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ORIGINAL ARTICLE

Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: A meta-analysis

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Abstract

Background: Esophageal squamous cell carcinoma (ESCC) is the predominant type of esophageal cancer and most clinically curable patients are diagnosed with locally advanced disease. While the efficacy of preoperative treatment is relatively clear and well characterized, the effect of postoperative treatment, especially postoperative chemotherapy, remains controversial, and its role in the treatment strategy is obscure. We conducted an updated meta-analysis to include recent developments.

Methods: A comprehensive search in the PubMed, Embase, and Cochrane databases was performed to identify studies published from the inception of each database to February 2018. The overall survival (OS) and disease-free survival (DFS) rates of patients treated with and without postoperative chemotherapy were analyzed and compared. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the associations between postoperative chemotherapy and patient survival. Potential publication bias was assessed using Egger's line regression test.

Results: A total of nine studies, including three randomized controlled trials and six retrospective studies, were retrieved from the databases, comprising a total of 1684 cases. The results showed that postoperative chemotherapy could improve OS (HR 0.78, 95% CI 0.66–0.91; $P = 0.002$) and DFS (HR 0.72, 95% CI 0.6–0.86; $P < 0.001$).

Conclusions: The current meta-analysis supports postoperative chemotherapy as an independent favorable prognostic factor for ESCC, which could improve both OS and DFS.

Introduction

The incidence and mortality of esophageal cancer rank ninth and sixth among all malignancies in the world, respectively, and over 80% of esophageal cancer cases occur in developing countries.[1] China has a high incidence of esophageal cancer, and esophageal squamous cell carcinoma (ESCC) is the predominant histopathological type. According to statistics, in 2016 the incidence and mortality of esophageal cancer ranked fifth and fourth among all malignancies in China, respectively.[2] Except for a few early lesions identified by screening in high-risk populations, most of the clinically curable patients are diagnosed with advanced disease, for which treatment with surgery alone results in unsatisfactory outcomes. Multidisciplinary regimens have received increasing attention and have gradually become the mainstream approach for treating esophageal cancer. The combination patterns of comprehensive treatment include preoperative therapy (chemotherapy/chemo-radiation) and postoperative therapy (chemotherapy/radiation/chemo-radiation). While the efficacy of preoperative treatment is relatively clear, the effect of postoperative treatment, especially postoperative chemotherapy, remains controversial, with no consensus being reached. The underlying reason is that trauma resulting from esophagectomy is profound, and patient tolerance to chemotherapy after surgery is poor; therefore, only a few patients can

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complete an adjuvant chemotherapy plan. This circumstance further leads to a lack of data.

However, postoperative chemotherapy has had remarkable success in many other solid tumors, such as non-small cell lung, breast, and colorectal cancers, and has become the recommended therapeutic option in the clinical guidelines for treating such tumors. As a result, postoperative chemotherapy continues to be administered for esophageal cancer, one of the major solid tumors. Unfortunately, because of the limitations of sample sizes, neither prospective clinical trials nor retrospective studies have resulted in a conclusion; for this reason, meta-analyses have stood out for their ability to improve the quality of data. Two meta-analyses regarding the influence of postoperative chemotherapy on the survival of esophageal cancer patients have been published, with differing conclusions. While one demonstrated that postoperative chemotherapy could not improve the survival of these patients, the other study concluded that for a particular subgroup of patients (with positive lymph nodes), postoperative chemotherapy could improve survival. Nevertheless, both meta-analyses shared limitations, such as mixed disease stages and patient heterogeneity. Therefore, the current study aimed to overcome this limitation and to conduct an updated meta-analysis of the associations between postoperative chemotherapy and survival of esophageal cancer patients including literature published after 2012.

Methods

Two senior attending surgeons from the Department of Thoracic Surgery independently searched the PubMed, Embase, and Cochrane databases using the keywords "esopha* or oesopha*," "cancer or carcinoma or neoplasm," "adjuvant or postoperative," and "therapy or chemotherapy or radiotherapy or chemo*therapy." All English language articles of human studies were retrieved from the inception of each database to 13 February 2018.

Study endpoints

The primary and secondary endpoints of this meta-analysis were the influence of postoperative chemotherapy on the overall survival (OS) and disease-free survival (DFS), respectively, of ESCC patients.

