therapy, although this did not reach statistical significance (RR = 1.005, 95% CI = 0.667-1.515, P =0.981). Conclusion: The results of this meta-analysis suggested that p53 status may be a useful predictive biomarker for response to neoadjuvant therapy in esophageal cancer, especially in Asian population.

Keywords: P53, biomarker, neoadjuvant therapy, esophageal cancer

Introduction

It is estimated that esophageal cancer is the sixth most common cause of cancer deaths all over the world [1]. In 2015, an estimated 16980 new esophageal cancer cases will occur and 15590 cases will eventually die of their disease in the United States [2]. However, it is more common in the developing nations and is the fourth cause of cancer deaths [1]. Despite advances in surgical treatment and chemotherapy, its prognosis remains poor, mainly because most tumours are diagnosed late either locally advanced or metastatic stages which lost the opportunities of radical surgery for the early stage. CROSS study and MAGIC trial have shown that neoadjuvant therapy significantly enhanced local control, increased resectability rate, and improved disease-free survival in patients with resectable esophageal and esophagogastric cancere [3, 4]. However, in these studies, only those patients who responded to neoadjuvant therapy with tolerable toxicity would potentially benefit from this approach, while a part of patients failed to respond to neoadjuvant therapy, or even progressed during therapy. It is therefore imperative to investigate the predictive markers to identify those individuals who would benefit from neoadjuvant therapy.

As the most studied gene, p53 may be the most suitable biomarker for predicting the response to neoadjuvant therapy [5]. P53, a tumor-sup-

pressor gene, has central cellular functions in regulating cell cycle, repairing cellular DNA and triggering apoptosis after cellular DNA is injured [6, 7]. P53 is the most frequently mutated gene in human cancer, with mutations occurring in at least 50% of human cancers, which plays a critical role in the process of development of human cancer [8]. Experimental evidence indicates that p53 plays a vital role in tumor apoptosis in response to genotoxic agents [9-11].

However, it is inconsistent that the research results for the use of p53 status as a biological marker to predict the response of esophageal cancer to neoadjuvant therapy. Some studies found that patients with wild-type form of p53 status often had a higher response rate to chemotherapy than those with mutant-form of p53 status [12-18]. Other studies, however, drew different conclusions [19-24]. Zhang conducted a meta-analysis and found that wild-type form of p53 status was associated with high response to chemotherapy-based treatment in esophageal cancer [25]. However, the correlation of p53 status with the response to neoadjuvant therapy was not analyzed in detail. Therefore, we proceeded with this meta-analysis with larger sample size specifically to assess p53 status as a Biomaker to predict the response of esophageal cancer to neoadjuvant therapy.

Materials and methods

Publication search

Using the following search terms: 'TP53', 'p53', 'p53 protein', 'p53 mutation', '17p13 gene', 'chemoradiotherapy', 'chemotherapy', 'neoadjuvant', 'preoperative' and 'esophageal cancer', studies were identified by a computerized search of the PubMed, Embase, and Web of Science databases (last search up to January 2016). All potentially eligible studies were retrieved and their references were carefully reviewed to identify other eligible studies. If multiple studies of the same patient population were identified, we included the published report with the largest sample size.

Inclusion and exclusion criteria

Studies included in this meta-analysis should suit all of the following features: (a) evaluation of p53 status for predicting the response to neoadjuvant therapy in esophageal cancer, (b) description clinical or pathological therapeutic response, (c) retrospective or prospective cohort study, (d) inclusion of adequate data to allow the estimation of a risk ratio (RR) with 95% confidence intervals (95% CI), and (e) only studies published in English language. Reviews, letters to the editor, and articles published in books were excluded.

Data extraction and definitions

The following information was extracted from each study: the first author's surname, publication year, country of origin, cases of patients analyzed, treatment, chemotherapy regimen, methods of detection of p53, p53 positive (overexpression or mutation) rate, type of therapeutic response, response criteria, and the response rate. Data was entered in tables showing the clinical or pathological response to neoadjuvant therapy with respect to p53 status. Data was carefully and independently extracted from all eligible publications by two reviewers (Haiyuan Xu and Xiangrong Lu). Any disagreement between the reviewers was resolved by discussions until a consensus was reached. A third reviewer (Zhaoliang Su) was employed to resolve the discrepancies when they failed to reach an agreement.

