Prognostic value of circulating tumor cells in esophageal cancer

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Abstract

AIM

To perform a meta-analysis of the related studies to assess whether circulating tumor cells (CTCs) can be used as a prognostic marker of esophageal cancer.

METHODS

PubMed, Embase, Cochrane Library and references in relevant studies were searched to assess the prognostic relevance of CTCs in patients with esophageal cancer. The primary outcome assessed was overall survival (OS). The meta-analysis was performed using the random effects model, with hazard ratio (HR), risk ratio (RR) and 95% confidence intervals (95%CIs) as effect measures.

RESULTS

Nine eligible studies were included involving a total of 911 esophageal cancer patients. Overall analyses revealed that CTCs-positivity predicted disease progression (HR = 2.77, 95%CI: 1.75-4.40, $P < 0.0001$) and reduced OS (HR = 2.67, 95%CI: 1.99-3.58, $P < 0.00001$). Further subgroup analyses demonstrated that CTCs-positive patients also had poor OS in different subsets. Moreover, CTCs-positivity was also significantly associated with TNM stage (RR = 1.48, 95%CI: 1.07-2.06, $P = 0.02$) and T stage (RR = 1.44, 95%CI: 1.13-1.84, $P = 0.003$) in esophageal cancer.

CONCLUSION

Detection of CTCs at baseline indicates poor prognosis in patients with esophageal cancer. However, this finding relies on data from observational studies and is potentially subject to selection bias. Prospective trials are warranted.

Core tip: The clinical validity of circulating tumor cells (CTCs) is still controversial and inconclusive in patients with esophageal cancer. Our meta-analysis provides strong evidence that detection of CTCs in peripheral blood at baseline is an independent prognosticator of poor survival outcomes in esophageal cancer patients.

INTRODUCTION

Esophageal cancer (EC) is the eighth most common malignant tumor worldwide[1] and is the sixth leading cause of cancer death[2]. However, the early diagnosis of EC is difficult due to the lack of specific symptoms in the early stages. In most cases, the disease is already at an advanced stage at presentation. EC ranks fourth among cancer-related deaths in China[3]. Surgical resection is the main treatment for EC, with a postoperative 5-year survival rate of only 34%-36%[2]. New treatment strategies including neoadjuvant radiochemotherapy[4,5], preoperative neoadjuvant chemotherapy[6,7], and three-field lymph node dissection[8] are helpful for improving the 5-year survival rate of EC patients. However, the outcomes are still unsatisfactory, and many patients die of local recurrence and distant metastasis[9]. Therefore, biomarkers which can be used to identify the recurrence or metastasis of EC are needed to facilitate timely diagnosis and treatment strategies and thus improve the prognosis of EC patients.

In the early stage of EC metastasis or recurrence, the clinical manifestations are occult and cannot be effectively predicted by routine laboratory tests. In recent years, circulating tumor cells (CTCs) have been recognized as the cause of tumor metastasis or recurrence[10,11]. CTCs are the cells that are shed from a primary or metastatic tumor into the peripheral circulation. Most CTCs will be cleared by the human immune system, whereas a small number of surviving CTCs can reach other parts of the body via the bloodstream, resulting in tumor metastasis[12]. CTCs can remain non-proliferative for a long period of time and can resist the anti-tumor effect of chemotherapy drugs[13,14]. At present, many studies on the correlations between CTC positivity and the prognoses of breast cancer[15], colorectal cancer[16],

gastric cancer[17], and lung cancer[18] have shown that CTCs-positivity can indicate poor prognosis.

Although many studies have demonstrated the relationship between CTCs and the prognosis and clinicopathological features of EC, their findings had certain limitations due to differences in CTC detection methods and EC treatment strategies. In addition, the role of CTC detection before surgical or non-surgical treatment in EC patients remains unclear. Therefore, in this meta-analysis, we summarized and analyzed the prognostic value of CTCs in EC patients before and after treatment in a quantitative and comprehensive manner.

MATERIALS AND METHODS

Literature search and selection criteria

A literature search of related studies was conducted using the PubMed, Embase, and Cochrane Library databases. The following search terms were used: (1) "circulating tumor cells" or "CTCs"; (2) "esophageal cancer" using MeSH or free words; and (3) a combination of (1) and (2). The last search was conducted on November 17, 2016.

Two authors, Xu HT and Miao J, independently retrieved the titles and abstracts of the primary studies identified in the electronic search. In addition, references of potentially relevant studies were examined. Duplicate studies were excluded.

