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ORIGINAL ARTICLE

Survival after neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: A meta-analysis

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Abstract

Background: The efficacy of surgery alone for patients with locally advanced esophageal cancer (EC) is still unsatisfactory. Presently, induction therapy followed by surgery is the standard treatment. Preoperative chemotherapy (CT) and chemoradiation (CRT) are proven effective induction therapies; however, few sample studies have addressed these treatments, thus, their superiority remains uncertain. We performed a systemic review and meta analysis to test the hypothesis that induction CRT prior to surgery could improve survival compared with induction CT alone.

Methods: A comprehensive search of PubMed and the Ovid database for relevant studies comparing EC patients undergoing resection after treatment with induction CT alone or induction CRT was conducted. Hazard ratios (HR) and 95% confidence intervals (95% CI) were extracted from these studies to provide pooled estimates of the effect of induction therapy on overall survival.

Results: Five studies met the criteria for analysis. Statistical analysis demonstrated a survival benefit of induction CRT compared with induction CT alone (HR0.73, 95% CI 0.61–0.89; $P = 0.002$). Further analysis showed that induction CRT perioperative mortality and complication rates were higher than for induction CT alone (HR 2.96, 95% CI 1.38–6.37; HR1.6, 95% CI 1.30–1.98; $P = 0.01$, respectively).

Conclusions: Published evidence comparing the different efficacies of induction CT and induction CRT is sparse, with few samples of adenocarcinoma. This analysis supports the view that, compared with induction CT, induction CRT could achieve a long-term survival benefit in EC patients.

Introduction

Esophageal cancer (EC) is a malignancy responsible for the eighth highest morbidity and sixth highest mortality rates worldwide, with more than 450 000 new cases diagnosed each year.[1] In China, EC morbidity and mortality rates sixth and fourth highest, respectively.[2] According to the Surveillance, Epidemiology, and End Results Program database, in the United States, where the morbidity of EC was traditionally thought to be low, new cases and deaths of EC in 2014 were still as high as 18 170 and 15 450, respectively.[3] Therefore, EC represents an important health issue, not only in China, but globally. Presently, surgery still is generally accepted as the main treatment for EC. Despite tremendous improvement in surgical techniques and comprehensive management, attributing to a reduction in perioperative complications and mortality, the long-term survival of EC patients who undergo surgery alone has not improved; most patients die of local recurrence and metastasis at different periods after surgery.[4] Compared with other malignancies, the prognosis of EC is dismal, with five-year survival ranging from 15–25%.[5] Most EC patients are diagnosed at locally advanced stage or even have distant metastasis, resulting in a poor prognosis.[6] In the past three decades, researchers have conducted clinical trials on comprehensive treatment based on surgery, aiming to improve the long-term survival of patients who receive surgery alone. Recently, neoadjuvant therapy has emerged as a potential treatment. Methods of neoadjuvant therapy include: induction radiation, induction chemotherapy (CT), and induction chemoradiation (CRT). Of these three treatments, induction radiation has gradually been rejected, as it increases perioperative complications and mortality without improving survival, whereas induction CRT and induction CT are presently thought to improve survival in EC patients.[7] Induction therapy is associated with its own toxic and side effects, however, and could also increase postoperative complications and mortality. The addition of induction radiation to induction CT could enhance these toxic and side effects; therefore, research comparing the long-term survival benefit between induction CT and induction CRT, as well as the differences in postoperative complication and mortality rates between the two treatment strategies, is of critical importance. The presently limited clinical trials and small samples regarding these therapy modalities have resulted in a lack of evidence to guide decisionmaking in clinical practice. Herein, we perform a systemic review and meta analysis of available data to determine if induction CRT is superior to induction CT alone in patients with resectable EC.

Materials and methods

Data sources and search strategy

Studies were identified by searching electronic databases and relevant publications. PubMed and the Ovid database were searched for English language articles published between January 1960 and December 2014 which met eligibility criteria. The search was limited to studies in humans.

Search terms included: ("preoperative chemotherapy" OR "neoadjuvant chemotherapy" OR "chemotherapy followed by surgery") AND ("preoperative chemoradiotherapy" OR "neoadjuvant chemoradiotherapy" OR "chemoradiotherapy followed by surgery") AND ("oesophagectomy" OR "oesophageal neoplasia" OR "esophageal carcinoma" OR "esophageal cancer").

