



Timing of surgery after neoadjuvant chemoradiotherapy affects oncologic outcomes in patients with esophageal cancer

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Abstract

BACKGROUND

The optimal time interval between neoadjuvant chemoradiotherapy (nCRT) and esophagectomy in esophageal cancer has not been defined.

AIM

To evaluate whether a prolonged time interval between the end of nCRT and surgery has an effect on survival outcome in esophageal cancer patients.

METHODS

We searched PubMed, Embase, Web of Science, the Cochrane Library, Wanfang and China National Knowledge Infrastructure databases for relevant articles published before November 16, 2019, to identify potential studies that evaluated the prognostic role of different time intervals between nCRT and surgery in esophageal cancer. The hazard ratios and 95% confidence intervals (95%CI) were merged to estimate the correlation between the time intervals and survival outcomes in esophageal cancer, esophageal squamous cell carcinoma and adenocarcinoma using fixed- and random-effect models.

RESULTS

This meta-analysis included 12621 patients from 16 studies. The results demonstrated that esophageal cancer patients with a prolonged time interval between the end of nCRT and surgery had significantly worse overall survival (OS) [hazard ratio (HR): 1.107, 95%CI: 1.014-1.208, $P = 0.023$] than those with a shorter time interval. Subgroup analysis showed that poor OS with a prolonged interval was observed based on both the sample size and HRs. There was also significant association between a prolonged time interval and decreased OS in

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Asian, but not Caucasian patients. In addition, a longer wait time indicated worse OS (HR: 1.385, 95%CI: 1.186-1.616, $P < 0.001$) in patients with adenocarcinoma.

CONCLUSION

A prolonged time interval from the completion of nCRT to surgery is associated with a significant decrease in OS. Thus, esophagectomy should be performed within 7-8 wk after nCRT.

Key words: Esophageal cancer; Neoadjuvant chemoradiotherapy; Esophagectomy; Time interval; Survival outcome; Meta-Analysis

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Core tip: Esophageal cancer is one of the most common malignant tumors worldwide. Neoadjuvant chemoradiotherapy (nCRT) is increasingly used as the standard treatment for most esophageal cancer patients. However, the optimal time interval for esophagectomy after nCRT in patients with esophageal cancer has not been defined. Therefore, we conducted a meta-analysis on 12621 patients from 16 studies to evaluate whether a prolonged time interval from the end of nCRT to surgery has an effect on survival outcome in esophageal cancer patients.

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INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related death worldwide^[1]. In China, esophageal cancer led to 375000 deaths annually^[2]. High-level evidence suggests that neoadjuvant chemoradiotherapy (nCRT) plus surgery compared with surgery alone improves survival in patients with local advanced esophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC), and pathological complete response (pCR) after nCRT may have a potential impact on survival outcome^[3,4]. However, there are many unclear factors which influence outcome in esophageal cancer patients.

The optimal time interval for esophagectomy after nCRT in patients with esophageal cancer has not been defined. According to current clinical practice, in most centers, patients usually undergo esophagectomy within 6 to 8 wk after completion of nCRT when they have fully recovered^[5]. In rectal cancer patients, evidence^[6] suggests that a longer waiting interval (more than 6-8 wk) significantly increases the rate of pCR without a detrimental outcome. Similarly, other studies^[7,8] have revealed that a prolonged interval between nCRT (> 8 wk) and esophagectomy is associated with a higher pCR, which may improve survival in esophageal cancer patients. However, Ranney *et al*^[9] and others^[10,11] have indicated that the prognostic role of the time interval in esophageal cancer is still controversial. For these reasons, it is necessary to perform a meta-analysis to systematically and comprehensively investigate the impact of different intervals on survival outcome. In the present study, a pooled analysis of relevant studies was undertaken to evaluate whether a prolonged time interval from the end of nCRT to surgery has an effect on survival outcome in esophageal cancer patients.

MATERIALS AND METHODS

Literature search

We performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We searched PubMed, Embase, Web of Science, the Cochrane Library, Wanfang and China National Knowledge Infrastructure databases for relevant studies published before November

16, 2019. We identified articles using Medical Subject Heading and Test-word search strategy. Keywords included “esophageal neoplasms”, “neoadjuvant therapy”, “esophagectomy”, and “time interval”. In addition, the references listed in the articles were also checked.

Study selection

The included studies satisfied the following criteria: (1) Comparisons were performed between longer time intervals and shorter time intervals from the completion of nCRT to surgery in esophageal cancer patients; (2) Survival-related outcomes were reported, such as overall survival (OS), progression-free survival (PFS) and disease-free survival; (3) Studies included human subjects; and (4) Articles were published in any language. The exclusion criteria were as follows: (1) Article types such as abstracts, letters, review articles, case reports and unpublished studies; (2) Studies with insufficient data to evaluate hazard ratio (HR) and 95%CI; and (3) For studies already reported or containing duplicate data, we included only the latest studies.

