Systematic Review and Meta-Analysis

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Prognostic significance of tumor length in patients with esophageal cancer undergoing radical resection

A PRISMA-compliant meta-analysis

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Abstract

Background: The prognostic significance of tumor length in esophageal cancer (EC) remains controversial. Hence, we conducted a meta-analysis to quantitatively assess the prognostic significance of tumor length in EC patients.

Method: A systematic literature search was conducted in the PubMed, EMBASE, and Web of Science. Hazard ratios (HRs) with their 95% confidence intervals (CIs) were used to assess the prognostic significance of tumor length for overall survival (OS), and disease-free survival (DFS) in EC patients.

Results: A total of 21 articles with 22 eligible studies involving 9271 patients were included in this meta-analysis. The results of our pooling analyses demonstrated that tumor length was an independent prognostic parameter for OS (HR = 1.38, 95% CI: 1.24–1.54, $P < .01$) and DFS (HR = 1.29, 95% CI: 1.11–1.50, $P < .01$) in EC patients. Moreover, our subgroup analysis and sensitivity analysis showed that the pooled HRs assessing the prognostic significance of tumor length did not significantly fluctuated, suggesting our pooling analyses were stable and reliable.

Conclusion: The results of this meta-analysis demonstrated that long tumor is an independent risk of poor OS and DFS in EC patients, suggesting that it may provide additional prognostic information and thus contribute to a better stratification of EC patients, especially for those with no lymph node metastasis. However, more well-designed prospective clinical studies with large sample size are needed to strength our conclusion due to several limitations in this meta-analysis.

Abbreviations: CI = confidence interval, DFS = disease-free survival, EAC = esophageal adenocarcinoma, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, LN = lymph node, NOS = Newcastle-Ottawa scale, NR = not report, OS = overall survival.

Keywords: esophageal cancer, meta-analysis, prognostic, tumor length

1. Introduction

Esophageal cancer (EC) ranks as the eighth most common malignancy around the world, and the sixth most common cause of cancer-related death, leading to more than 400,000 deaths annually.[1,2] Regardless of recent improvements in diagnosis and therapy, EC is still one of the most fatal diseases, with a 5-year overall survival (OS) less than 20%.[1,2]

Prognostic stratification of EC patients plays a crucial role in formulating the optimal treatment modalities available. Nowadays, the tumor, node, metastasis (TNM) staging system has been widely applied to evaluate prognosis and direct therapy for cancer patients. In the current 8th edition of American Joint Committee on Cancer (AJCC) TNM staging system, EC staging is based on the depth of the tumor (T classification), lymph node (LN) involvement (N classification), distant metastasis (M classification), histological grading, and tumor location, but not tumor length.[3] In recent years, some researchers showed that tumor length was an independent prognostic parameter for EC and even recommended incorporating tumor length into TNM staging system to stratify EC patients.[4–18] However, others found that there were no relationships between tumor length and oncological outcomes in EC patients.[19–23] Therefore, the prognostic significance of tumor length remains controversial. Because an individual study is likely to provide a biased result that may partly result from the small sample size, we conducted a systematic review and quantitative meta-analysis to comprehensively assess the prognostic significance of tumor length in EC patients.

2. Methods

This meta-analysis was conducted based on preferred reporting items for systematic reviews and meta-analyses statement.[24] Furthermore, this study was approved by the Ethics Committee of Lanzhou University Second Hospital.

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2.1. Literature search strategy

A comprehensive literature search was conducted in PubMed, EMBASE, and Web of Science databases from inception to October, 2018.[25] The main search terms included "tumor length" and "esophageal or esophagus" and "cancer or carcinoma or tumor or adenocarcinoma or neoplasm or malignancy" and "survival or prognosis or prognostic or outcome". The search strategy in PubMed is as following: ((tumor length[Title/Abstract]) AND ((((((cancer[Title/Abstract]) OR carcinoma[Title/Abstract]) OR tumor[Title/Abstract]) OR adenocarcinoma[Title/Abstract]) OR neoplasm[Title/Abstract]) OR malignancy[Title/Abstract])) AND ((((survival[Title/Abstract]) OR prognosis[Title/Abstract]) OR prognostic[Title/Abstract]) OR outcome[Title/Abstract]). Besides, potentially eligible studies were identified through screening the references of the relevant studies. Two authors (Jianbao Yang and Yahong Liu) performed the search independently.