Inclusion and exclusion criteria

Two authors independently screened titles and abstracts eligible for the study and decided which articles to include in the meta-analysis after reading the full text. Inclusion criteria were: (i) ESCC patients as subjects; (ii) studies that focused on adjuvant therapy for esophageal cancer and included comparisons between adjuvant chemotherapy and surgery alone; (iii) independent clinical trials with an analysis of clinical data; and (iv) articles that reported prognostic hazard ratios (HRs) and 95% confidence intervals (CIs) of OS and DFS. Other criteria considered for article inclusion or exclusion were as follows: (i) the disease classification and sample size; (ii) the number of patients receiving adjuvant chemotherapy; and (iii) the completeness and reliability of statistical information. Disagreement between the two investigators regarding the inclusion or exclusion of studies was reconciled by consulting a third more senior physician. The quality of the studies in this meta-analysis was assessed using the Newcastle Ottawa Scale (NOS), and papers with scores ≥ 6 were defined as high quality.

Statistical analysis

Statistical analysis was performed using Stata 12.0 software (Stata Corp., College Station, TX, USA). The study endpoints were demonstrated by OS, DFS, and their respective HRs and 95% CIs. Heterogeneity among the included studies was assessed by the Q test and I^2 statistic. If $I^2 \leq 50\%$, a fixed effect model was used; if $I^2 > 50\%$, a random effect model was applied. Egger's test was used to evaluate publication bias in the literature.

Result

Literature search

After the initial screening, we identified 3225 related publications, including 691 from PubMed, 1873 from Embase, and 661 from Cochrane. A total of 548 duplicates were identified and excluded. After reading the titles and abstracts of the remaining 2677 publications, 2657 were discarded for the following reasons: (i) irrelevant to adjuvant therapy for esophageal cancer (n = 2554); (ii) non-original studies, such as reviews or meta-analyses (n = 39); (iii) completely irrelevant to prognosis (n = 20); (iv) inclusion of only adenocarcinoma or other types of cancer, with no squamous cell carcinoma (n = 22); and (v) inclusion of only adjuvant radiation or adjuvant chemoradiation, with no adjuvant chemotherapy (n = 22). The remaining 20 articles were further screened by carefully reading the full text to exclude those that did not report the HR or 95% CI of either OS or DFS (n = 11). Finally, nine articles were included in this meta-analysis (Fig 1).

Study characteristics

The study characteristics by research group, including author, publication year, country, study type, histological classification, numbers in surgery alone and adjuvant

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chemotherapy groups, pathological staging, R0 resection status, regimen of chemotherapy, number of cycles of chemotherapy, and either OS or DFS, are detailed in Table 1. The nine studies in the meta-analysis were published between 1996 and 2016, with a total of 1684 patients; the pathological type was ESCC for all included patients. All the included literature was evaluated as high quality (NOS ≥ 6).

Result of meta-analysis

Overall survival

A total of nine publications (n = 1684) reported the influence of adjuvant chemotherapy on OS, and a heterogeneity test of the included articles showed I^2 = 0.0% and P = 0.465; therefore, the fixed effect model was used for analysis. The results showed that ESCC patients receiving postoperative chemotherapy could achieve improved OS (HR 0.78, 95% CI 0.66–0.91; P = 0.002) (Fig 2).

Disease-free survival

A total of five publications (n = 1102) reported the influence of adjuvant chemotherapy on DFS, and a heterogeneity test of the included articles showed I^2 = 0.0% and P = 0.689; therefore, the fixed effect model was used for analysis. The results showed that ESCC patients receiving postoperative chemotherapy could also achieve improved DFS (HR 0.72, 95% CI 0.6–0.86; P < 0.001) (Fig 3).

Publication bias

Risk analysis of publication bias was assessed using Egger's test, and the results showed no obvious publication bias among the included studies, indicating that the levels of heterogeneity and bias were acceptable (Fig 4).