The inclusion criteria were as follows: (1) population: patients with esophageal cancer; (2) intervention: CTCs-positivity; (3) comparison: CTCs-negativity; (4) outcome: the primary outcome assessed was overall survival (OS), and clinicopathological characteristics and other prognostic outcomes were assessed as secondary outcomes; (5) design: randomized controlled trials (RCTs) or observational studies; (6) samples used in these studies should be collected from peripheral blood (PB) and at baseline; and (7) sufficient data to calculate hazard ratio (HR) or risk ratio (RR) with 95% confidence intervals (95%CIs) as comparable effect estimates.

Exclusion criteria included the following: (1) review articles, letters, comments and case reports; and (2) studies where it was impossible to retrieve or calculate data of interest.

Data extraction and quality assessment

Data extraction was performed by Xu HT and Miao J independently. The following information was extracted from each study: (1) first author, year of publication, country and study type; (2) number and characteristics of patients in both the CTCs positivity and negativity groups; and (3) outcome data including follow-up period, OS and other prognostic outcomes such as disease-free survival (DFS) or progression-free survival (PFS) or relapse-free survival (RFS).

All relevant texts, tables and figures were reviewed for data extraction, and entered into an Excel file.
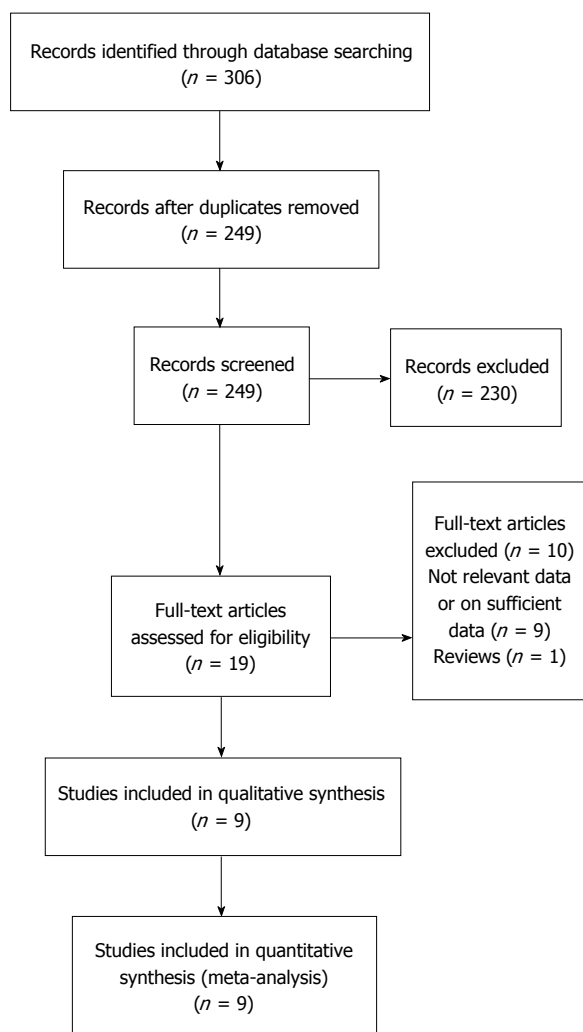
Records identified through database searching
(*n* = 306)

Records after duplicates removed
(*n* = 249)

Records screened
(*n* = 249)

Records excluded
(*n* = 230)

Full-text articles
assessed for eligibility
(*n* = 19)

Full-text articles
excluded (*n* = 10)
Not relevant data
or on sufficient
data (*n* = 9)
Reviews (*n* = 1)

Studies included in qualitative synthesis
(*n* = 9)

Studies included in quantitative
synthesis (meta-analysis)
(*n* = 9)

Figure 1 Selection process for studies included in the meta-analysis.

Furthermore, we included only the most recent or complete studies to avoid duplication of information. Discrepancies between the two reviewers were resolved by discussion and consensus.

The Cochrane risk of bias tool was adopted to assess the risk of bias in RCTs[19]. Observational studies were evaluated using the Newcastle-Ottawa Scale[20].

Statistical analysis

Analyses were performed using Cochrane RevMan 5.3. For time-to-event data, HR and 95%CIs were obtained directly or indirectly from studies according to the method described by Tierney[21]. RR was used to compare dichotomous variables. Heterogeneity was tested using the I^2 statistic. Studies with an I^2 statistic of 0%, 25%, 50% and 75% represented no, low, moderate and high heterogeneity[22,23]. The random effect models were used for the analysis, as this model can obtain more conservative results and better fit the multi-center clinical studies due to the existence of heterogeneity[24]. The Generic Inverse Variance method was used to calculate pooled HRs and 95%CIs. The Mantel-Haenszel method was used to calculate pooled

RRs and 95%CIs.

Moreover, a sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results. Visual inspection of the funnel plot was carried out to assess publication bias.