Data extraction, endpoints and quality assessment

Two reviewers (Yi-Min Gu, Qi-Xin Shang) evaluated all potential eligible studies. Then, another two investigators (Han-Lu Zhang, Xiang-Yu Zhang) completed the full-text review independently. If disagreement occurred, a third investigator (Yu-Shang Yang) joined the discussion until a consensus was reached. The following information was extracted from the selected articles: First author, study year, study region, study design, ethnicity, sample size, age, nCRT regimen, cut-off value, outcome, follow-up, clinical stage, histological type and HR with 95%CI. The time interval was defined as the period of time from the completion of nCRT to surgery. When several time interval groups were included in the study, the subgroup events were combined at the cut-off value of 7-8 wk in order to compare the longer interval with the shorter time interval. Some studies have suggested an interval of 7-8 wk for esophageal cancer patients (Table 1); and a similar classification was used in a previously published meta-analysis of esophageal cancer^[34]. OS was selected as the primary end point, while PFS and disease-free survival were secondary end points. The included studies quality was rated according to the Newcastle-Ottawa Scale (NOS) by two independent investigators (Yi-Min Gu, Wei-Peng Hu). Studies with NOS scores of 6 or higher were considered to be of high quality.

Statistical analysis

HRs) and 95%CI were extracted from each article and combined to estimate the prognostic value. HR > 1 indicated a worse oncologic outcome in esophageal cancer patients with a longer time interval between nCRT therapy and surgery. If the study did not provide HRs and 95%CI directly but a Kaplan-Meier curve instead, Engauge-Digitizer version 12 (<http://markummittchell.github.io/engauge-digitizer/>) was used to derive estimates from survival curves according to the method proposed by Parmar *et al*^[12]. Cochran's Q test and Higgins I-squared statistic were used to assess the heterogeneity of the included studies. Pooled estimates of HR and 95%CI were calculated initially with a fixed-effect model (Mantel-Haenszel method). If significant heterogeneity existed (Q-test, $P < 0.10$ or $I^2 > 50\%$ was defined as statistically significant heterogeneity), a certified analysis using the random-effect model (DerSimonian-Laird method) was performed. Begg's funnel plot and Egger's linear regression test were carried out to detect publication bias. All P -values were two-sided and significant publication bias was defined as $P < 0.05$. Multivariate models were chosen for a more accurate estimate of the effect of time interval on survival outcomes when both univariate and multivariate Cox regression analyses were performed. Subgroup analyses were performed on the basis of variables including histology, study design, ethnicity, sample size, and HR type. All statistical analyses were performed with Stata/SE 12.0 software (Stata Corp LLC, version 12.0 4905 Lakeway Drive College Station, TX, United States).

RESULTS

Identification of relevant studies

We screened 2308 eligible studies and identified 19 studies including two relevant articles from the same study by Franko *et al*^[13,14] and two studies^[15,16] without sufficient data to calculate HR and 95%CI. Sixteen studies were finally selected for the meta-analysis to determine whether the time interval from completion of nCRT to surgery has an effect on survival outcome^[5,7-11,14,17-25]. Of these studies, HRs and 95%CI were directly provided in three studies, while the other 13 studies all provided Kaplan-Meier curves; thus, we were able to obtain estimated HRs and 95%CI indirectly.