Inclusion and exclusion criteria

Eligibility assessment was first performed independently by two authors who screened the titles and abstracts identified. Disagreements between reviewers were resolved by consensus. The full texts of shortlisted studies were reviewed and further assessed. All review authors decided on study inclusion. Inclusion criteria were as follows: (i) clinical trials comparing induction CT followed by surgery and induction CRT followed by surgery in EC patients; (ii) the survival rate was demonstrated in the study; (iii) the study included cases of pathologically confirmed EC, including gastroesophageal junction carcinoma; and (iv) all patients received primary treatment for resectable EC.

Exclusion criteria were as follows: (i) patients received non-surgical treatment; (ii) patients received no induction treatment; (iii) survival time was not documented; and (iv) no comparison between neoadjuvant CT and neoadjuvant CRT was made.

Quality assessment of literature

A modified Jadad rating scale was adopted to assess the methodology of the literature.[8] The content of the assessment included: (i) whether the study was randomized; (ii) whether the randomization methods were appropriate; (iii) whether the study was conducted as double blind; (iv) whether the double blind methods were appropriate; and (v) reasons why any case was lost to follow-up.

Data collection

The items of data collected included: first author names; date of publication; number of cases; pathological type; neoadjuvant CT regimen; neoadjuvant CRT methods and radiation dose; perioperative mortality; postoperative complication rate; and survival data.

Outcome indices of literature

Outcomes of the study included: overall survival (OS); disease-free survival (DFS); perioperative mortality; and postoperative complication rates.

Statistical analysis

All of the indices in the study were enumeration data and disposed by STATA 12.0 statistical software (Stata Corp., College Station, TX, USA). The results were demonstrated by hazard ratio (HR) and 95% confidential interval (CI). A Q test was used to evaluate the heterogeneity between groups, where $I^2 > 50\%$ was viewed as heterogeneous. When warranted, results were pooled under a random effect model, in view of anticipated differences in clinical design. A Z test was used to analyze the effect size, 0.05 was determined as the standard of significance, and a Begg's test was applied to explore publication bias.

Results

General information

The initial PubMed search yielded 1108 studies; 1102 were discarded after an abstract and title review demonstrated that they did not meet inclusion criteria: (i) no comparison of neoadjuvant CT and neoadjuvant CRT; or (ii) the study was not a clinical trial. Full texts of the remaining six studies were further examined. One of these studies was eliminated because of incomplete survival information. Thus, a total of five clinical trials were included in the systematic review,

Table 1 Clinical trials of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy

Author, Date	Patient Group	Pathology	Regimen
Stahl, 2009[9]	cT3-4NxM0, n = 119 CT (n = 59) CRT (n = 60)	Adenocarcinoma	CT: 2.5 courses of cisplatin, fluorouracil, leucovorin (PLF) CRT: 2 courses of PLF + 30 Gy RT in 15 fractions + cisplatin + etoposide
Burmeister, 2011[10]	cT2-3N0-1, n = 75 CT (n = 36) CRT (n = 39)	Adenocarcinoma	CT: 2 courses of cisplatin, fluorouracil (CF) CRT: 2 courses of CF + 35 Gy RT in 15 fractions
Swisher, 2010[11]	cT1-3N0-1, n = 157 CT (n = 76) CRT (n = 81)	Adenocarcinoma (85%) Squamous (15%)	CT: 3 courses of CF (n = 44) 3–5 courses of CF + arabinoside (n = 32) CRT: 2 courses of TPF + 45 Gy RT in 25 fractions +TF (n = 38) 2 courses of cisplatin + CPT-11 + 45 Gy RT in 25 fractions + TF (n = 43)
Morgan, 2007[12]	cT3N0-1, n = 205 CT (n = 88) CRT (n = 117)	Adenocarcinoma (n = 161) Squamous (n = 44)	CT: 2 courses of cisplatin (n = 76) 4 courses of CF + epirubicin (n = 41) CRT: 2 courses of CF + 45 Gy RT in 25 fractions +CF
Luu, 2008[13]	cII-IV, n = 122 CT (n = 58) CRT (n = 64)	Adenocarcinoma (n = 96) Squamous (n = 26)	CT: platin-based therapy (n = 53) Etoposide + 5-FU + leucovorin (n = 5) CRT: platin-based therapy + RT From 45 Gy to 60Gy