The definitions and standardizations for 'p53' and 'response to neoadjuvant therapy' we used were in the light of the study reported by Pakos et al. [26]. For consistency, we used 'p53 status' to refer to both the gene and protein markers. Mutation-type form of p53 status means patients with high expression of p53 protein and/or mutant p53 gene. Wild-type form of p53 status means patients with low expression of p53 protein and/or normal p53 gene. Response was defined as grade 3 or complete response (CR), grade 1b+2 or grade 2 or partial response (PR), or major response (MR) (MR = grade 3+ grade 1b+2 or MR = CR+PR), according to the guidelines for the clinical and pathologic studies on carcinoma of the gastric by JSED (the Japanese Society for Esophageal Disease), WHO (World Health Organization) or RECIST (Response Evaluation Criteria in Solid Tumors) criteria [27-30]. For consistency, we defined the response classification in **Table 1** [31].

Statistical analysis

STATA version 12 (StataCorp, College Station, TX) was applied to perform the data analysis.

Table 1. Criteria for response evaluation and standard definition

Criteria	Standard definition		
	Minor response	Major response	Complete response
WHO [29]	NC+PD, <50% decrease in tumor load	PR+CR, >50% decrease in tumor load	CR, disappearance of all known disease
RECIST [30]	PD+SD, <30% regression of the disease	PR+CR, >30% regression of the disease	CR, 100% regression of the disease
JSED [27, 28]	PD+SD, Grade 0+1, viable cancer cells account for more than 1/3	PR, Grade 2+3, viable cancer cells account for less than 1/3	CR, Grade 3, no residual viable tumor cells
Beardsmore et al. [17]	No response, absence of tumor dowstaging	PR+CR, evidence of downstaging	CR, absence of tumor in resected specimen
Nasierowska et al. [32]	PR2+SD	PR1+CR, single cells or small nests of cancer cells or no cancer cells	CR, no microscopic evidence of cancer cells
Miyata et al. [13]	RR, Residual viable cancer cells	SR, no residual cancer cells	SR, no residual cancer cells
Sarbia et al. [33]	PD+NC, PD: increasing tumor diameter assessed by CT; NC: <50% regression of tumor extension, and no progression	CR+PR, >50% reduction assessed by CT	Normal barium esophagogram, no visible tumor by esophagoscopy, biopsies free of tumor tissue, and normal CT
Yang et al. [34]	ORT, grossly residual tumor and/or residual tumor in 2 or more tissue blocks	NRT+MRT, absence of tumor either grossly or microscopically	NRT, absence of tumor both grossly and microscopically

WHO World Health Organization, RECIST Response Evaluation Criteria in Solid Tumors, JSED Japanese Society for Esophageal Disease, CR complete response, PR partial response, PD progressive disease, SD stable disease, NR no record, NC no change.