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Year	Study region	Ethnicity	Study design	No. (M/F)	Age (yr)	NCRT regimen	Cut-off (d)	Out-come	Follow-up (mo)	Clinical stage	Histo-logy	HR type	NOS score
Ruol <i>et al</i> ^[17]	2010	Italy	Caucasian	Prospective	129 (99/30)	60.8	DDP+5FU U ci/DDP +PTX/ OXA+5FU U ci+CF RT 45- 50.4 Gy	46	OS	60	I-IV ¹	SCC	U	8
Kim <i>et al</i> ^[18]	2012	United States	Caucasian	Prospective	266 (235/31)	SI, 57; LI, 60	Plati-num- based RT 45Gy	56	OS/DFS	99	II-IVa ¹	AC and SCC	U	8
Chiu <i>et al</i> ^[10]	2013	China	Asian	Retrospective	276 (268/8)	SI, 56.8; LI, 53.5	5FU ci+DDP RT 30 Gy	56	OS	60	II-IV ¹	SCC	U	7
Shapiro <i>et al</i> ^[7]	2014	United States	Caucasian	Retrospective	325 (253/72)	60	PTX+CB P RT 41.4 Gy	45	OS/DFS	60	cT1-4 ² , N0-1 ¹	AC and SCC	U/M	8
Tessier <i>et al</i> ^[19]	2014	France	Caucasian	Prospective	257 (227/30)	NR	5FU ci+DDP RT 45 Gy	49	OS	135	I-III ¹	AC and SCC	U	8
Shaikh <i>et al</i> ^[20]	2015	United States	Caucasian	Retrospective	88 (62/26)	61	5FU- based/ PTX- based RT 45-60 Gy	50	OS	87.7	I-IV ²	AC and SCC	U	7
Wang <i>et al</i> ^[21]	2015	China	Asian	Prospective	665 (636/29)	53	NA	59	OS	60	I-III ²	SCC	U	7
Haisley <i>et al</i> ^[5]	2016	United States	Caucasian	Prospective	234 (191/43)	64	PTX+ CBP/ 5FU ci+DDP NA	56	OS	152	I-IV ²	AC and SCC	U	8
Kathiravetpillai <i>et al</i> ^[22]	2016	Netherlands	Caucasian	Prospective	190 (169/21)	NR	PTX+ CBP/ PTX+ CBP+5FU U RT41.4 Gy	56	OS/DFS	60	cT1-3 ² , N0-3 ²	AC	U	7
Lee <i>et al</i> ^[11]	2016	United States	Caucasian	Retrospective	5393 (4533/860)	62	NA RT 39.6-64.8 Gy	64	OS	96	I-IV ²	AC and SCC	M	8
Ranney <i>et al</i> ^[9]	2017	United States	Caucasian	Retrospective	2444 (2193/251)	61	NA RT 40.4-50.4 Gy	56	OS	60	II-III ²	AC	M	8
Tsang <i>et al</i> ^[23]	2017	China	Asian	Prospective	107 (91/16)	63	5FU ci+DDP RT 40 Gy	64	OS	60	I-III ²	SCC	U	7
Franko <i>et al</i> ^[14]	2018	United States	Caucasian	Retrospective	1244 (810/434)	60.5	NA RT 45 Gy	49	OS	75	NR	SCC	U	6
Furukawa <i>et al</i> ^[24]	2018	Japan	Asian	Retrospective	134 (116/18)	NR	5FU+ DTX/ 5FU+ DDP/ NDP RT 40 Gy	56	OS/DFS	60	I-IV ²	SCC	U	7

Singla <i>et al</i> ^[25]	2018	United States	Caucasian	Prospective	226 (210/16)	61	DDP+ Irinotecan/CBP+ PTX/OXA+ CAPE/5-FU+DDP RT 50.4 Gy	49	OS/PFS	110	I-IV ²	AC and SCC	U	6
Kleverbrot <i>et al</i> ^[8]	2019	Sweden	Caucasian	Prospective	643 (536/107)	SI, 64; LI, 65	DDP+ 5FU RT 40 Gy	49	OS	60	I-IVa ²	AC and SCC	U	7

nCRT: Neoadjuvant chemoradiotherapy; NR: Not reported; LI: Longer time interval; SI: Shorter time interval; DDP: Cisplatin; 5FU: Fluorouracil; PTX: Paclitaxel; OXA: Oxaliplatin; CBP: Carboplatin; NDP: Nedaplatin; DTX: Docetaxel; RT: Radiotherapy; NA: None; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; HR: Hazard ratio; M: Multivariate analysis; U: Univariate analysis; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; NOS: Newcastle-Ottawa Quality Assessment Scale.

¹6th AJCC/UICC classification.

²7th AJCC/UICC classification.

Moreover, in 13 studies, HRs were evaluated by univariate analysis and in three by multivariate analysis. The included articles were assessed to be of high quality, with a median quality score of 7.3 (range, 6-8). The identification of relevant studies is summarized in the flowchart (Figure 1).

Study characteristics

The included studies were carried out in seven countries (United States, China, France, Italy, Netherlands, Japan, and Sweden) and published between 2010 and 2019. Of these studies, seven were retrospective and nine were prospective. The participants were Caucasian in 12 studies and were Asian in four studies. The median number of patients in each study was 789 (range, 88-5393), with a total of 12 621 patients, consisting of 7522 patients with a shorter time interval, and 5099 patients with a longer time interval between nCRT and surgery. The sample size in five studies was < 200 patients and was ≥ 200 patients in 11 studies. In addition, 1029, 219 and 189 patients underwent esophagectomy via Ivor-Lewis, McKeown and transhiatal approaches, respectively, while six studies^[5,8,11,20-22] did not provide the method of esophagectomy. The cut-off values in each study were not consistent and ranged from 45 d to 64 d. Six articles applied a cut-off value of 8 wk and five studies used 7 wk. Seven studies included whole stages, and three studies included advanced stage. Additional comprehensive characteristics of the relevant studies are shown in Table 1.