2.2. Inclusion and exclusion criteria

The eligible studies were identified according to the following criteria:

(1) diagnosis of EC was confirmed by pathological examination;
(2) the patients who did not received neoadjuvant radiotherapy or chemotherapy. In general, neoadjuvant therapy may reduce tumor length of EC. However, different patients may show inconsistent sensitivity to neoadjuvant therapy, which also affects the influence of neoadjuvant therapy on tumor length. Therefore, to remove the confounding influence of neoadjuvant therapy on evaluating the prognostic value of tumor length, we did not include the studies that enrolled patients treated with neoadjuvant therapy.
(3) The patients received curative resection;
(4) the patients were divided into short tumor group and long tumor group; and
(5) hazard ratios (HR) and their 95% confidence intervals, which assessed the association of tumor length with prognosis (OS or DFS) in EC patients, were directly provided, meanwhile they were obtained from multivariate analysis based on cox proportional hazard model.

The exclusion criteria included:

(1) abstracts, reviews, case reports, and reports from conferences were excluded; and
(2) the less informative study was excluded if relevant data of overlapped population was analyzed in different studies.

2.3. Data extraction and quality assessment

Two authors (Jianbao Yang and Yahong Liu) extracted the data independently. If there were inconsistencies in data extraction, the other authors intervened to solve these inconsistencies together. The data extracted from each study included: first author, publication year, country, sample size, median age, tumor location, LN metastasis, T classification, anti-cancer therapy after surgery, median follow-up time, accrual period, cut-off value, and HRs for OS and DFS.

The quality of each study was evaluated using the Newcastle-Ottawa scale (NOS).[26] Three aspects were assessed: selection, comparability, and exposure. A maximum of one star can be awarded to an article for selection or exposure, and each study can be given a maximum of 2 stars for comparability. Thus, a study can be awarded 9 stars at most. In this meta-analysis, a study with no less than 6 was defined as high-quality study.

2.4. Statistical analysis

This meta-analysis was performed using STATA software (version 12.0; Stata Corporation, College Station, TX). HRs and 95% CIs were used as effect measures when assessing the link between tumor length and survival of EC patients. Cochran Q test and I^2 statistics were used to evaluate heterogeneity. $I^2 > 50\%$ and $P < .05$ indicated that there was statistically significant heterogeneity. If significant heterogeneity existed, a random effect model was used. Otherwise, a fixed-effect model was applied. The concurrence of HR > 1 (short tumor used as reference), 95% CI not containing 1 and P value <.05 mean the higher risk of poor OS/DFS of EC patients with short tumor. Subgroup analyses were performed based on country, sample size, cut-off value, pathological type, the percentage of patients with LN metastasis, and the percentage of patients with T3-T4 classification to explore the potential sources of heterogeneity and evaluate the stability of our pooled results. Additionally, sensitivity analysis was also conducted by sequentially omitting single study to further assess the robustness of our pooled results. The Begg[27] and Egger tests[28] were used to quantitatively evaluate the extent of publication bias. If there was obvious publication bias, trim-and-fill method was used to assess the effect of publication bias on the robustness of our pooled results.[29] P value threshold of statistical significance was set at .05 in this meta-analysis.

3. Results

3.1. Search results and study characteristics

A total of 921 potentially eligible articles were initially identified by searching databases. Before screening records, we removed a total of 633 duplicated records by a literature manager software. Next, 239 articles were excluded in the process of title/abstract screening for irrelevant topics, reviews, and conference abstracts. Then, the remaining 49 articles were further screened throughout full-text, in which 28 articles were further excluded for preoperative anti-cancer therapy, non-multivariate analysis, lack of available data and overlapped population. Finally, a total of 21 eligible articles with 22 studies involving 9271 patients were included in this meta-analysis.[4–23,30] The detailed flow chart was presented in Figure 1.

These 22 studies were published between 2013 and 2018, and the accrual periods of these studies were inconsistent, ranging from 1983 to 2014. Seventeen studies were from China,[4–12,15,18–23,30] 2 studies were from Italy,[13] 1 study each from USA,[16] the Netherlands,[14] and Turkey.[17] The sample sizes of the included studies ranged from 80 to 1435 (mean of 421 patients). The cut-off values of long tumor were inconsistent across these 17 studies, ranging from 3 to 5. Of these 22, 21 studies investigated the relationship of tumor length to OS of EC patients,[4–16,18–23,30] and 8 studies reported about DFS.[5,7,10,14,17,19,20,22] The characteristics of the included studies were summarized in Table 1.