In addition, subgroup analyses of the studies were conducted according to region (Asia *vs* non-Asia), curative method (surgery *vs* non-surgery), and method used to detect CTCs (CellSearch *vs* RT-PCR *vs* other methods). The subgroup analyses were performed only for OS.

RESULTS

Study selection

A total of 306 studies were identified from the initial database search. Fifty-seven studies were excluded due to duplicates, and 230 studies were excluded for various reasons based on the titles and abstracts (reviews, case reports, or clearly irrelevant to the analysis). Ten studies were excluded due to reviews or the lack of an outcome of interest. In total, 9 studies were included in the meta-analysis[25-33]. The selection process is shown in Figure 1.

Study characteristics

The main characteristics of the included studies are shown in Table 1. The studies were conducted in three countries (China, Japan and Germany) and published between 2009 and 2016. Of the included studies, none were RCTs, 5 were prospective cohort studies[25,27-29,31], and 4 were cohort studies[25,30,32,33]. The sample size ranged from 38 to 244 (CTCs-positive group, *n* = 336; CTCs-negative group, *n* = 575). All studies assessed CTCs at baseline. Of the 9 studies, 7 studies contained data on clinicopathological characteristics[26-31,33], 8 had HRs for OS[25-29,31-33], 2 had HRs for PFS[25,30], 2 had HRs for DFS[26,31], and 2 had HRs for RFS[27,33].

Quality assessment

Assessment of risk of bias in the studies is shown in Table 2. Based on the Newcastle-Ottawa Scale to assess the risk of bias in cohort studies, 7 studies were rated as having a total score of > 5[25-29,31,32], and 2 as having a score of ⩽ 5, indicating a high risk of bias[30,33].

Correlation between CTCs and OS

The HRs for OS were available in 8 studies[25-29,31-33], including 779 EC patients. The pooled results showed that CTCs-positive EC patients had significantly poorer OS than CTCs-negative patients (HR = 2.67, 95%CI: 1.99-3.58, *P* < 0.00001), and heterogeneity was statistically nonsignificant (I^2 = 14%, *P* = 0.32) (Figure 2).

We performed subgroup analyses to further assess whether CTCs status had prognostic value in different subsets (Table 3). We first evaluated the effects of CTCs status on OS regarding region and found that

Table 1 Characteristics of the included studies

Ref.	Country	Study design	Number (M/F)	Age, yr (range)	Population	Detection method	Sample time	Rate% (n/N)[1]	Cut-off criteria	Curative method	Follow-up	Outcome
Li et al[26], 2016	China	Cohort	140 (117/23)	62.8 ± 8.5 (36-78)	ESCC	Fluorescent IHC	Baseline	44 (62/140)	> 2/5 mL	Surgery	3 yr	OS, DFS
Su et al[25], 2016	China	Prospective cohort	57 (55/2)	54 (36-78)	EC	Flow cytometry	Baseline	50 (29/57)	≥ 21/mL	CCRT	3 yr	OS, PFS
Reeh et al[27], 2015	Germany	Prospective cohort	100 (77/23)	66 (32-85)	EC	CellSearch	Baseline	18 (18/100)	≥ 1/7.5 mL	Surgery	37.5 mo (median)	OS, RFS
Matsushita et al[28], 2015	Japan	Prospective cohort	90 (78/12)	65 (46-98)	ESCC	CellSearch	Baseline and after treatment	27 (25/90)	≥ 1/7.5 mL	Chemotherapy or CRT	10.3 mo (median), range 0.3-36.4 mo	OS
Tanaka et al[29], 2015	Japan	Prospective cohort	38 (30/8)	63 (43-87)	EC	CellSearch	Baseline and after treatment	50 (19/38)	≥ 2/7.5 mL	Chemotherapy or CRT	19 mo (median)	OS
Yin et al[30], 2012	China	Cohort	72 (54/18)	63 (46-83)	ESCC	RT-PCR	Baseline and after treatment	69 (50/72)	Expression of any one of CEA, CK19, survivin	Radiotherapy	2 yr	PFS
Tanaka et al[31], 2010	Japan	Prospective cohort	244 (212/32)	64 (NR)	ESCC	RT-PCR	Baseline and after treatment	13 (34/244)	Expression of any one of CEA, SCCA	Surgery	24.3 mo (median)	OS, DFS
Hoffmann et al[32], 2010	Germany	Cohort	62 (53/9)	61 (NR)	EC	RT-PCR	Baseline	77 (48/62)	Expression of survivin	Surgery	3 yr (median)	OS
Gao et al[33], 2009[2]	China	Cohort	108 (85/23)	58.9 (36-82)	ESCC	RT-PCR	Baseline	47 (51/108)	Expression of survivin	Surgery	19.5 mo (median), range, 1-33 mo	OS, RFS