CT, chemotherapy; CRT, chemoradiation; RT, radiotherapy.

including three randomized controlled trials (RCTs), one non-randomized cross-comparison study, and one retrospective study. The five clinical trials included in the study were published in 2007–2011, with a total of 678 patients, among which 317 received neoadjuvant CT and 361 received neoadjuvant CRT. The gender distribution of the patients was 585 men and 93 women. Pathological type included 94 squamous cell carcinoma and 584 adenocarcinoma, with two studies only including adenocarcinoma patients.

The studies had all adopted the tumor node metastasis (TNM) staging system, and patients in most of the studies were clinical stage II/III patients, while 21 patients from two studies were clinical stage IV patients. The neoadjuvant CT regimen mainly adopted was a platinum-based combination CT, ranging from 2–5 cycles with radiation doses ranging from 30–60 Gy. Table 1 details the characteristics of the therapy regimes.

Overall survival of esophageal cancer (EC) patients: Neoadjuvant chemoradiation (CRT) versus neoadjuvant chemotherapy (CT)

The comparison of OS between neoadjuvant CRT plus surgery and neoadjuvant CT plus surgery is demonstrated in Figure 1. All five clinical trials (with a total of 678 cases) offered overall survival information, and all reported that patients who underwent surgery after neoadjuvant CRT tended to obtain longer survival compared with those who received surgery after neoadjuvant CT; however, only one study showed a statistically significant survival difference. Pooling the survival results showed that long-term survival of patients treated with induction CRT was better than induction CT alone, and the differences were statistically significant (HR 0.73, 95% CI 0.61–0.89; $P = 0.02$). No between-group variability was observed ($I^2 = 0.0\%$).

Disease-free survival of EC patients: Neoadjuvant CRT versus neoadjuvant CT

Induction CRT improved DFS over induction CT alone in resectable EC patients. A DFS comparison between induction CRT and induction CT alone in resectable EC patients is illustrated in Figure 2. Two clinical trials (with a total of 279 cases), offered DFS information, and concluded that EC patients who received induction CRT plus surgery tended to obtain longer DFS compared with those who received induction CT plus surgery; however, a statistically significant difference was only observed in one study. Pooling of data from these studies demonstrated a statistically significant DFS benefit of induction CRT versus induction CT alone (HR 0.73, 95% CI 0.54–0.98; $P = 0.037$). The estimated proportion of between-study variability (I^2) was 64%, indicating heterogeneity.

Postoperative pathologic complete response rate in resectable EC patients: Induction CRT versus induction CT alone

The postoperative pathologic complete response (pCR) rate comparison between induction CRT and induction CT alone in resectable EC patients is illustrated in Figure 3. All five clinical trials (with a total of 678 cases) offered pathological pCR rates. Individually, each of the five studies demonstrated a higher postoperative pCR rate for induction CRT versus induction CT alone; three clinical trials reported a statistically significant difference. Pooling of data from these five studies