Time interval and OS, PFS in esophageal cancer

Sixteen studies were included in the meta-analysis on the effect of the time interval between nCRT and surgery on the OS of esophageal cancer patients. Notable heterogeneity was detected among the studies ($I^2 = 48.8\%$, $P = 0.015$; Figure 2); thus, a random-effect model was used. The results of our meta-analysis showed that esophageal cancer patients with a shorter wait time correlated with prolonged OS compared with an extended wait time, with a poor HR of 1.107 (95%CI: 1.014-1.208, $P = 0.023$; Table 2). Three studies which included 590 patients demonstrated that a longer time interval was related to shorter PFS (HR: 1.263, 95%CI: 0.976-1.633, $P = 0.075$; Table 2) without obvious heterogeneity ($I^2 = 48.4\%$, $Ph = 0.144$; Figure 2).

Time interval and OS in AC

Two studies with 2634 patients reported data on a longer time interval and OS in AC patients. Pooled data from the two studies demonstrated that a prolonged time interval was significantly associated with worse OS with a HR estimate of 1.385 (95%CI: 1.186-1.616, $P < 0.001$; Table 2) without apparent heterogeneity ($I^2 = 22.00\%$, $Ph = 0.257$; Figure 3).

Time interval and OS in SCC

Meta-analysis of six studies revealed that SCC patients with a longer time interval had poor OS (HR: 1.096, 95%CI: 0.896-1.341, $P = 0.371$; Table 2) with significant heterogeneity ($I^2 = 57.2\%$, $Ph = 0.039$; Figure 3).

Subgroup analysis

Subgroup analyses were conducted to investigate potential sources of heterogeneity across studies and to evaluate the consistency of the conclusions among different

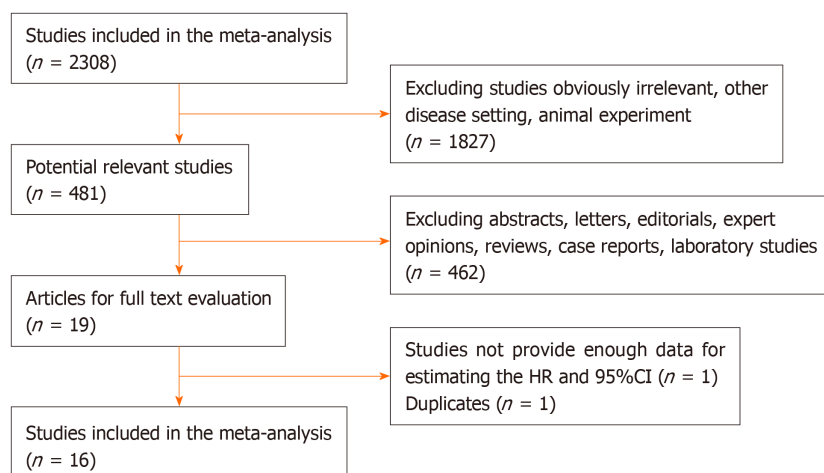


Figure 1 Flow chart of study selection.

subpopulations of patients. Subgroup analyses based on study design, demonstrated that the merged HR was 1.073 (95%CI: 0.964-1.194, $P = 0.064$) for prospective cohort studies and 1.094 (95%CI: 1.034-1.158, $P = 0.001$) for retrospective analyses (Table 2).

Based on classifications by sample size, the merged HR was 1.254 (95%CI: 0.985-1.579, $P = 0.067$) for a sample size < 200 and 1.089 (95%CI: 0.995-1.190, $P = 0.063$) for a sample size ≥ 200 . Stratification by ethnicity, revealed a combined HR of 1.091 (95%CI: 0.995-1.197, $P = 0.150$) in Caucasian populations and 1.251 (95%CI: 0.922-1.696, $P = 0.023$) in Asian cases. In addition, subgroup analysis was performed by univariate analysis (HR: 1.029, 95%CI: 0.949-1.115, $P = 0.492$) and multivariate analysis (HR: 1.194, 95%CI: 1.010-1.411, $P = 0.037$). The results demonstrated that sample size (< 200 and ≥ 200) and statistical analysis approach (univariate and multivariate analyses) were both potential causes of significant heterogeneity (Table 2).

Sensitivity analysis

Due to the conspicuous heterogeneity among the studies, a sensitivity analysis was performed. We found that the combined results were still stable after the exclusion of any single study (Figure 4).

Publication bias

Investigations using Begg's funnel plot (Figure 5) and Egger's linear regression test did not indicate publication bias in the meta-analyses on the association between time to surgery and OS ($Pr > |z| = 0.344$ for Begg's test and $P > |t| = 0.432$ for Egger's test).

DISCUSSION

The role of preoperative chemoradiotherapy in improving survival among patients with potentially curable esophageal cancer is recognized in many randomized controlled studies^[3,4]. However, esophagectomy cannot be performed immediately, as patients need to recover from the side effects of chemoradiotherapy, and an appropriate interval can induce the maximal radiotherapy response^[26]. A strong relationship between the time interval and survival outcome has been reported for pancreatic tumor^[27], rectal cancer^[28], and non-small cell lung cancer^[29].