4. Meta-analysis

4.1. The prognostic significance of tumor length in EC patients

A total of 21 studies referred to the prognostic significance of tumor length for OS in EC patients.[4–16,18–23,30] Because

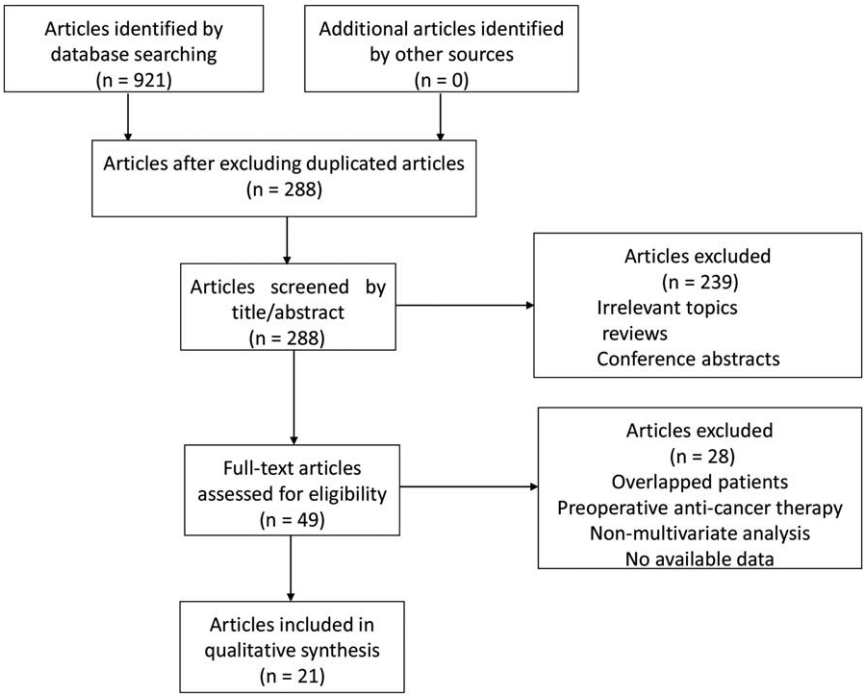

Figure 1. Flow diagram of study selection process.

of significant heterogeneity ($I^2 = 84.7\%$, $P < .01$, Fig. 2), a random-effect model was used for pooling analysis. The result suggested that long tumor was significantly related to poor OS (HR = 1.38, 95% CI = 1.24–1.54, $P < .01$, Fig. 2). Additionally, eight studies reported about the prognostic significance of tumor length for DFS in EC patients.[5,7,10,14,17,19,20,22] Our pooled result indicated that long tumor was also significantly associated with poor DFS (HR = 1.29, 95% CI = 1.11–1.50, $P < 0.01$, Fig. 3). A random-effect model was applied for this pooling analysis, due to significant heterogeneity ($I^2 = 75.5\%$, $P < .01$, Fig. 3). In this meta-analysis, only studies that applied multivariate analysis to assess the prognostic significance of

Table 1

The main characteristics of the included studies.

Author Publication year	Accrual period	Patient sources	No. of patients	Median age (years)	Pathological type	T3-T4 (% of total)	LN metastasis (% of total)	Cut-off value (cm)	Tumor location (% of total)			Anti-cancer therapy after surgery (% of total)	Median follow up (months)	NOS
									Upper	Middle	Lower			
Bai. G et al 2018	2012	China	80	NR	ESCC	46	52	5	30	45	25	NR	28	6
Chen. J. Q et al 2012	1993–2007	China	945	NR	ESCC	82.9	100	5	333.3	220	46.7	37.5	NR	7
Duan. J. J et al 2016	2006–2010	China	328	61	ESCC	68.3	42.4	4.2	73.3	661.6	31.1	100	44.9	8
Feng. J. F et al 2013	2001–2009	China	132	>60	ESCC	73.5	24.3	4	44.5	441.7	53.8	0	NR	6
Gao. S. H et al 2016	2006–2014	China	126	NR	ESCC	46.8	85	4	NNR	NNR	NR	NR	NR	6
Heijl. M. V et al 2010	1994–2000	The Netherlands	199	64	ESCC, EAC	70.9	72.4	4	NNR	NNR	NR	NR	> 60	8
Hsu. P. K et al 2014	1995–2006	China	391	>60	ESCC	63.1	55	5	9.4	42.1	48.5	12.5	22	6
Hwang. J. Y et al 2015	2008–2011	China	294	55	ESCC	70	58.9	3.2	17.3	38.7	44	37.9	20.4	7
Jia. W et al 2016	2009–2011	China	83	NR	ESCC	59	56.6	5	9.6	53	37.4	NR	NR	6
Li. J. B et al 2017	2007–2012	China	294	58	ESCC	66.3	67.3	5	2	47.2	50.8	41.5	26	7
Li. S. P et al 2016	2009–2011	China	100	NR	ESCC	52	55	4	20	37.2	42.8	NR	NR	6
Ma. M. Q et al. 2015	1999–2007	China	362	NR	ESCC	82.3	21.3	4	7.7	64.6	27.7	31.2	84	8
Ma. Q. L et al 2016	2006–2010	China	725	58	ESCC	NR	46.5	5	NR	NR	NR	NR	NR	8
Miao. L. S et al 2014	2006–2012	China	1342	<60	ESCC, EAC	57.5	47.8	4	0	51.4	48.6	NR	30	7
Tian. R et al 2016	2005–2010	China	442	60	ESCC	74.7	47.5	5	8.8	62.7	28.5	17.2	NR	7
Valmasoni. M et al a 2016	1983–2014	Italy	357	>60	ESCC	63	51	3	25	41	34	NR	NR	7
Valmasoni. M et al b 2016	1983–2014	Italy	305	>60	EAC	68	66	3	0	2	98	NR	NR	7
Wu. J et al 2016	2003–2010	China	1435	NR	ESCC	70	46.7	4	2.3	48.2	49.5	19.1	24	7
Yang. Y. S et al 2017	2005–2009	China	508	NR	ESCC	66.5	40.9	4	15.3	51.1	33.6	65.9	41.2	7
Yendamuri. S et al 2009	1995–2005	USA	209	64	ESCC, EAC	43.6	45.5	3	1.4	12.9	85.6	NR	NR	6
Zeybek. A et al 2013	2000–2010	Turkey	116	60	ESCC, EAC	87.9	65.5	3	8.6	31.1	60.3	NR	NR	6
Zhang. X. W et al 2017	2007–2014	China	498	59	ESCC	67.3	41	3	NR	NR	NR	NR	47.2	7