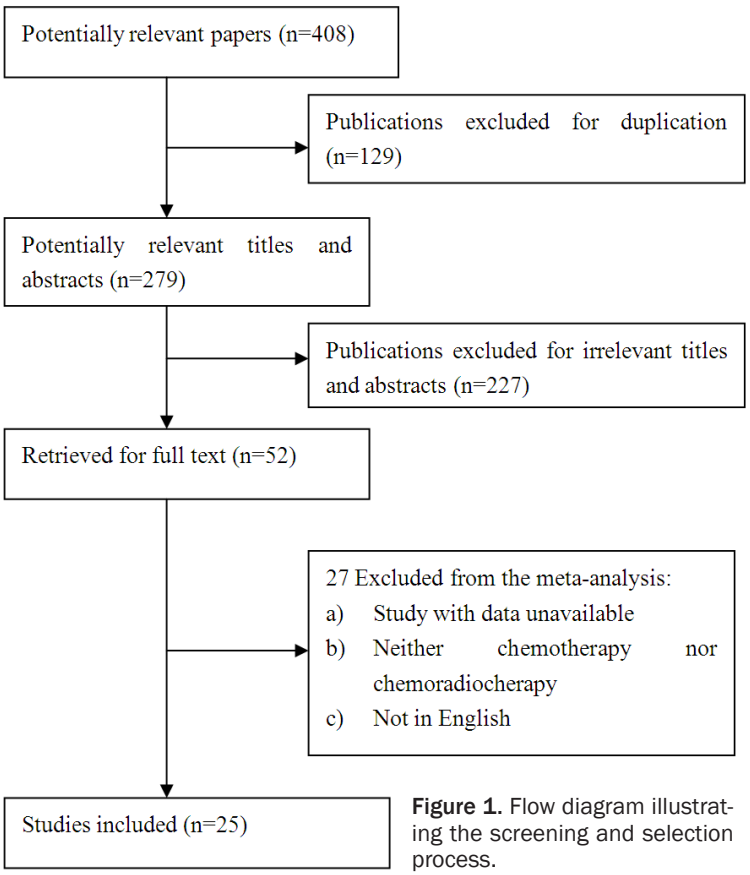

Figure 1. Flow diagram illustrating the screening and selection process.

The statistical heterogeneity for each pooled estimate was assessed and quantified by the Q test and the I^2 statistic. According to the heterogeneity, the pooled RR was calculated using a random-effects model (the DerSimonian and Laird method) or a fixed-effects model (the Mantel-Haenszel method). Pooled analysis was performed using the Mantel-Haenszel model and reported as risk ratio (RR) with 95% CIs. The significance of the pooled RR was determined by the z test. P<0.05 was considered to be statistically significant. The potential publication bias was estimated by the Begg's funnel plot and Egger's test. We also performed sensitivity analysis by omitting each study or specific studies to find potential outliers.

Results

Eligible studies

On the basis of different combinations of key terms, 408 studies were identified by literature search. As the search flow diagram (**Figure 1**) demonstrated, 25 studies and a total of 1238 patients were finally included in our analysis. The main characteristics and response rates to neoadjuvant therapy of the included studies are shown in **Table 2**. Among the included 25 studies, 17 neoadjuvant chemoradiotherapy (NCRT), 6 used neoadjuvant chemotherpay (NCT), 1 consisted of both NCRT and NCT, and 1 study contained NCRT, NCT and neoadjuvant radiotherapy (NRT). The sample sizes in all the eligible studies ranged from 18-107 patients (median = 41 patients, mean = 49 patients, standard deviation [SD] = 2.43). 18 studies were done in Asian populations (902 patients), 2 in American populations (117 patients), 1 in Oceanian populations (36 patients), and other 5 studies were in European populations (179 patients).

Evidence synthesis

Among the studies of esophageal cancer patients undergoing neoadjuvant therapy, 25 studies encompassing 1234 patients contributed data on total OR (clinical OR+pathological OR). Wild-type form of p53 status was significantly associated with improved total OR among patients undergoing neoadjuvant therapy (RR = 1.306; 95% CI = 1.131-1.507; P<0.001, **Figure 2**). 3 studies used both clinical and pathological response, the later data was adopted, but also examined the clinical response data and found similar results (data not shown). As most studies employed protein detection with immunohistochemistry (IHC), only 1 study used gene detection, 1 study employed both IHC and gene detection, we adopted the data of the detection of IHC method, and also conducted a statistical analysis for these gene detection results and found similar results (data not shown).