Similarly, several studies have shown an association between time interval and survival in esophageal cancer patients. Shapiro *et al*^[7] found that a prolonged interval after nCRT increased the pCR rate and may improve survival. However, the findings in some current studies do not support those of previous research. Ranney *et al*^[9] found that OS was worse in the long-interval subgroup (HR: 1.44, 95%CI: 1.22-1.71, $P < 0.001$). This result is consistent with that of Chiu *et al*^[10] who revealed that survival outcome did not improve following a long-term wait. In contrast, subgroup analysis showed that later resection may be hazardous, especially in patients who had a good response to nCRT.

This meta-analysis included 12621 esophageal cancer patients from 16 cohort studies, and demonstrated that patients with a longer time interval between nCRT and esophagectomy had significantly worse OS (HR: 1.107, 95%CI: 1.014-1.208, $P = 0.023$; Figure 2) than those with a shorter time interval. Subgroup analysis showed that OS with a prolonged interval was poor based on both the sample size and the

Table 2 Meta-analysis and subgroup analyses

Analysis	n	Ref.	Random-effects model		Fixed-effects model		Heterogeneity	
			HR (95%CI)	P value	HR (95%CI)	P value	I ²	Ph
Esophageal cancer OS	16	[5,7-11,13,16-24]	1.107 (1.014-1.208)	0.023	1.089 (1.036-1.145)	0.001 ^a	48.80%	0.015
DFS	3	[17,21,23]	1.300 (0.883-1.913)	0.184	1.263 (0.976-1.633)	0.075	48.40%	0.144
Subgroup 1: Study design	16	[5,7-11,13,16-24]	1.107 (1.014-1.208)	0.196	1.089 (1.036-1.145)	0.196	0.00	0.865
Prospective	9	[5,8,16-18,20-22,24]	1.073 (0.964-1.194)	0.064	1.073 (0.964-1.194)	0.002 ^a	76.30%	0.000
Retrospective	7	[7,9-11,13,19,23]	1.150 (0.992-1.332)	0.023 ^a	1.094 (1.034-1.158)	0.001 ^a	48.80%	0.015
Subgroup 2: Samplesize	16	[5,7-11,13,16-24]	1.107 (1.014-1.208)	0.023 ^a	1.089 (1.036-1.145)	0.001 ^a	48.80%	0.015
< 200	5	[16,19,21-23]	1.294 (0.946-1.771)	0.107	1.254 (0.985-1.597)	0.067	34.70%	0.190
≥ 200	11	[5,7-11,13,17,18,20,24]	1.089 (0.995-1.190)	0.063	1.082 (1.028-1.139)	0.002 ^a	54.20%	0.016
Subgroup 3: Ethnicity	16	[5,7-11,13,16-24]	1.107 (1.014-1.208)	0.064	1.107 (1.014-1.208)	0.064	48.80%	0.015
Caucasian	12	[5,7-9,11,13,16-19,21,24]	1.091 (0.995-1.197)	0.150	1.091 (0.995-1.197)	0.150	49.30%	0.027
Asian	4	[10,20,22,23]	1.251 (0.922-1.696)	0.023 ^a	1.251 (0.922-1.696)	0.023 ^a	57.60%	0.069
Subgroup 4: HR type	16	[5,7-11,13,16-24]	1.107 (1.014-1.208)	0.023 ^a	1.089 (1.036-1.145)	0.001 ^a	48.80%	0.015
Univariate	13	[5,8,10,13,16-24]	1.053 (0.952-1.166)	0.314	1.029 (0.949-1.115)	0.492	23.20%	0.209
Multivariate	3	[7,9,11]	1.194 (1.010-1.411)	0.037 ^a	1.130 (1.059-1.204)	0.000 ^a	81.00%	0.005
Squamous cell carcinoma OS	6	[10,13,16,20,22,23]	1.096 (0.896-1.341)	0.371	1.009 (0.908-1.120)	0.874	57.20%	0.039
Adenocarcinoma OS	2	[9,21]	1.360 (1.111-1.664)	0.003 ^a	1.385 (1.186-1.616)	0.000 ^a	22.00%	0.257

^aStatistical significance. n: Number of studies; HR: Hazard ratio; 95%CI: 95% confidence interval; Ph: P values of Q test for heterogeneity test; OS: Overall survival; DFS: Disease free survival.

HRs. There was also a significant association between a prolonged interval and worse OS in Asian, but not Caucasian patients. In addition, we found that a prolonged interval indicated worse OS (HR: 1.385, 95%CI: 1.186-1.616, $P < 0.001$; Table 2) in patients with AC. In contrast, a prolonged interval resulted in shorter OS without statistical significance (HR: 1.096, 95%CI: 0.896-1.341, $P > 0.05$; Table 2) in SCC patients. Taking all of these findings into consideration, worse OS was noted in the longer time interval group. There are several possible explanations for this result. One possible explanation may be the disproportionate number of medically complex patients between the two groups, which could have decreased the OS^[5]. Patients need to optimize medical comorbidities during see-and-wait follow-up. As a result, disease-specific survival may be closer to the real evaluation rather than OS. Another possible explanation is that the longer wait time was not due to preference or chance in the patients, but due to their poor physical condition after nCRT, which may have put them at an inherent disadvantage in terms of survival.