Discussion

Perioperative comprehensive treatment is superior to surgery alone

Esophagectomy has long been the primary treatment for esophageal cancer. However, with recent technological advances, intramucosal carcinoma has been successfully treated by endoscopic mucosal resection. Conversely, patients with distant metastasis are usually considered incurable, and palliative care is the most common treatment option for this group. Except in these circumstances, all patients with ESCC are potentially curable, and approximately 80% have locally advanced disease. The five-year OS of these patients after surgery alone ranges from 15% to 24%,[12] which is far from satisfactory. It is believed that perioperative treatment could improve the long-term survival of patients, and, indeed, the effect of preoperative treatment is relatively clear. Strong evidence has been documented in the CROSS study (median survival of patients in the preoperative chemoradiation and surgery alone groups was 49.4 and 24 months, respectively; P = 0.003),[13] the OEO2 study (five-year OS of patients in the preoperative chemotherapy and surgery alone groups was 23% and 17.1%, respectively; P = 0.03)[14] and the JCOG9907 study (five-year OS of patients in the preoperative chemotherapy and postoperative chemotherapy groups was 55% and 43%, respectively; P = 0.04).[15] There is also evidence to indicate that postoperative chemotherapy could improve patient survival; the results of the JCOG9204

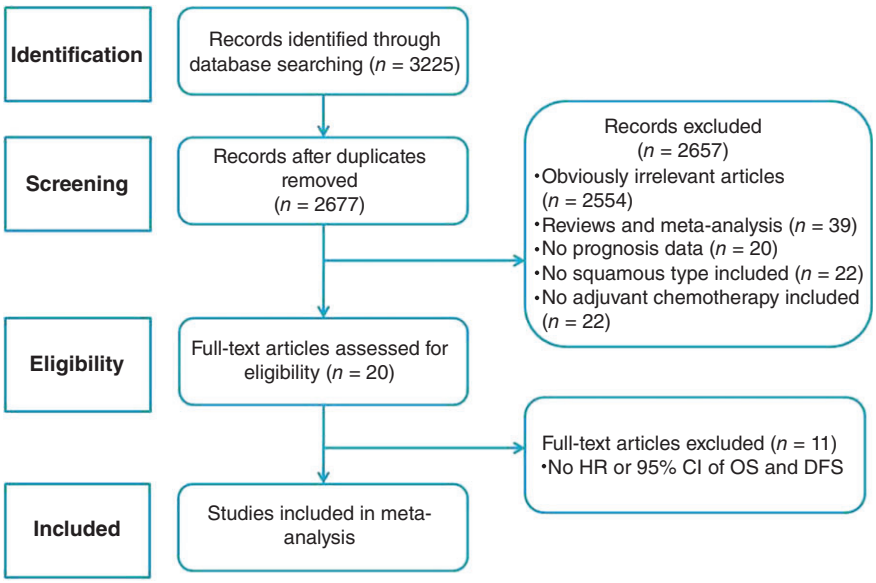

Figure 1 Flow chart of the screened, excluded, and analyzed publications, including the preferred reporting systems for systematic review and meta-analysis. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

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Table 1 Characteristics and quality of the included studies (NOS)

Study	Publication year	Country	Study type	Pathological type	Surgery alone (*n*)	Adjuvant therapy (*n*)	Pathological staging	Margin status	Regimen	Cycles of chemo	OS HR (95% CI)	DFS HR (95% CI)	NOS
Pouliquen *et al.*[3]	1996	France	RCT	Squa	38	24	LN +, M1	R0,R+	Cisplatin 100 mg/m^2, 5-Fu 1000 mg/m^2	6–8	0.923 (0.31–2.746)	N/A	6
Ando *et al.*[4]	1997	Japan	RCT	Squa	100	105	I–IV	R0	Cisplatin 70 mg/m^2, Vindesine 6 mg/m^2	2	0.84 (0.57–1.24)	N/A	8
Herooret *al.*[5]	2003	Japan	Non-RCT	Squa	117	94	I–IV	R0	Cisplatin 70 mg/m^2, Vindesine 3 mg/m^2; Cisplatin70 mg/m^2, 5-Fu 700 mg/m^2	2	1.175 (1.005–2.962)	N/A	6
Ando *et al.*[6]	2003	Japan	RCT	Squa	122	120	II–IV	R0	Cisplatin 80 mg/m^2, 5-Fu 800 mg/m^2	2	0.82 (0.54–1.25)	0.75 (0.52–1.07)	8
Lee *et al.*[7]	2005	South Korea	Non-RCT	Squa	52	40	II–IV	R0	Cisplatin 60 mg/m^2, 5-Fu 1000 mg/m^2	3	0.7 (0.36–1.37)	0.67 (0.38–1.19)	7
Hashiguchi *et al.*[8]	2014	Japan	Non-RCT	Squa	88	51	II–III	R0	Cisplatin 60 mg/m^2, 5-Fu 500 mg/m^2, Docetaxel60 mg/m^2	2	1.01 (0.59–1.71)	0.99 (0.59–1.65)	6
Lyu *et al.*[9]	2014	China	Non-RCT	Squa	143	52	II–III	R0	Cisplatin 50 mg/m^2, Paclitaxel 150 mg/m^2	5	0.488 (0.314–0.795)	0.71 (0.46–1.08)	6
Pasquer *et al.*[10]	2015	France	Non-RCT	Squa	53	51	LN+	R0	Platinum, 5-Fu, +/–Epirubicin	4	N/A	N/A	8
Qin *et al.*[11]	2016	China	Non-RCT	Squa	321	113	II–III	R0	Docetaxel 60–75 mg/m^2, Paclitaxel 150–175 mg/m^2	4	0.716 (0.512–1.002)	0.632 (0.463–0.864)	8