NR = not report; ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma; LN = lymph node; NOS = Newcastle-Ottawa scale.

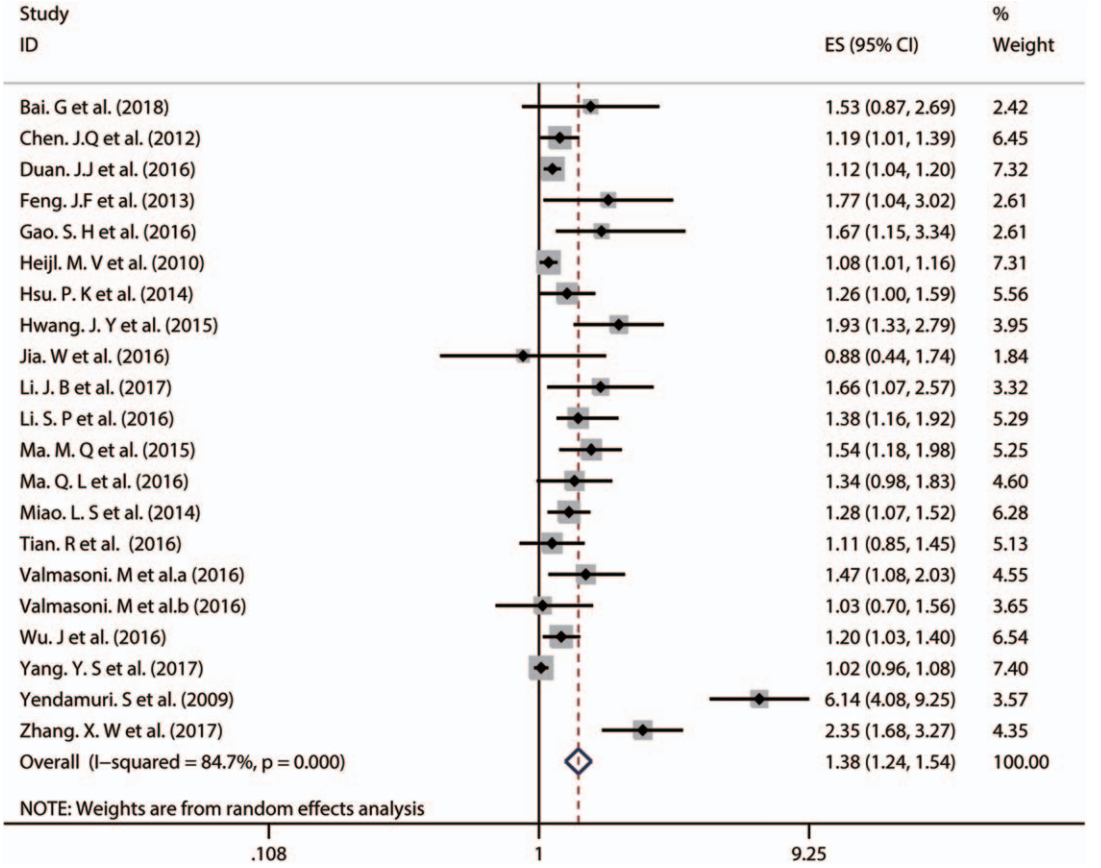

Figure 2. Forest plot of the pooled hazard ratio (HR) assessing the prognostic significance of tumor length for overall survival (OS) in esophageal cancer (EC) patients.