Some studies have shown that radiation-induced fibrosis may also make surgical dissection technically demanding with delayed surgery leading to higher complication rates^[2]. In contrast, Haisley *et al*^[5] found no effect on mortality and no increase in complications in the longer time interval group. Another source of uncertainty is cancer stage; however, no significant difference in initial clinical stage was observed between the longer time interval and shorter time interval groups^[14,23]. In addition, due to the heterogeneity of genotype and phenotype in esophageal cancer as well as constitutive resistance to individual cytotoxic drugs^[30], chemotherapy is rarely beneficial in all patients, and some researchers have reported that the pCR rate following preoperative chemoradiation for esophageal cancer could reach 20%-35%^[31]. Further well-designed and large-scale studies are needed to determine whether the time interval from the end of nCRT to surgery has an effect on survival outcome and to assess whether disease-specific survival differs by type of pathological response.

The strength of our study is that this is the first meta-analysis to investigate whether the time interval between nCRT and surgery affects survival outcome using pooled HRs. The total sample size in the 16 included studies was 12 621 patients with a survival of five or more years. Moreover, the larger number of included studies ensured the inclusion of subgroup analyses. To date, three similar meta-analyses have been published. The earliest meta-analysis by Lin *et al*^[32] included only five eligible studies and found that a longer time interval did not impact the five-year OS and pCR rates. The next meta-analysis was performed by Tie *et al*^[33], but did not reveal if a prolonged time interval had a significant impact on the five-year OS and pCR rates. Moreover, this study included conference abstracts, which may have introduced potential bias. The third study by Qin *et al*^[34] found that a prolonged interval between