Chemo, chemotherapy; DFS, disease-free survival; HR, hazard ratio; LN+, lymph node positive; N/A, not available; NOS, Newcastle Ottawa Scale; OS, overall survival; R+, incomplete resection; R0, complete resection; RCT, randomized controlled trial; Squa, squamous cell carcinoma.

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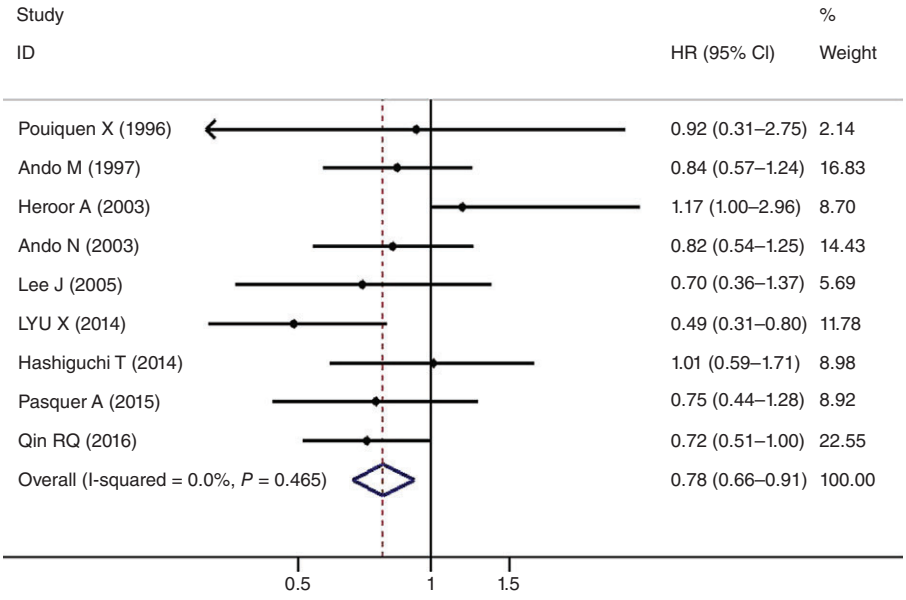

Figure 2 Forest map of the associations between adjuvant chemotherapy and overall survival of esophageal squamous cell carcinoma patients. CI, confidence interval; HR, hazard ratio.