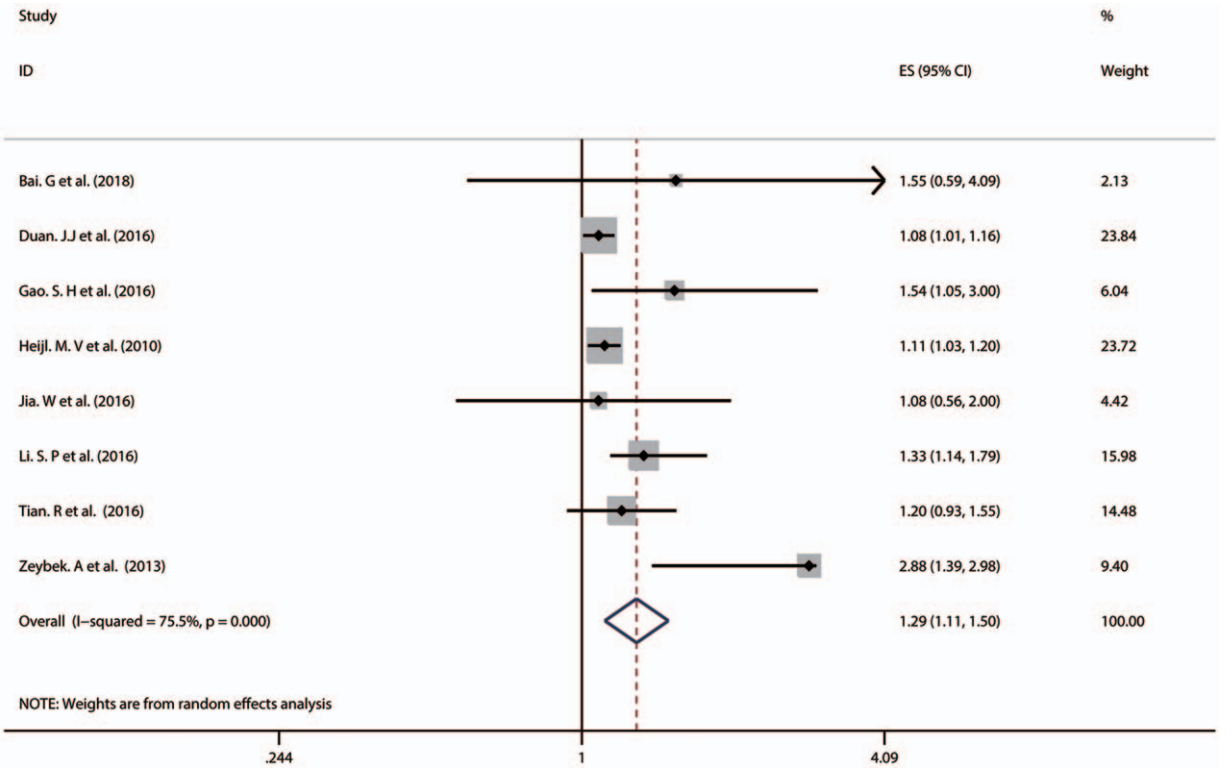

Figure 3. Forest plot of the pooled hazard ratio (HR) assessing the prognostic significance of tumor length for disease-free survival (DFS) in esophageal cancer (EC) patients.

tumor length were included, so our pooling results might demonstrated that tumor length was an independent prognostic parameter for OS and DFS in EC patients.

4.2. Subgroup and sensitivity analysis

We performed subgroup analyses, based on country (China and the others), sample size (<400 and ≥400), cut-off value (3, 3.2, 4, 4.2, and 5 cm), pathological type (ESCC and ESCC + EAC), the percentage of patients with LN metastasis (<60% and ≥60%), and the percentage of patients with T3-T4 classification (<60% and ≥60%), to explore the potential sources of heterogeneity for pooled result of OS. The results of subgroup analyses showed that the heterogeneity did not decreased substantially (Table 2), suggesting that these factors might not account for the major heterogeneity for the pooled result of OS. In general, it was found that long tumor was significantly correlated with poor OS in all subgroups, which suggested our pooled result for OS was stable and reliable. Because of the limited number of eligible studies about DFS, subgroup analysis was not applied to explore the potential sources of heterogeneity for the pooled result of DFS.

Our results of sensitivity analyses showed that the pooled HRs for OS (Fig. 4 A) and DFS (Fig. 4B) were not substantially influenced when single eligible study was omitted sequentially, further confirming the robustness of our pooled results.