Subgroup analysis

Among the 25 studies, 18 studies used NCRT and 7 studies used NCT, we also have these data for statistical analysis respectively, and found that wild-type form of the p53 status was associated with improved response to NCRT

Table 2. Characteristics of studies included in the meta-analysis

Author	Year	Country	Cases	Pathology	Treatment	Detection	p53 (%)	Response	Response criteria	Standard definition response			Response rate (%)	
										Minor response	Major response	Complete response	Major response	Complete response
Kandioler et al. [18]	2014	Australia	36	SCC+AC	NCT	Gene	50	pathologic	RECIST	PD+SD	PR	CR	50	8
Arsenijevic et al. [23]	2012	Serbia	41	SCC	NCRT	IHC	85	clinical	RECIST	PD+SD	PR	CR	44	7
Yamamoto et al. [22]	2012	Japan	37	SCC	NCT	IHC	49	pathologic	JSED	G0+1	G2+3	NR	41	NR
								clinical	RECIST	PD+SD	PR+CR	NR	65	NR
Makino et al. [35]	2010	Japan	64	SCC	NCRT	IHC	66	pathologic	JSED	G0+1	G2+3	NR		NR
						gene	31							
Sarbia et al. [36]	2007	Japan	90	SCC	NCRT	IHC	78	clinical	WHO	NC+PD	PR+CR	NR	54	NR
								pathologic		>10% residual tumor cells	<10% residual tumor cells	NR	64	NR
Ishida et al. [37]	2007	Japan	32	SCC	NCRT	IHC	53	pathologic	JSED	G1+2	G3	G3		38
Sunada et al. [38]	2005	Japan	36	SCC	NCRT	IHC	58	clinical	WHO	NC+PD	PR	NR	69	NR
Okumura et al. [39]	2005	Japan	62	SCC	NCRT	IHC	44	clinical	JSED	NC+PD	PR+CR	CR	71	2
								pathologic					53	22
Heeren et al. [24]	2004	Netherlands	30	AC	NCT	IHC	73	clinical	WHO	NC+PD	PR+CR	NR	28	NR
Kishi et al. [21]	2003	Japan	107	SCC	NCT	IHC	70	clinical	RECIST	PD+SD	PR+CR	NR	62	NR
								pathologic	JSED	G0+1a	G1b+2	NR	27	NR
Beardsmore et al. [17]	2003	UK	48	SCC+AC	NCRT+NCT	IHC	71	clinical	Beardsmore et al.	No response	PR+CR	NR	69	3
								pathologic						
Takeuchi et al. [12]	2003	Japan	41	SCC	NCRT	IHC	56	clinical	JSED	NC+PD	PR+CR	NR	71	NR
Kajiyama et al. [19]	2002	Japan	22	SCC	NCRT	IHC	68	pathologic	JSED	G0+1	G2+3	NR	86	NR
			60		NCT		58	pathologic	JSED	G0+1	G2+3	NR	10	NR
Shimada et al. [20]	2002	Japan	52	SCC	NCRT	IHC	58	clinical	JSED	NC+PD	CR+PR	NR	69	NR
Kishi et al. [15]	2002	Japan	77	SCC	NCRT	IHC	61	pathologic	JSED	G0+1	G2+3	G3	47	25
Takeno et al. [40]	2001	Japan	34	SCC	NCRT	IHC	29	pathologic	JSED	G0+1	G2+3	G3	41	9
Szumilo et al. [41]	2000	Japan	34	SCC	NCT	IHC	68	pathologic	Nasierowka et al.	PR2+SD	PR1+CR	NR	24	NR
Shimada et al. [16]	2000	Japan	59	SCC	NCT	IHC	44	pathologic	JSED	G0+1a	G1b+2	NR	15	NR
Miyata et al. [13]	2000	Japan	47	SCC+AC	NCRT	IHC	72	pathologic	Miyata et al.	NR		CR		30
Krasna et al. [14]	1999	USA	22	SCC+AC	NCRT	IHC	77	pathologic	CR	NR	CR	CR		36
Yamamoto et al. [42]	1999	Japan	30	SCC	NCRT	IHC	50	pathologic	JSED	G0+1	G2+3	NR	63	NR
Yang et al. [34]	1999	USA	64	AC	NCRT	IHC	72	pathologic	Yang et al.	ORT	NRT+MRT	NRT	36	NR
			31	SCC										
Sarbia et al. [33]	1998	Germany	38	SCC	NCRT	IHC	53	clinical	CR	NC+PD	PR+CR	NR	42	NR
Puglisi et al. [43]	1996	Italy	22	SCC	NCRT	IHC	77	pathologic	CR	NR	CR	CR		55
Muro et al. [44]	1996	Japan	18	SCC	NCRT	IHC	56	clinical	CR	NR	CR	CR		50