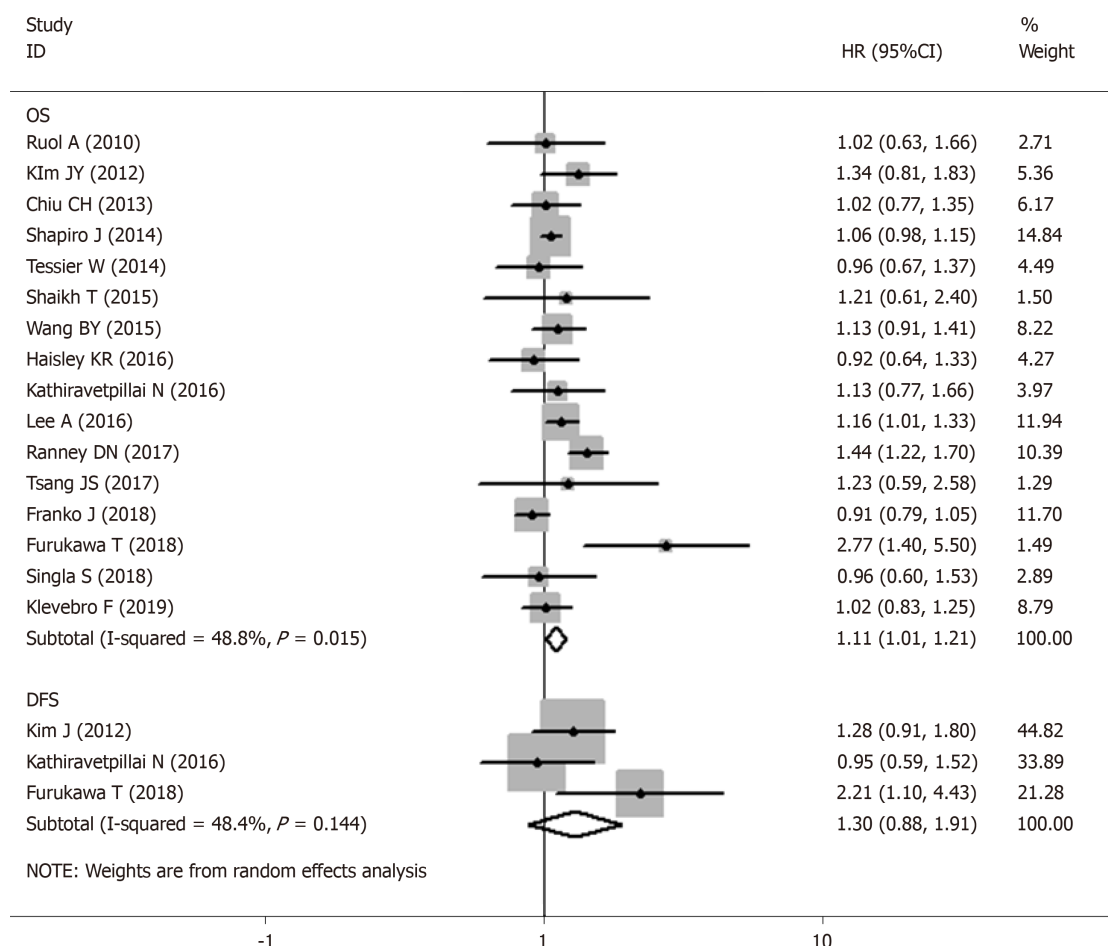


Figure 2 Forest plot of the association between time interval and overall survival/progression-free survival of esophageal cancer patients.

nCRT and surgery was significantly correlated with higher pCR and surgical mortality rate in esophageal cancer patients. Their study included only nine articles containing 5830 patients with a five-year survival, which were less than half of the sample size in our study. In addition, they did not investigate the association between time interval and survival outcomes.

Several limitations in our studies should be carefully addressed. The most important limitation was the fact that most of the studies included were retrospective. An additional uncontrolled factor is that heterogeneity was a potential factor that may have affected interpretation of the results. The source of heterogeneity in this study could be age, nCRT regimen, cut-off value, and ypTNM stage.

In conclusion, despite these limitations, this meta-analysis confirmed that a prolonged time interval between the completion of nCRT and surgery is related to decreased OS of esophageal cancer patients. It is suggested that esophagectomy should be performed within 7-8 wk after nCRT in view of OS, especially in patients with good recovery and response to nCRT. As some potential biases were hardly adjusted, our results still require further confirmation.

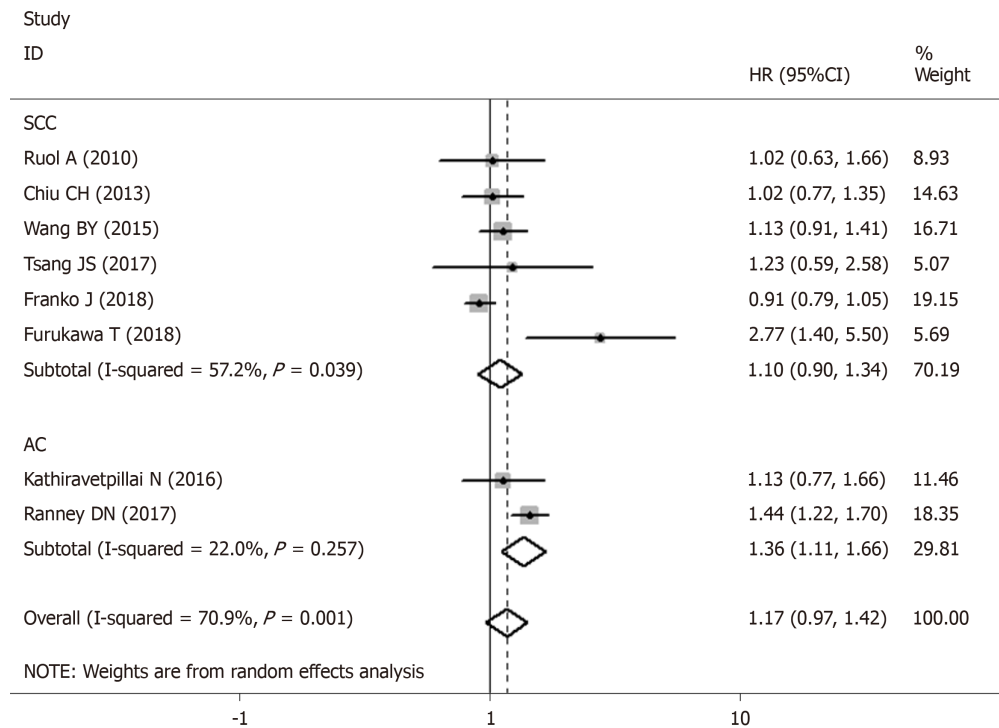


Figure 3 Forest plot of the association between time interval and overall survival of patients with squamous cell carcinoma and adenocarcinoma.