[1]Positive CTCs at baseline; [2]Only 48 patients were available for follow-up. M/F: Male/Female; ESCC: Esophageal squamous cell carcinoma; EC: Esophageal cancer; IHC: Immunohistochemistry; CCRT: Concurrent chemoradiotherapy; CRT: Chemoradiotherapy; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; RFS: Relapse-free survival; CEA: Carcinoembryonic antigen; CK19: Cytokeratin 19; SCCA: Squamous cell carcinoma antigen.

for both Asians and non-Asians, detection of CTCs predicted a poor prognosis (Asian: HR = 2.46, 95%CI: 1.77-3.40, I^2 = 14%, P < 0.00001; non-Asian: HR = 3.74, 95%CI: 1.98-7.05, I^2 = 0%, P < 0.0001). We then determined the effects of CTCs status on OS with regard to curative method and discovered that for both surgery and non-surgery, detection of CTCs at baseline indicated an increased risk of poor prognosis (surgery: HR = 2.81, 95%CI: 1.72-4.58, I^2 = 50%, P < 0.0001; non-surgery: HR = 2.70, 95%CI: 1.70-4.30, I^2 = 0%, P < 0.0001). We also assessed the effects of CTCs status on OS with regard to detection method and found that CTCs detection by CellSearch or RT-PCR or other methods indicated a worse prognosis (CellSearch: HR = 2.91, 95%CI: 1.78-4.74, I^2 = 0%, P < 0.0001; RT-PCR: HR = 3.44, 95%CI: 1.42-8.34, I^2 = 70%, P = 0.006; other methods: HR = 2.22, 95%CI: 1.38-3.58, I^2 = 0%, P = 0.001). In addition, the stratified results showed that compared to CTCs-negative patients, CTCs-positive patients had a higher risk for poor OS in these subgroups.

The funnel plot did not show obvious asymmetry (Figure 3). Therefore, no significant publication bias was observed.

Correlation between CTCs and disease progression (DFS, RFS and PFS)

The HRs for disease progression (DFS, RFS and PFS) were available in 6 studies[25-27,30,31,33], involving 661 EC patients. The overall analysis revealed that compared with CTCs-negative EC patients, the CTCs-positive patients had a higher risk of disease progression (HR = 2.77, 95%CI: 1.75-4.40, I^2 = 55%, P < 0.0001) (Figure 4). Sensitivity analyses confirmed the stability of our results, and indicated that our results were not obviously affected or dominated by a single study.

Correlation between CTCs and clinicopathological characteristics

Six studies reported the relationship between CTCs status and TNM stage[26,27,29-31,33]. Pooled analysis showed that CTCs-positivity in stage Ⅲ and Ⅳ was greater than that in Ⅰ and Ⅱ (RR = 1.48, 95%CI: 1.07-2.06, I^2 = 47%, P = 0.02) as shown in Figure 5A. Studies assessed by pooled analysis showed a significant association
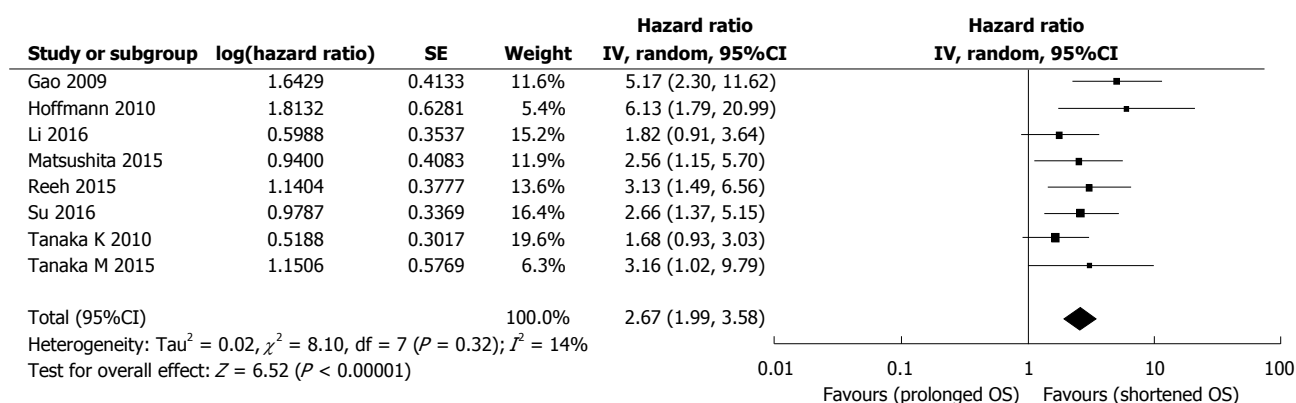
Table 2 Assessment of the risk of bias in each cohort study using the Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Li *et al*[26], 2016	NS	S	S	S	NS	S	S	S	6
Su *et al*[25], 2016	S	S	S	S	NS	S	S	S	7
Reeh *et al*[27], 2015	S	S	S	S	NS	S	S	S	7
Matsushita *et al*[28], 2015	NS	S	S	S	NS	S	S	S	6
Tanaka *et al*[29], 2015	S	S	S	S	NS	S	NS	S	6
Yin *et al*[30], 2012	NS	S	S	S	NS	S	NS	S	5
Tanaka *et al*[31], 2010	NS	S	S	S	NS	S	S	S	6
Hoffmann *et al*[32], 2010	S	S	S	S	NS	S	S	S	7
Gao *et al*[33], 2009	NS	S	S	S	NS	S	NS	NS	4