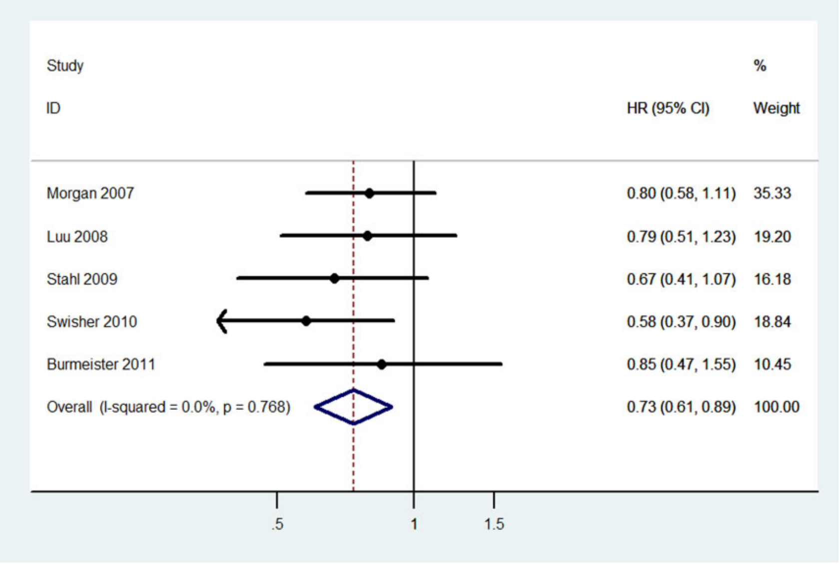

Figure 1 Meta analysis comparing the overall survival between induction chemoradiation plus surgery and induction chemotherapy plus surgery. CI, confidence interval; HR, hazard ratio.

(n = 678 patients) demonstrated a significantly higher pCR rate for induction CRT versus induction CT alone (response rate [RR] 6.48, 95% CI 3.36–12.49; $P < 0.001$]. No between-study variability was observed ($I^2 = 0.0\%$).

Perioperative mortality in resectable EC patients: Induction CRT versus induction CT alone

A perioperative mortality comparison between induction CRT and induction CT alone in resectable EC patients is illustrated in Figure 4. All five clinical trials (with a total of 678 patients) offered perioperative mortality data; four of these studies demonstrated that patients who received induction CRT plus surgery tended to suffer higher perioperative mortality compared with those who received induction CT alone plus surgery. One study showed statistical significance, while another demonstrated no perioperative patient death in either of the two groups. Pooling of the data from these five studies showed a statistically significant higher postoperative mortality rate of induction CRT versus induction CT alone (HR 2.96, 95%

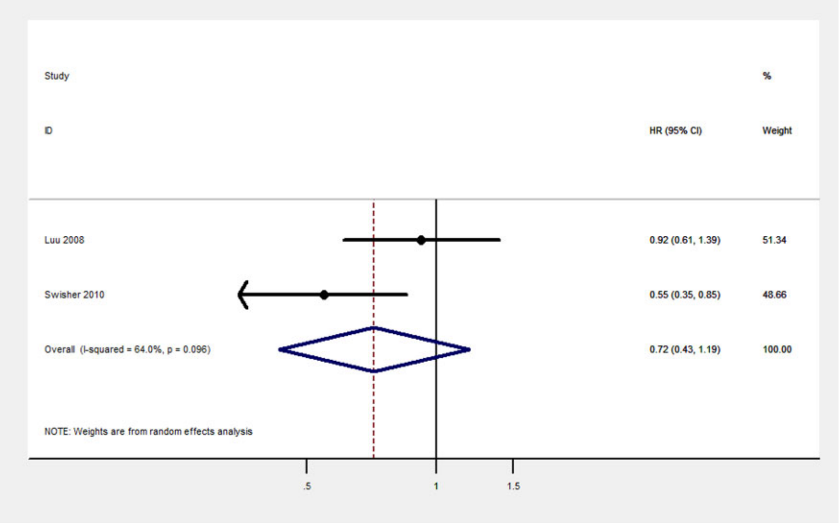

Figure 2 Meta analysis comparing the disease-free survival of patients receiving induction chemoradiation plus surgery and induction chemotherapy alone plus surgery. CI, confidence interval; HR, hazard ratio.