SCC squamous cell carcinoma, AC adenocarcinoma, NCT neoadjuvant chemotherapy, NCRT neoadjuvant chemoradiotherapy, IHC immunohistochemistry, WHO World Health Organization, RECIST Response Evaluation Criteria in Solid Tumors, JSED Japanese Society for Esophageal Disease, CR complete response, PR partial response, PD progressive disease, SD stable disease, NR no record, NC no change.

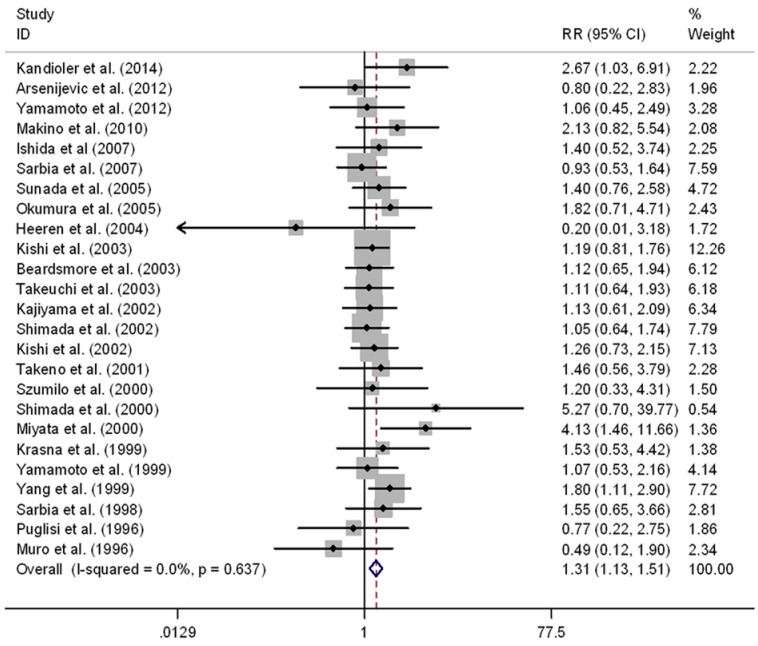

Figure 2. Forest plots of RR were estimated for association between p53 status and good response among esophageal cancer patients treated with neoadjuvant therapy.

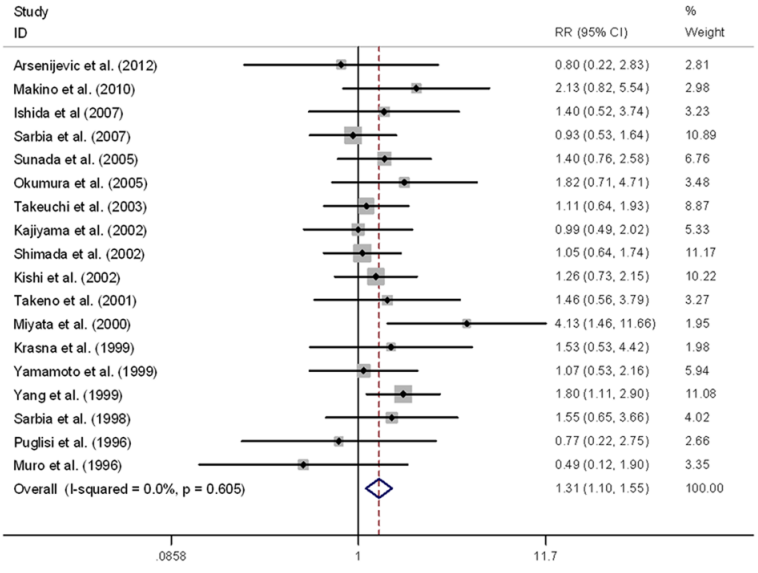

Figure 3. Forest plots of RR were estimated for association between p53 status and good response among esophageal cancer patients treated with NCRT.