A higher overall score corresponds to a lower risk of bias; a score of ≤ 5 (out of 9) indicates a high risk of bias. S: The study is satisfied the item; NS: The study is not satisfied the item.

Table 3 Subgroup analyses of the effects of circulating tumor cells on overall survival in esophageal cancer patients

	No. of studies	No. of patients	HR (95%CI)	*P* value	Heterogeneity	
					I^2	*P* value
Region						
Asia	6	637	2.46 (1.77-3.40)	< 0.00001	14%	0.33
Non-Asia	2	162	3.74 (1.98-7.05)	< 0.0001	0%	0.36
Curative method						
Surgery	5	594	2.81 (1.72-4.58)	< 0.0001	50%	0.09
Non-surgery	3	185	2.70 (1.70-4.30)	< 0.0001	0%	0.95
Detection method						
CellSearch	3	228	2.91 (1.78-4.74)	< 0.0001	0%	0.93
RT-PCR	3	354	3.44 (1.42-8.34)	0.006	70%	0.04
Other methods	2	197	2.22 (1.38-3.58)	0.001	0%	0.44

Study or subgroup	log(hazard ratio)	SE	Weight	Hazard ratio IV, random, 95%CI	Hazard ratio IV, random, 95%CI
Gao 2009	1.6429	0.4133	11.6%	5.17 (2.30, 11.62)	
Hoffmann 2010	1.8132	0.6281	5.4%	6.13 (1.79, 20.99)	
Li 2016	0.5988	0.3537	15.2%	1.82 (0.91, 3.64)	
Matsushita 2015	0.9400	0.4083	11.9%	2.56 (1.15, 5.70)	
Reeh 2015	1.1404	0.3777	13.6%	3.13 (1.49, 6.56)	
Su 2016	0.9787	0.3369	16.4%	2.66 (1.37, 5.15)	
Tanaka K 2010	0.5188	0.3017	19.6%	1.68 (0.93, 3.03)	
Tanaka M 2015	1.1506	0.5769	6.3%	3.16 (1.02, 9.79)	
Total (95%CI)			100.0%	2.67 (1.99, 3.58)	

Heterogeneity: $Tau^2 = 0.02$, $\chi^2 = 8.10$, df = 7 ($P = 0.32$); $I^2 = 14\%$
Test for overall effect: $Z = 6.52$ ($P < 0.00001$)

Figure 2 Forest plots of the hazard ratios for overall survival. OS: Overall survival; IV: Inverse variance; df: Degrees of freedom.

between CTCs-positivity and T stage (RR = 1.44, 95%CI: 1.13-1.84, $I^2 = 0\%$, $P = 0.003$) (Figure 5B)[26-29,31,33], but a non-significant association between CTCs-positivity and histological differentiation (RR = 1.01, 95%CI: 0.79-1.30, $I^2 = 0\%$, $P = 0.93$) (Figure 5C)[26,27,30,31]. Six studies assessed the relationship between CTCs-positivity and N stage (RR = 1.47, 95%CI: 1.09-1.98, $I^2 = 36\%$, $P = 0.01$)[26-28,30,31,33]. However, when the Yin 2012 study was removed, no statistical significance in the five remaining studies was observed (RR = 1.51, 95%CI: 0.98-2.32, $I^2 = 48\%$, $P = 0.06$).