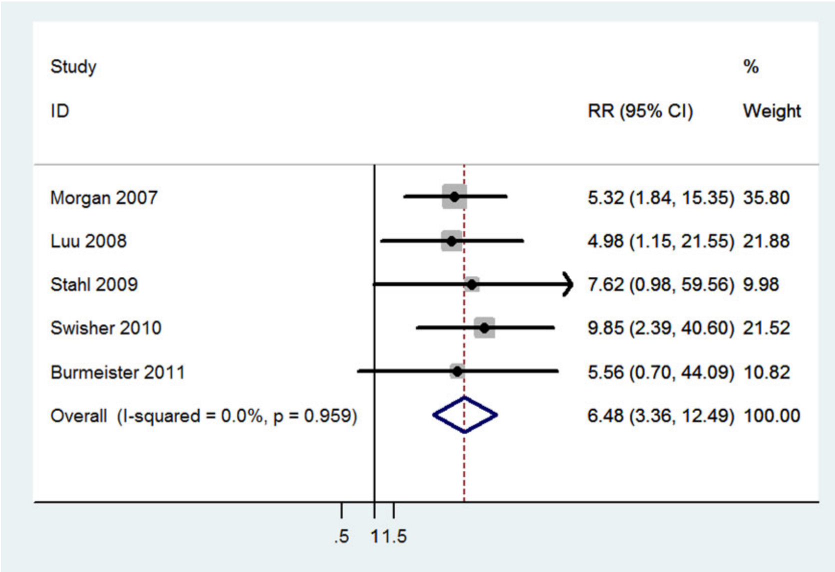

Figure 3 Meta analysis comparing the postoperative pathologic complete response rate of patients receiving induction chemoradiation plus surgery and induction chemotherapy alone plus surgery. CI, confidence interval; HR, hazard ratio.

CI 1.38–6.37; $P = 0.005$). No between-study variability was observed ($I^2 = 0.0\%$).

Postoperative complication rate in resectable EC patients: Induction CRT versus induction CT alone

A comparison of postoperative complication rates between induction CRT and induction CT alone in resectable EC patients is illustrated in Figure 5. Four of the five clinical trials (with a total of 559 cases) offered postoperative complication data; three studies reported that patients who received induction CRT plus surgery tended to suffer from higher postoperative complication rates compared with those who received induction CT alone plus surgery; however, only one study showed statistical significance. Pooling of the data from these four studies (n = 559 patients) demonstrated a statistically significant higher postoperative complication rate for

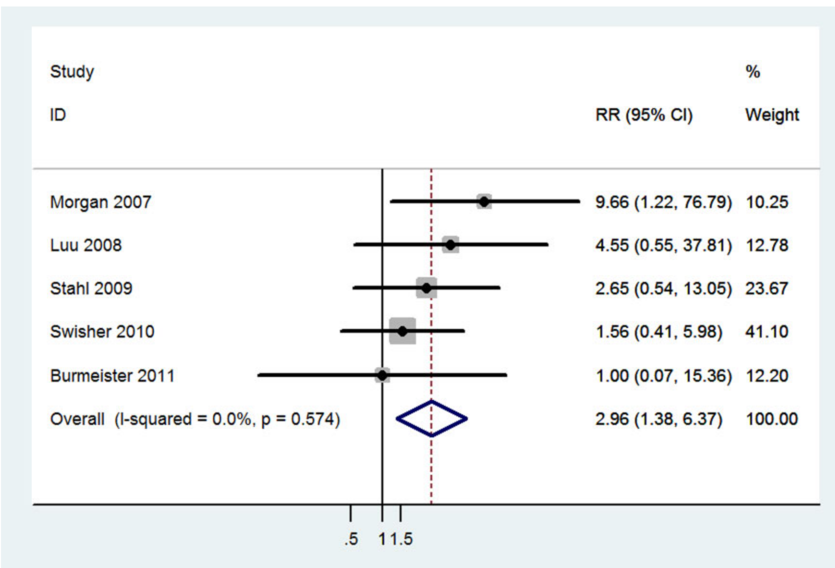

Figure 4 Meta analysis comparing the perioperative mortality of patients receiving induction chemoradiation plus surgery and induction chemotherapy alone plus surgery. CI, confidence interval; HR, hazard ratio.