(RR = 1.308, 95% CI = 1.104-1.551, P = 0.002, **Figure 3**) and NCT (RR = 1.436, 95% CI = 1.052-1.960, P = 0.023, **Figure 4**). Ten of the studies supplied complete response data. We found that patients with wild-type form of p53 status had high complete response rate to neoadjuvant therapy (RR = 1.844, 95% CI = 1.262-2.694, P = 0.002, **Figure 5**). In the studies that histopathology revealed squamous cell carcinoma, we found that wild-type form of p53 status had improved response rate to neoadjuvant therapy (RR = 1.194, 95% CI = 1.109-1.398, P = 0.028). 17 studies were conducted in Asian populations (902 patients), whereas 5 studies were conducted in European populations (179 patients). The results of the Asian subgroup and the European subgroup were therefore calculated separately (**Table 3**). Wild-type forms of p53 status was associated with improved response in esophageal cancer patients who received neoadjuvant therapy in Asian subgroup (RR = 1.268; 95% CI = 1.074-1.499; P = 0.005, **Figure 6**). In European subgroup, however, patients with wild-type form of p53 status trended to have a high response rate to neoadjuvant therapy, but did not reach statistical significance (RR = 1.005, 95% CI = 0.667-1.515, P = 0.981).

Publication bias and sensitivity analysis

Both Begg's funnel plot and Egger's test were performed to assess the potential publication bias of the included literatures. The shapes of the funnel plots indicated no evidence of obvious asymmetry (**Figure 7**), and Egger's test showed the absence of publication bias (P>0.05). Furthermore, sensitivity analysis was conducted to evaluate the influence of each study on the summary effect. No individual study dominated this meta-analysis, and the removal of any single study had no significant effect on the overall results (data not shown).

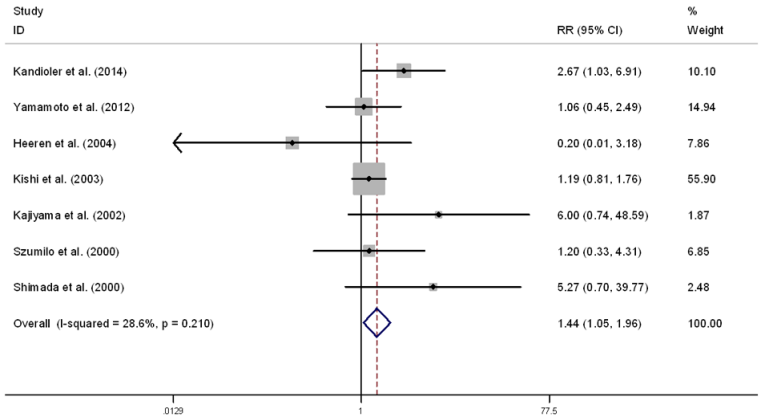

Figure 4. Forest plots of RR were estimated for association between p53 status and good response among esophageal cancer patients treated with NCT.

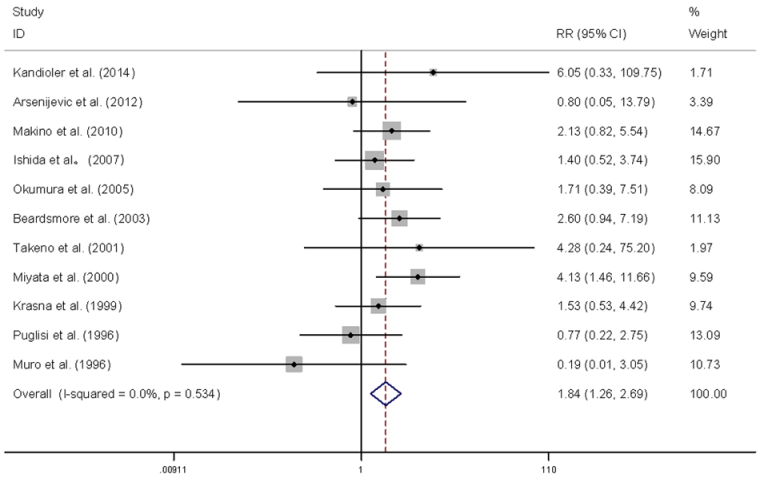

Figure 5. Forest plots of RR were estimated for association between p53 status and complete response among esophageal cancer patients treated with neoadjuvant therapy.