DISCUSSION

Although radical surgery and neoadjuvant radiochemotherapy have been widely used in EC patients, metastasis or recurrence of EC still poses a significant challenge for doctors and patients. Therefore, biomarkers which can be used to identify the recurrence or metastasis of EC are needed to facilitate the timely diagnosis and treatment strategies for EC patients. CTCs, released by primary tumors, are regarded as a key stage of tumorigenesis[34]; their further development leads to metastatic lesions, which
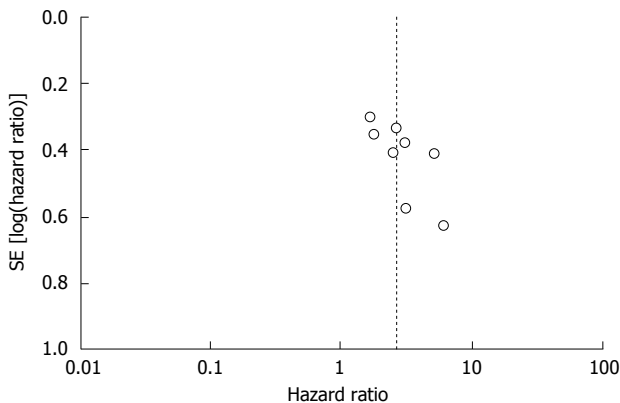
Figure 3 Funnel plot of the studies on overall survival.

can be explained by the "seed and soil" theory[35]. It is generally believed that lymph node metastasis occurs prior to blood-borne metastasis; however, the detection of CTCs in early tumors indicates that blood-borne metastasis can occur even in the early stage of tumorigenesis, *i.e.,* before the occurrence of lymph node metastasis[36]. In one study[31], peripheral venous blood CTCs were detected before and after the surgical treatment of EC; it was found that the preoperative positive expression of CTCs was not correlated with prognosis, whereas the postoperative positive expression of CTCs was significantly correlated with prognosis. However, in another study[27], positive CTCs in peripheral venous blood before treatment were thought to be correlated with prognosis. Thus, the value of CTC detection before surgical or non-surgical treatment in EC patients requires further investigation.

In this meta-analysis, we conducted a comprehensive literature search and demonstrated that detection of peripheral venous blood CTCs in EC patients can predict disease progression and poor prognosis. Compared with a previous study[37], in the present study, we included most recent literature and restricted the CTCs detection time to "before treatment". It is well known that EC patients who have received surgical treatment or non-surgical treatment had different prognoses. Our subgroup analysis of EC treatment further showed that detection of CTCs before treatment is valuable for predicting the prognosis of EC patients, and the expression of CTCs was not significantly correlated with treatment mode. In addition, considering the differences in treatment mode and observation time, we combined DFS, RFS, and PFS as "disease progression" and carried out a subgroup analysis accordingly.

Regional differences and differences in treatment modes and CTCs examination methods can also result in clinical heterogeneity; in this regard, we also carried out a subgroup analysis. As shown in our study, there was no significant heterogeneity when the relationship between CTCs status and the OS of EC patients was analyzed, and subgroup analysis also showed stable results. However, heterogeneity was found

in the relationship between CTC status and disease progression. The sensitivity analysis showed that the exclusion of any of the articles did not affect the outcome, and the heterogeneity was generated from the difference in the clinical observation time points among different studies. Also, different studies came to different conclusions regarding the relationship between CTC status and clinicopathological factors. Li *et al*[26] and Matsushita *et al*[28] concluded that positive CTC expression was correlated with TNM stage, but not with T stage, N stage, and the degree of differentiation; Reeh *et al*[27] and Tanaka *et al*[31] found that the CTC status was not correlated with TNM stage, T stage, and lymph node metastasis; and other studies[33,38] found that CTC positivity was correlated with N stage. In the present study, we found that CTC status was associated with TNM stage and T stage, but not with lymph node metastasis or degree of differentiation. Because different TNM staging methods were used among studies, and the clinical stages and pathological stages also differed, heterogeneity was inevitable in the present study. The results were unstable during the pooled analysis of the relationship between N stage and CTC status. However, when one article by Yin *et al*[30] 2012 was removed, the research outcome changed, which may be explained by the fact that the N stage in five other articles[26-28,31,33] was the pathological stage, whereas Yin *et al*[30] used clinical N stage.

Our meta-analysis had some limitations. First, potential biases such as gender, age, and race could not be avoided or controlled during the pooled analysis,which contains females are less susceptive to this type of cancer,white man in certain countries are more susceptible and in Asia(specifically in China) the squamous esophageal cancer is detected more than esophageal adenocarcinoma *etc*. Second, although no publication bias was found during analysis of the relationship between CTC positivity and the survival rate of EC patients, all the included articles were published in the English literature, which may have led to the omission of some non-English literature with negative results. In addition, most studies were conducted in Asian countries and areas and hence were less representative. Third, some of the included literature did not explicitly provide HR and 95%CI values, which had to be extracted from the relevant data and curves in the literature. Fourth, the differences in CTC detection methods, EC therapeutic approaches, and EC staging methods could also have affected the judgment of prognosis. Despite these limitations, we still demonstrated the relationships between CTCs and the prognosis and clinicopathological factors of EC.