4.3. Publication bias

The Begg funnel plot and Egger tests were conducted to assess the potential publication bias for the pooled result of OS. From the results, we found that the funnel plot of Begg test was asymmetric (Fig. 4C), indicating that there was significant publication bias. Besides, the presence of publication bias was further verified by the p values of the Begg funnel plot ($P = .035$) and Egger tests ($P = .001$). Therefore, we used trim-and-fill method to assess whether the publication bias substantially influenced the dependability of the pooled HR for OS. The results showed that the adjusted funnel plot became symmetric (Fig. 4D). Meanwhile, the adjusted pooled HR for OS was still more than 1 and its CI did not contain 1. Therefore, although there was publication bias, it did not substantially influence the stability and reliability of our pooled result of OS. Because of less than 10 eligible studies about DFS, the publication bias assessment was not conducted in this analysis.

5. Discussion

Regardless of recent improvements in therapy, EC is still one of the most lethal diseases, with a 5-year OS less than 20%.[1,2] A more accurate and practical disease staging system is urgently needed to identify those patients who are suitable for surgery alone, or who need preoperative or postoperative chemo-radiotherapy. An increasing number of studies showed that tumor length was an independent prognostic parameter for EC, and even suggested that the incorporation of tumor length into TNM staging system may obtain a better prognostic stratification of EC patients. However, the conclusions regarding the prognostic significance of tumor length were inconsistent. Therefore, we performed this meta-analysis to further assess the prognostic significance of tumor length in EC patients. In agreement with most of the previous studies, our overall pooled results also demonstrated that tumor length was an independent prognostic parameter for OS and DFS in EC patients. Moreover, our subgroup analysis and sensitivity analysis showed that the pooled HRs assessing the prognostic significance of tumor length did not significantly fluctuated, suggesting our pooled analyses were stable and reliable.

Our meta-analysis may have important clinical implications. On one hand, several studies suggested that tumor length was significantly associated with LN metastasis of EC, which might

Table 2

The prognostic significance of tumor length with OS in different subgroups.

Subgroups	No. of studies	HR (95% CI)	Heterogeneity		Model
			I^2 (%)	*P* value	
(1) Country					
China	17	1.32 [1.19, 1.45]	73	<.01	Random
Italy	2	1.26 [0.89, 1.78]	46.5	.172	Fixed
The Netherlands	1	1.08 [1.01, 1.16]	–	–	–
USA	1	6.14 [4.08, 9.25]	–	–	–
(2) Pathological type					
ESCC	18	1.13 [1.19, 1.45]	72.7	<.01	Random
ESCC + EAC	3	1.94 [1.07, 3.53]	97.1	<.01	Random
(3) Sample size					
<400	14	1.49 [1.27, 1.76]	86	<.01	Random
≥400	7	1.89 [1.67, 2.14]	82	<.01	Random
(4)Cut-off value					
5 cm	7	1.23 [1.11, 1.37]	0	.627	Fixed
4.2 cm	1	1.12 [1.04, 1.20]	–	–	–
4 cm	8	1.22 [1.09, 1.36]	73.1	<.01	Random
3.2 cm	1	1.93 [1.33, 2.80]	–	–	–
3 cm	4	2.15 [1.08, 4.30]	93.2	<.01	Random
(5) The percentage of lymph node metastasis					
<60%	16	1.45 [1.26, 1.67]	87.9	<.01	Random
≥ 60%	5	1.17 [1.03, 1.34]	41	.148	Fixed
(6) The percentage of T_3-T_4 classification					
<60%	6	1.73 [1.08, 2.77]	90.3	<.01	Random
≥60%	15	1.26 [1.15, 1.38]	76.6	<.01	Random