Discussion

Studies have shown that p53 status play a key role in the response to a large panel of anticancer drugs and radiation-based therapy. However, the conclusion is inconsistent that p53 mutation might be either sensitive or resistant to neoadjuvant therapy in patients with esophageal cancer, because most of the available clinical reports involved small sample sizes, and the results were therefore unable to determine the value of p53 status for predicting the response to neoadjuvant therapy. Thus, we supposed that a meta-analysis might be the best way to evaluate the association between p53 status and the response to neoadjuvant therapy in a large population with esophageal cancer.

The present meta-analysis of 25 studies systematically estimated the relationship between p53 status and response to neoadjuvant therapy in a large population. The results showed that wild-type form of p53 status may predict the good response rate to neoadjuvant therapy in patients with esophageal cancer. The wild-type form of p53 status was associated with improved total OR. Stratification according to different population indicated that wild-type form of p53 status was significantly associated with increased OR in Asian population. And with respect to the NCRT and NCT respectively, results showed there were good response rate in patients with the wild-type form of p53 status. Significant association was also found in patients with the wild-type form of p53 status and high complete response rate to neoadjuvant therapy.

However, despite our attempts to perform a comprehensive analysis, there were still some limitations of this meta-analysis. First, selection bias might occur because only studies published in English language were included in our meta-analysis, and we did not search conference proceedings and abstract books. Second, the evaluation criterion of response to treatment among the studies was of a great difference and variety. Standardization is therefore of great importance for obtaining an accurate assessment of the clinical significance of p53 status. Despite of our considerable efforts to standardize definitions, some variability among studies was inevitable. Third, different regimens of treatment were employed among these studies and the dose of chemotherapy or

Table 3. Risk ratio for the association between wild-form of p53 status and good response to chemotherapy

	N	RR (95% CI)	z	P	χ^2	Ph
Response						
All studies	25	1.306 (1.131-1.507)	3.64	0.000	21.03	0.637
CR	11	1.844 (1.262-2.694)	3.16	0.002	8.98	0.534
Treatment						
NCRT	18	1.308 (1.104-1.551)	3.10	0.002	14.87	0.605
NCT	7	1.436 (1.052-1.960)	2.28	0.023	8.40	0.210
Area						
Asian	17	1.268 (1.074-1.499)	2.80	0.005	13.26	0.654
European	5	1.005 (0.667-1.515)	0.02	0.981	2.71	0.607
Type of measurement						
IHC	24	1.267 (1.103-1.455)	2.34	0.001	19.28	0.685
IHC+gene	23+2	1.307 (1.138-1.502)	3.78	0.000	22.93	0.524
Type of pathology						
SCC	20	1.194 (1.019-1.398)	2.19	0.028	9.26	0.969

Subgroup analysis was performed when at least five studies were in a subgroup. N, number of studies; z, the test statistics of z test; P, *p* value of the z test; χ^2, the test statistics of I^2 statistic for heterogeneity; Ph, *p* value of the I^2 statistic.