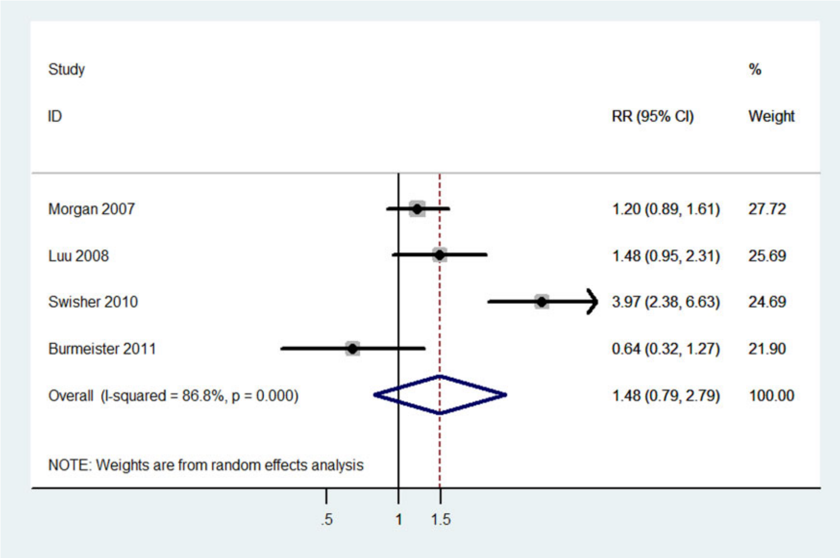

Figure 5 Meta analysis comparing the postoperative complication rate between induction chemoradiation plus surgery and induction chemotherapy alone plus surgery. CI, confidence interval; HR, hazard ratio.

induction CRT versus induction CT alone (HR 1.61, 95% CI 1.30–1.98; $P < 0.01$]. However, between-study variability was observed ($I^2 = 86.8\%$).

Bias test of the literature

Of the five studies in this meta analysis, after performing a Begg's test, no asymmetry in the funnel plot was observed, indicating that no significant publication bias existed in the OS major research index (Fig 6).

Discussion

The status quo of EC treatment

To date, surgery is the main treatment for EC, and is an effective treatment modality for early stage patients, with five-year survival reaching more than 70%.[14] Unfortunately, over two thirds of patients are in locally advanced stage at diagnosis (>T2 or > = N1); thus, the efficacy of surgery alone for these patients is relatively unsatisfactory.[6] Presently, preoperative

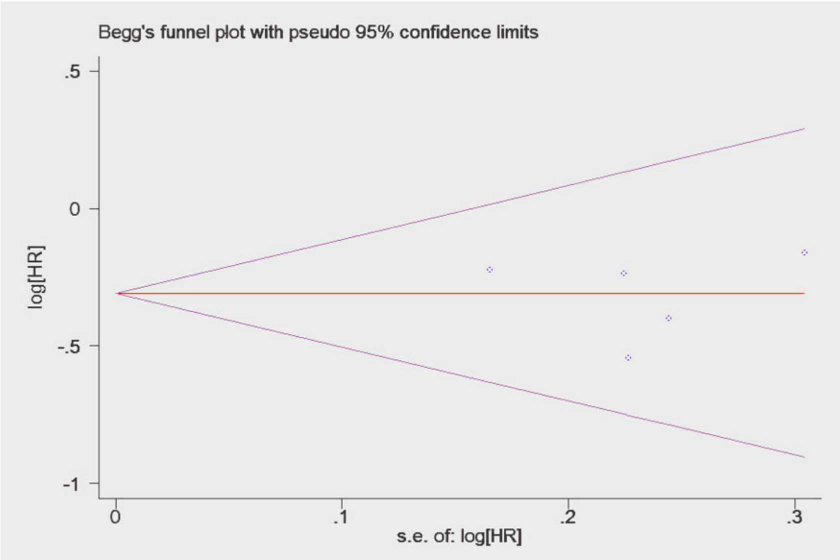

Figure 6 Funnel plot of the overall survival between patients receiving induction chemoradiation plus surgery and those receiving induction chemotherapy plus surgery. HR, hazard ratio; SE, standard error.

therapy, particularly preoperative CT and preoperative CRT, have been proven to improve patient survival. The Medical Research Council Oesophageal Cancer Working Group conducted a prospective randomized controlled clinical trial (OEO2) comparing the efficacy of preoperative CT plus surgery versus surgery alone for resectable EC patients.[15] The study enrolled a total of 802 patients, from March 1992 to June 1998, which were randomized into two groups: 400 patients in the neoadjuvant CT plus surgery group and 402 patients in the single surgery group. The regimen of neoadjuvant CT was two cycles of cisplatin plus 5-fluorouracil. Their results demonstrated that the R0 resection rate in the neoadjuvant CT plus surgery group was higher compared with the surgery alone group (60% vs. 54%; $P < 0.001$), without an increase in postoperative complication rate (41% vs. 42%, respectively). The median and two-year survival rates of patients in the neoadjuvant group were longer than in the surgery alone group (16.8 vs. 13.3 months; 43% vs. 34%, respectively). The study concluded that two cycles of CT before surgery could prolong the OS and DFS of patients without increasing perioperative risk. This clinical trial also laid the foundation for induction CT in the comprehensive treatment of EC in Europe and concluded an ongoing argument upon whether neoadjuvant CT could prolong the survival of EC patients. A few years later, van Hagen *et al.* conducted the famous CROSS trial, comparing the efficacy of induction CRT followed by surgery and single surgery in the treatment of EC.[16] The study enrolled a total of 366 patients from August 2004 to December 2008 with 178 patients grouped randomly into a neoadjuvant CRT group and 188 patients into a single surgery group. Again, the results confirmed that induction CRT based on paclitaxel plus carboplatin followed by surgery could prolong the median survival time of EC patients (49.4 vs. 24 months) and improved their overall survival (HR 0.675, 95% CI 0.495–0.971; $P = 0.003$) This study, in turn, laid the foundation for neoadjuvant CRT in the comprehensive treatment of EC. However, a lack of evidence of the effects of neoadjuvant CT and neoadjuvant CRT means that clinicians have difficulty in deciding upon appropriate treatment. Thus, a definitive conclusion is urgently needed in order to guide treatment decisions in clinical practice.