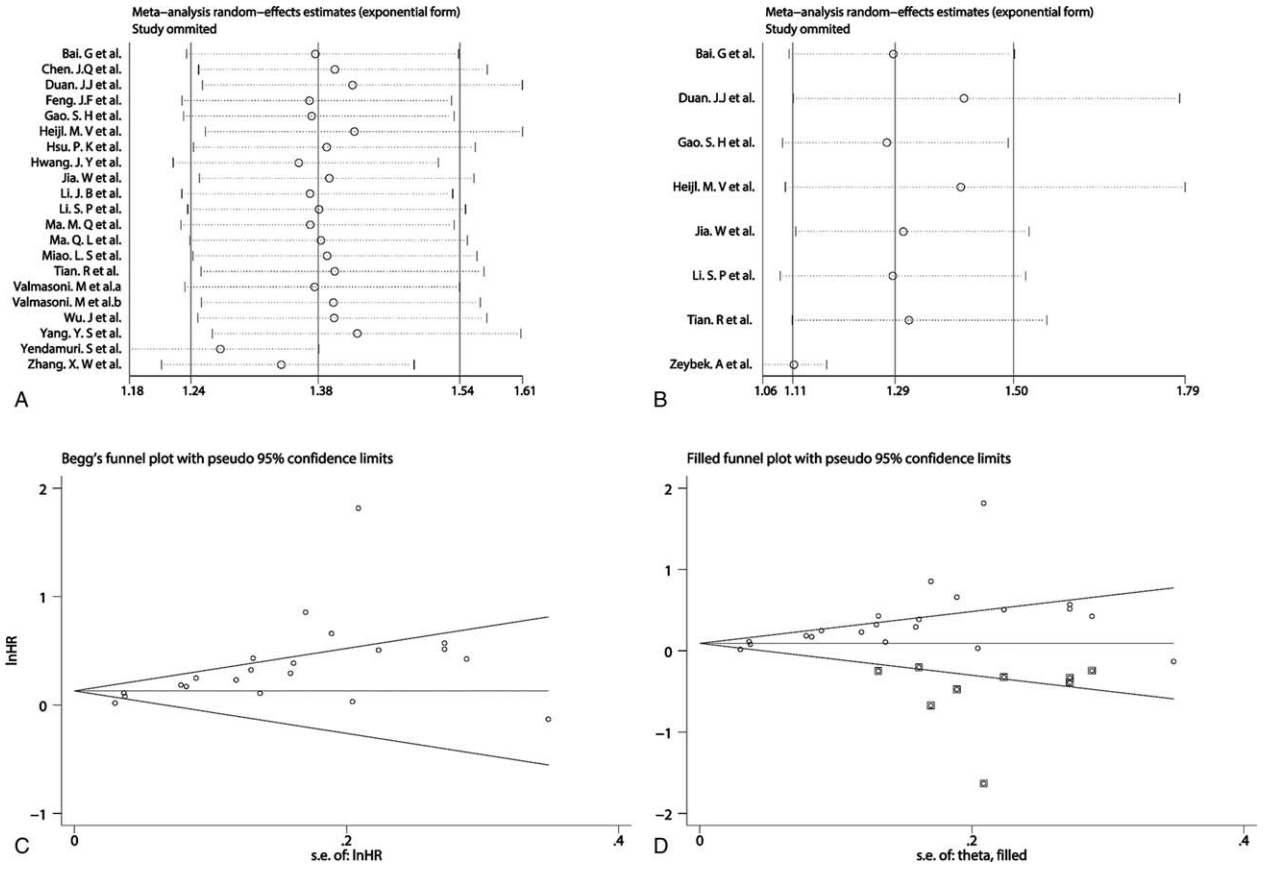

Figure 4. Sensitivity analyses for assessing the effect of each eligible study on the pooled HRs assessing the prognostic significance of tumor length for OS (A) and DFS (B); The Begg test funnel plot of the publication bias for the pooled HR assessing the prognostic significance of tumor length for OS (C); The adjusted Begg test funnel plot of the publication bias for the pooled HR assessing the prognostic significance of tumor length for OS (D). DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

partly explain the prognostic significance of tumor length. However, as compared with LN metastasis, tumor length is more easily and accurately estimated by using endoscopy or measuring surgical specimens. Generally speaking, endoscopy and pathological specimen measurement could provide direct-viewing measurement of tumor length, and they not easily influenced by the manipulation proficiency of medical technicians. LN metastasis is mainly identified by imaging techniques or through checking the resected tissues. However, imaging techniques could only provide an indirect evaluation of LN metastasis, and the accurate and sufficient resection of peritumoral tissues containing LN metastasis is closely related with the proficiency of surgeon. Therefore, it may be more accurate to identify tumor length by endoscopy and pathological specimen measurement than to identify LN metastasis in clinical practice. Therefore, there is a possibility to refine the current 8th edition of AJCC TNM staging system into a simplified edition through replacing tumor length with N classification. Of course, more high-quality and large-sample size studies are required to confirm the inherent correlation of tumor length with LN metastasis of EC. On the other hand, in the majority of included studies, the cox proportional hazard models used for multivariate survival analysis incorporated the TNM system variables, including T classification, N classification, tumor grade and localization, suggesting that the prognostic significance of tumor length might be independent of these TNM system variables. In line with this, Song et al and Valmasoni et al reported that patients with long tumor had poor survival than patients with short tumor even if there was no evidence of LN metastasis,[13,31] and they explained this result with the theory that tumor length may be associated with the lymphatic vessels invasion tendency.[32,33] Therefore, tumor length may provide additional prognostic information, probably contributing to a better stratification of EC patients with no LN metastasis.