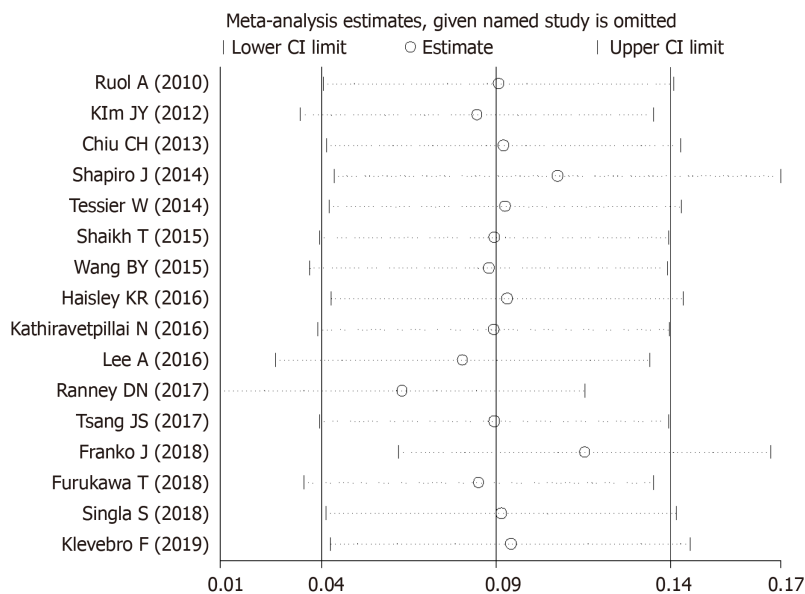


Figure 4 Sensitivity analysis of the association between time interval and overall survival. Combined results were still stable after the exclusion of any single study.

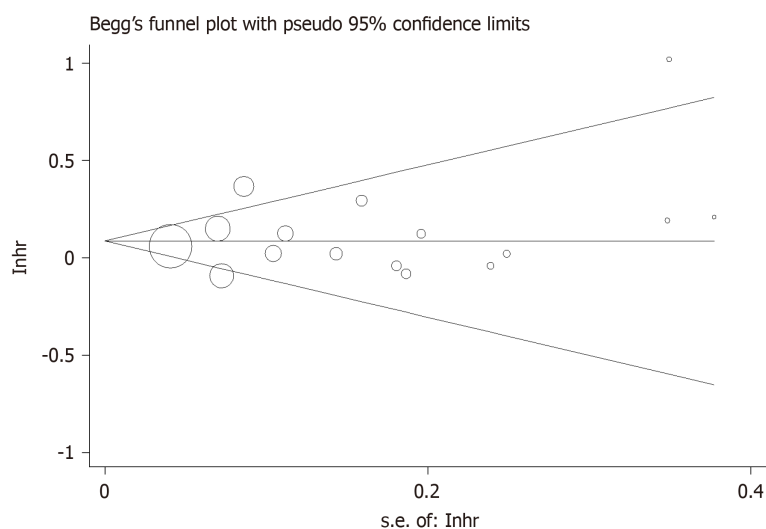


Figure 5 Begg's funnel plot of the association between time interval and overall survival. The Begg's funnel plot did not indicate publication bias in the meta-analyses on the association between time to surgery and overall survival ($P_{r>|z|} = 0.344$ for Begg's test).

ARTICLE HIGHLIGHTS

Research background

The optimal time interval for esophagectomy after neoadjuvant chemoradiotherapy (nCRT) in patients with esophageal cancer has not been defined.

Research motivation

Some studies have revealed that a prolonged interval (> 8 wk) between nCRT and esophagectomy is associated with a higher pathological complete response, which may improve survival in esophageal cancer patients. However, others have indicated that the prognostic role of the time interval in esophageal cancer is still controversial. For these reasons, it is necessary to perform a meta-analysis to systematically and comprehensively investigate the impact of different intervals on survival outcome in these patients.

Research objectives

To evaluate whether a prolonged time interval between the end of nCRT and surgery has an effect on survival outcome through meta-analysis.

Research methods

The research methods meta-analysis that were adopted to realize the objectives.

Research results

The results demonstrated that esophageal cancer patients with a prolonged time interval between the end of nCRT and surgery had significantly worse overall survival (OS) (HR: 1.107, 95%CI: 1.014-1.208, $P = 0.023$) than those with a shorter time interval. Subgroup analysis showed that poor OS with a prolonged interval was observed based on both the sample size and HRs. There was also significant association between a prolonged time interval and decreased OS in Asian, but not Caucasian patients. In addition, a longer waiting time resulted in worse OS (HR: 1.385, 95%CI: 1.186-1.616, $P < 0.001$) in patients with adenocarcinoma.

Research conclusions

This meta-analysis confirmed that a prolonged time interval between the completion of nCRT and surgery is related to decreased OS of esophageal cancer patients. It is suggested that esophagectomy should be performed within 7-8 wk after nCRT in view of OS, especially in patients with good recovery and response to nCRT.

Research perspectives

Several limitations in this analysis should be carefully addressed. The most important limitation was the fact that most of the studies included were retrospective. An additional uncontrolled factor is that heterogeneity was a potential factor that may have affected interpretation of the results. The source of heterogeneity in this study could be age, nCRT regimen, cut-off value, and ypTNM stage. As some potential biases were hardly adjusted, further well-designed and large-scale studies are needed to determine whether the time interval from the end of nCRT to surgery has an effect on survival outcome and to assess whether disease-specific survival differs by type of pathological response.

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