In conclusion, CTC detection may be a valuable tool for improving the prognosis of EC patients, and it may be possible to carry out individualized therapy based on the results of CTC detection in the future. For postoperative EC patients, CTCs monitoring can provide individualized clinical information during the
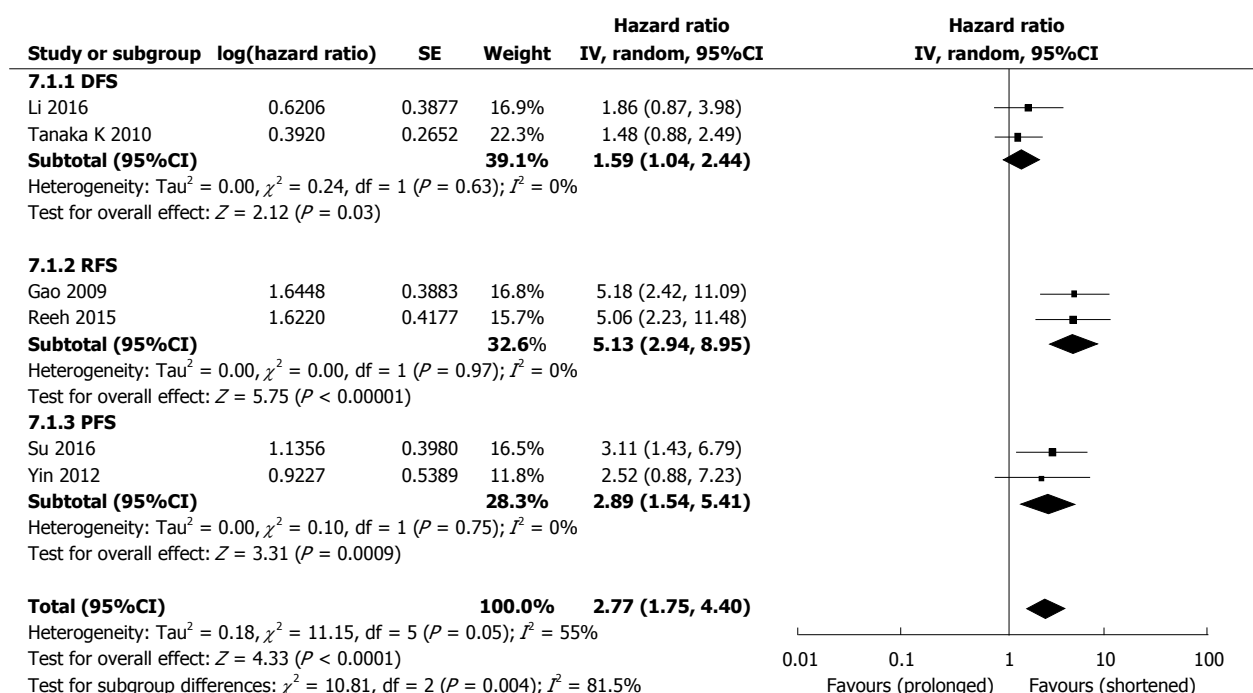
Figure 4 Forest plots of the hazard ratios for disease progression. HRs: Hazard Ratios; DFS: Disease-Free Survival; PFS: Progression-Free Survival; RFS: Relapse-Free Survival; IV: Inverse variance; df: degrees of freedom.
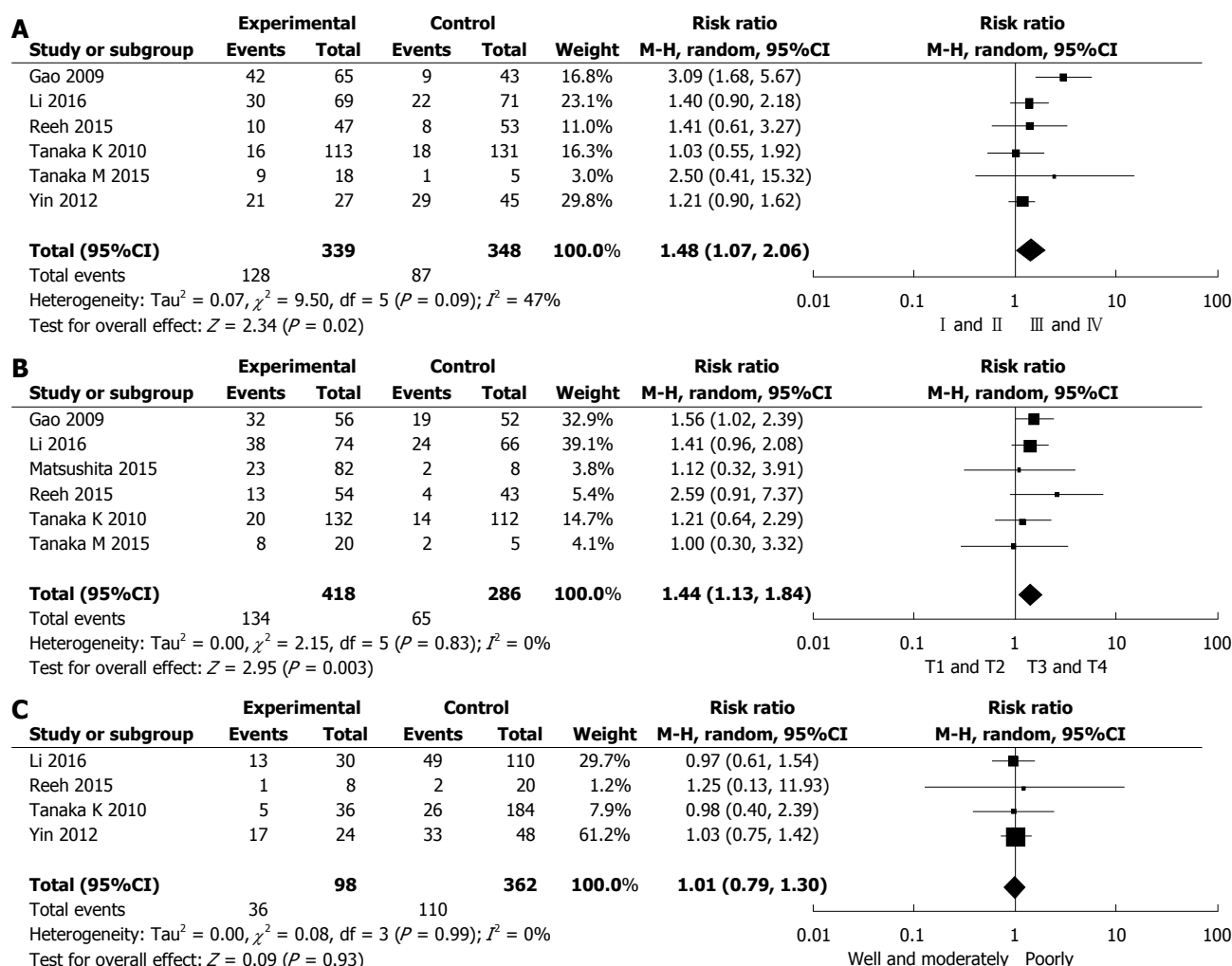