The potential pros and cons of induction CT and induction CRT in EC treatment

The esophagus is located at the bottom of the laryngopharynx and leads down to the abdominal cavity to connect the stomach through the posterior mediastinum. The cervical, thoracic, and abdominal anatomic sites of the esophagus are surrounded by many vital organs; thus, an esophagectomy is a highly traumatic surgery with high mortality and complication rates.[17] In order to reduce the high risks associated with esophagectomy, perioperative treatment for EC patients needs to be developed. Presently, the preferred perioperative treatment is induction therapy. Induction CT offers the following potential benefits: (i) a downstage in tumor stage; (ii) eradication of subclinical micro metastasis; (iii) reduction in the risk of implantation metastasis; (iv) better patient tolerance compared with patients receiving induction CRT, which allows the patient to complete the whole treatment; and (v) tumors are usually rich in blood supply, which provides better efficacy using CT.[18] There are several potential advantages of induction CRT compared with induction CT alone: (i) an increase in the R0 resection rate enables more patients to undergo complete resection; (ii) an increase in pCR rate improves patient survival; and (iii) prolonged DFS. However, the potential disadvantages are as follows: (i) an increase in postoperative complication and mortality rates; (ii) radiation therapy is associated with its own complications, including radiation-induced pneumonitis and pulmonary fibrosis; (iii) adding induction radiation to induction CT may prolong the treatment cycle; and (iv) an increase in medical expense.[19]

Long-term survival: Induction CRT versus induction CT alone

As a result of the need for development of preoperative therapy for EC, debate on the efficacy of preoperative treatment and single surgery remains. Studies regarding the superiority of induction therapies are limited.[20,21] Sjoquist *et al.* assessed the efficacy of neoadjuvant CRT plus surgery and neoadjuvant CT plus surgery in a meta analysis of two RCTs, with a total of 194 cases.[20] The results demonstrated no superiority of preoperative CRT to preoperative CT (HR 0.77, 95% CI 0.53–1.12; $P = 0.17$). However, the meta analysis did not compare perioperative complication and mortality or RRs between the two induction treatment modalities; thus, the authors finally concluded that a clear advantage of neoadjuvant CRT over neoadjuvant CT had not been established. The present meta analysis synthesized the results of five clinical trials with a total of 678 patients; we found that induction CRT improved the OS of EC patients compared with induction CT alone (HR 0.73, 95% CI 0.61–0.89; $P = 0.002$) and the pCR rate was higher in the induction CRT group (RR 6.48, 95% CI 3.36–12.49; $P < 0.001$).

We further analyzed the perioperative mortality and complication rates of the two groups, and our results demonstrated that, compared with neoadjuvant CT, perioperative mortality and the postoperative complication rate were higher in the neoadjuvant CRT group (HR 2.96, 95% CI 1.38–6.37; $P = 0.005$; HR 1.61, 95% CI 1.30–1.98; $P < 0.001$, respectively). Therefore, it is of critical importance to determine how to to maintain survival benefits and reduce the mortality and complication rates of induction CRT in EC patients.