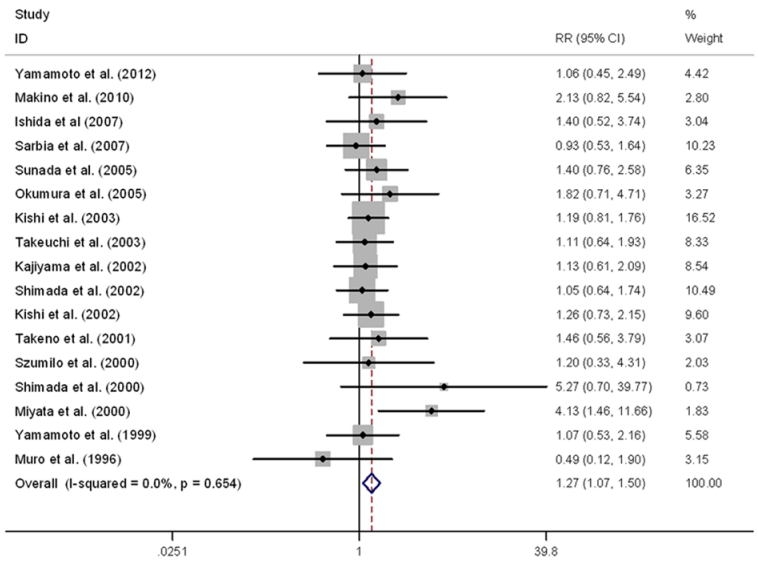

Figure 6. Forest plots of RR were estimated for association between p53 status and good response to neoadjuvant treatment in Asian population with esophageal cancer.

radiation and courses of treatment were variable. Forth, the sample size is relatively small. Especially, the stratified studies regarding Asians and Europeans might have in sufficient statistical power to expound the real association.

Despite the limitations above, compared to the previously published meta-analysis, our study has the following highlight: (1) this meta-analysis is the first meta-analysis specialized in evaluating the usefulness of p53 status for predicting the response of esophageal cancer patients to neoadjuvant therapy, (2) the sample size is relatively larger and provides more potent statistical power in comparison to other relevant meta-analysis, (3) has included the latest studies to increase coverage and minimize selection bias, (4) our data indicated that p53 status might be a useful predictive biomarker for evaluating response to neoadjuvant therapy in esophageal cancer patients, especially in Asian population. However, future prospective studies with larger sample sizes and better study designs are required to evaluate the predictive role of p53 status in clinical practice.

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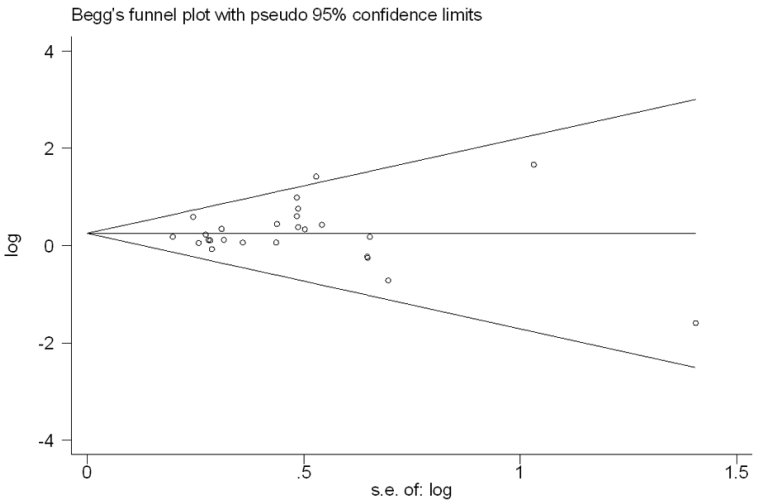

Figure 7. The funnel plot showed that there was no obvious indication of publication bias for the outcome of good response setting.

design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

Authors' contribution

HY-X, ZL-S, XR-L contributed to the conception and design of the study, the analysis and interpretation of data, the revision of the article as well as final approval of the version to be submitted. MB-C, XL, ZY-J participated in the design of the study, performed the statistical analysis, searched and selected the trials, drafted and revised the article. All authors read and approved the final version of the manuscript.

Abbreviations

CI, Confidence interval; IHC, Immunohistochemistry; RR, Relative risk; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; JSED, Japanese Society for Esophageal Disease; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; NR, no record; NC, no change; SCC, squamous cell carcinoma; AC, adenocarcinoma; NCT, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy.

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