Figure 5 Forest plots of the RRs for clinicopathological characteristics. A: TNM stage; B: T stage; C: Histological differentiation. RRs: Risk Rataios; M-H: Mantel-Haenszel; df: Degrees of freedom.

follow-up. For EC patients requiring radiochemotherapy, CTCs monitoring may help identify the risk of tumor progression and enable some patients to benefit from second-line therapy. However, some problems still need to be addressed before CTC detection is applied in clinical settings. First, a variety of methods have been developed for detecting CTCs[39]; therefore, multi-center studies are required to standardize the CTC detection techniques and define CTCs reference values. Second, the CTC detection results may be negative in peripheral blood samples in some EC patients with dominant metastasis[40,41], which may be because the detection markers for metastatic lesions are not expressed or because the expression levels of these markers are below the detection thresholds. Therefore, efforts should be made to optimize the detection platforms for CTCs to improve the sensitivity of CTC detection. Finally, the value of CTC detection in predicting prognosis and the risk of EC recurrence/metastasis still need to be validated in large multi-center clinical trials.

COMMENTS

Background

Circulating tumor cells are cells released from the primary tumor into peripheral blood and are considered to be the main cause of tumor metastasis. The prognostic role of circulating tumor cells in esophageal cancer has been widely investigated.

Research frontiers

The clinical validity of circulating tumor cells is still controversial and inconclusive in patients with esophageal cancer. The aim of this meta-analysis was to include available studies to assess whether circulating tumor cells can be used as a prognostic marker in esophageal cancer.

Innovations and breakthroughs

This meta-analysis provides strong evidence to indicate that detection of circulating tumor cells in peripheral blood at baseline is an independent prognosticator of poor survival outcomes in esophageal cancer patients. More convincing results will be obtained by increasing the sample size.

Applications

Circulating tumor cells detected in peripheral blood can predict aggressive disease progression and poor overall survival in patients with esophageal cancer.

Peer-review

It is a well written article. Statistical analysis is comprehensive and well presented. The paper will attract attention of clinical scientists and surgeons in the field of esophageal cancer worldwide.

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