Limitations of the study

Among the five studies included in our meta analysis, only three were RCTs, at level II levels of evidence; one was a non-randomized cross-comparison study; and the other was a retrospective cohort study, at a level III level of evidence. The survival data of the present study were completely based on original literature; therefore, we were unable to subanalyze different pathological types of EC and patients' responsiveness to induction therapy. In addition, the definitions of postoperative complications in the varied literature were disparate, leading to a gap in postoperative complication rates among individual studies.

The meta analysis we conducted demonstrated that research regarding the superiority of induction CRT and induction CT in EC treatment is limited, with a small sample size. In addition, adenocarcinoma was the dominant pathological type, with as few as 94 squamous cancer patients, among which 70 cases were in non-RCT trials.

Thus, randomized controlled clinical trials with large samples are urgently required in order to guide clinicians in choosing an induction treatment modality for esophageal squamous cancer, a major pathological type of EC. Additionally, more clinical trials are required to compare the survival of patients in which induction therapy was effective and ineffective, in order to yield detailed information of induction treatment.

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Disclosure

No authors report any conflict of interest.

References

1 Ferlay J, Soerjomataram I, Ervik M *et al*. *GLOBOCAN 2012 V 1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No 11 [Internet]*. International Agency for Research on Cancer, Lyon, France 2013.

2 Chen W, Zheng R, Zhang S *et al*. Report of incidence and mortality in China cancer registries, 2009. *Chin J Cancer Res* 2013; **25**: 10–21.

3 Howlader N, Noone AM, Krapcho M *et al*. *SEER Cancer Statistics Review*. National Cancer Institute, Bethesda MD 1975–2011.

4 Hyngstrom JR, Posner MC. Neoadjuvant strategies for the treatment of locally advanced esophageal cancer. *J Surg Oncol* 2010; **101**: 299–304.

5 Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2013; **381**: 400–12.

6 Pennathur A, Farkas A, Krasinskas AM *et al*. Esophagectomy for T1 esophageal cancer: Outcomes in 100 patients and implications for endoscopic therapy. *Ann Thorac Surg* 2009; **87**: 1048–54.

7 Arnott SJ, Duncan W, Kerr GR *et al*. Low dose preoperative radiotherapy for carcinoma of the oesophagus: Results of a randomized clinical trial. *Radiother Oncol* 1992; **24**: 108–13.

8 Jadad AR, Moore RA, Carroll D *et al*. Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. *Control Clin Trials* 1996; **17**: 1–12.

9 Stahl M, Walz MK, Stuschke M *et al*. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851–6.

10 Burmeister BH, Thomas JM, Burmeister EA *et al*. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011; **47**: 354–60.

11 Swisher SG, Hofstetter W, Komaki R *et al*. Improved long-term outcome with chemoradiotherapy strategies in esophageal cancer. *Ann Thorac Surg* 2010; **90**: 892–8.

12 Morgan MA, Lewis WG, Crosby TD *et al*. Prospective cohort comparison of neoadjuvant chemoradiotherapy versus chemotherapy in patients with oesophageal cancer. *Br J Surg* 2007; **94**: 1509–14.

13 Luu TD, Gaur P, Force SD *et al*. Neoadjuvant chemoradiation versus chemotherapy for patients undergoing esophagectomy for esophageal cancer. *Ann Thorac Surg* 2008; **85**: 1217–23.

14 Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: Esophagus and esophagogastric junction. *Ann Surg Oncol* 2010; **17**: 1721–4.

15 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: A randomised controlled trial. *Lancet* 2002; **359**: 1727–33.

16 van Hagen P, Hulshof MC, van Lanschot JJ *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074–84.

17 Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011; **364**: 2128–37.

18 Mulligan ED, Dunne B, Griffin M, Keeling N, Reynolds JV. Margin involvement and outcome in oesophageal carcinoma: A 10-year experience in a specialist unit. *Eur J Surg Oncol* 2004; **30**: 313–7.
19 Shah AA, Berry MF, Tzao C *et al*. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* 2012; **93**: 1807–12.
20 Sjoquist KM, Burmeister BH, Smithers BM *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol* 2011; **12**: 681–92.
21 Hamilton E, Vohra RS, Griffiths EA. What is the best neoadjuvant regimen prior to oesophagectomy: Chemotherapy or chemoradiotherapy? *Int J Surg* 2014; **12**: 196–9.