However, there were several limitations in this meta-analysis. First, all included studies were retrospectively designed. Second, some studies enrolled patients diagnosed in from 1983 to 2016, during which diagnostic criteria and standards of treatment has changed greatly, likely causing a degree of bias and heterogeneity of this meta-analysis. Third, most of the included studies were from China and thereby it may not be persuasive to generate our conclusions to patients in other countries. There may be 2 reasons for why most of the included studies were from China. In one hand, we performed the literature selection in this meta-analysis with a language restriction of English since English is an international language and most of researchers understand it. Actually, there is a possibility that the language restriction in our meta-analysis probably led us to exclude some eligible studies published in non-Chinese or English, which may partly account for why most of the included studies were performed in China. In another hand, in this meta-analysis the publication bias assessment indicated that there was significant publication bias and the trim-and-fill analysis suggested that a total of 8 studies may not be permitted for publication due to the negative results

about the prognostic value of tumor length in EC patients. It may be possible that the 8 studies showing no association of tumor length with survival in EC patients were performed in other countries other than China, which may partly explain why most of the included studies were performed in China as well and introduce a degree of bias into our pooled analysis. Of course, this kind of bias can be overcome by prospective studies. Fourth, most of included studies enrolled patients with ESCC, 4 studies enrolled patients with ESCC or EAC, and only 1 study enrolled patients with EAC. Therefore, it may not be reliable to generate our conclusions to patients with EAC, and thus more studies are required to explore the prognostic value of tumor length in patients with EAC. Fifth, T stages of EC in most included studies were T3/4 stages. Thus, more studies should be performed to further confirm the prognostic value of tumor length in EC patients with early T stages (Tis, T1 or T2), which may contribute to optimizing individualized treatment for EC patients. According to the American College of Gastroenterology (ACG) clinical guideline, patients with high-grade dysplasia and T1a EC are usually treated with endoscopic techniques. Besides, some evidence also support the selective endoscopic treatment for T1b EC.[34] However, esophagectomy for T1a orT1b EC is recommended in patients with poor differentiation, lymphovascular invasion, or incomplete resection by endoscopic treatment.[34] In our meta-analysis, we found that long tumor is an independent risk of poor OS and DFS in EC patients. Therefore, esophagectomy may give a better oncological outcome for early EC patients (Tis, T1a, or T1b) with long lesion compared to endoscopic treatment. However, this issue should be further confirmed in future clinical studies. Sixth, the majority of the included studies did not report the determination methods of tumor length. Besides, although a few of the included studies reported the determination methods of tumor length, the methods were not consistent. Moreover, the cut-offs of long tumor in the included studies were not consistent either. Thus, more well-designed studies are required to explore whether the determination methods of tumor length affect its prognostic values in EC patients, and to determine an optimal cut-off value of long tumor, which helps to make clinical decision. Seventh, lesion site, as an important biological behavior of EC, is closely associated with surgical treatment types. Upper or Middle EC is usually treated with esophagectomy, while lower EC, especially for siewert III tumor, is treated with a radical total gastrectomy or in combination with esophagectomy. However, tumor sites of different patients in each included study were inconsistent. Therefore, in future it is imperative to conduct more studies to investigate whether tumor site affects the prognostic values of tumor length in EC patients. Eighth, although most studies adjusted their HRs and 95% CIs by multivariate analysis, variables incorporated into cox proportional hazard models were inconsistent among the included studies. This might also lead to a degree of bias of bias and heterogeneity. Last but not least, only studies published in English were considered in this meta-analysis, which increased the bias risk.

6. Conclusion

The results of this meta-analysis demonstrated that long tumor is an independent risk of poor OS and DFS in EC patients, suggesting that it may provide additional prognostic information and thus contribute to a better stratification of EC patients, especially for those with no LN metastasis. However, more well-designed prospective cohort studies with large sample size are needed to strength our conclusion due to several limitations in this meta-analysis. With respect to the key points of the prospective study design, I have to emphasize that participants should be enrolled in to short and long EC groups strictly based on the identical inclusion and exclusion criteria. That is, it is necessary to unify the key survival-related baseline characteristics between short and long EC groups to the most degree, such as gender, sex, pathological type, tumor differentiation, tumor site, the determination method of tumor method, neoadjuvant therapy, types of surgical treatment, and postoperative adjuvant chemotherapy, which may help to reveal the authentic association between tumor length and survival in EC by eliminating the interference of those confounding factors. Of course, such a prospective study may be challenged with the limitation of insufficient samples. Therefore, if it is, we will cooperate with other clinical centers to advance this study.

Author contributions

Cheng Wang initiated and designed this meta-analysis; Jianbao Yang searched the eligible studies, extracted the data, wrote this manuscript and revised this manuscript; Yahong Liu searched the eligible studies and extracted the data; Bin Li and Peng Jiang performed the statistical analysis.
Conceptualization: Cheng Wang.
Data curation: Jianbao Yang, Yahong Liu.
Formal analysis: Bin Li.
Investigation: Peng Jiang.
Methodology: Jianbao Yang, Yahong Liu.
Resources: Jianbao Yang, Yahong Liu.
Software: Bin Li, Peng Jiang.
Supervision: Cheng Wang.
Validation: Peng Jiang.
Writing – Original Draft: Jianbao Yang.
Writing – Review & Editing: Yahong Liu.

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