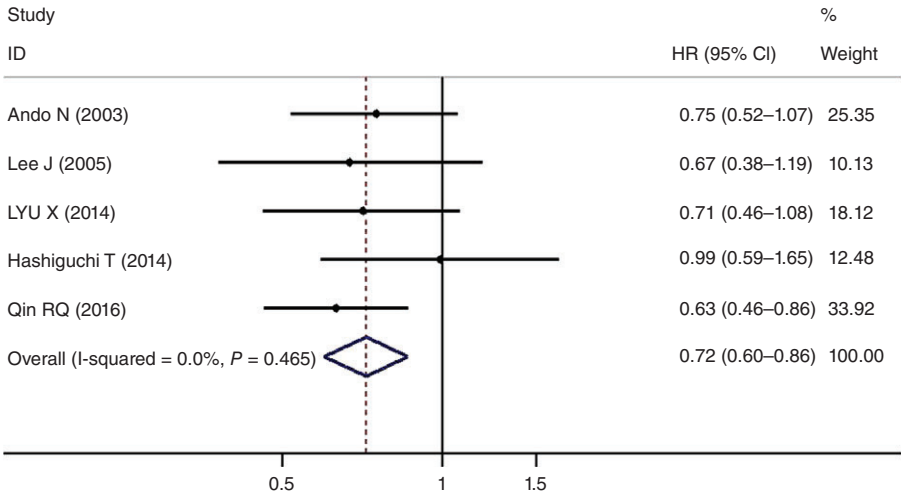

Figure 3 Forest map of the associations between adjuvant chemotherapy and disease-free survival of esophageal squamous cell carcinoma patients. CI, confidence interval; HR, hazard ratio.

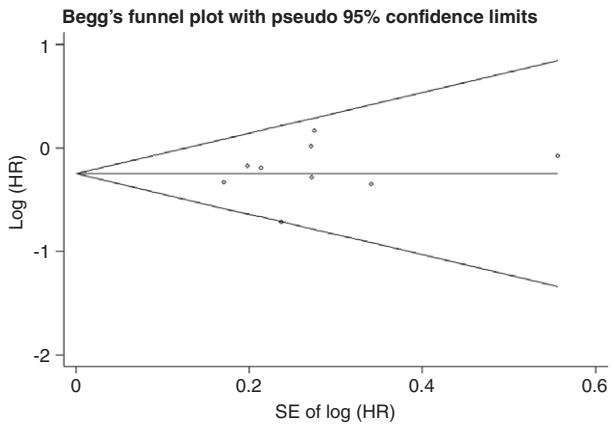

Figure 4 Funnel map of publication bias risk. SE, standard error.

study demonstrated that the five-year DFS of patients in the postoperative chemotherapy and surgery alone groups were 55% and 45%, respectively ($P = 0.037$).[6] Therefore, we are confident that for patients with advanced esophageal cancer, the effect of perioperative comprehensive treatment is superior to that of surgery alone.

New data on postoperative chemotherapy plus esophagectomy

Esophagectomy is a surgical procedure involving the anatomic regions of the cervical, thoracic, and abdominal fields that exerts extensive trauma, strongly interferes with physiology, carries an extremely high risk (mortality and complications after surgery are high), and has a slow recovery process, particularly in regard to digestive

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function. Therefore, few patients can tolerate adjuvant chemotherapy after esophagectomy, which leads to the lack of high-quality data with strong evidence from either prospective clinical trials or retrospective studies. Currently, because of limitations relating to sample size, no single study has yielded a definitive conclusion on the superiority or inferiority of a certain treatment strategy. As the most effective tool to solve this problem, meta-analyses have been conducted regarding this topic.

In 2008, Zhang *et al.* concluded that postoperative chemotherapy could not elicit survival benefits for esophageal cancer patients.[16] They included six studies published from the inception of the searched databases to July 2007, using the keywords "esophageal neoplasms" and "adjuvant chemotherapy," and included a total of 1001 esophageal cancer cases. Although their results showed that adjuvant chemotherapy could not improve patient prognosis, subgroup analysis of N^+ patients showed that adjuvant chemotherapy could elicit survival benefits for these patients.

In 2014, Zhang *et al.* conducted a meta-analysis to explore whether postoperative chemotherapy could improve the prognosis of ESCC patients. They included the keywords "esophageal cancer" or "esophageal neoplasms," "adjuvant chemotherapy" or "postoperative chemotherapy," and "surgery alone."[17] The meta-analysis included 11 articles published between 1995 and May 2012, with a total of 2047 cases divided into adjuvant chemotherapy (n = 887) and surgery alone (n = 1160) groups. The results showed that the three-year OS between the two groups was not significantly different (relative risk [RR] 0.89; P = 0.25). Compared to surgery alone, the adjuvant chemotherapy group had a significantly better one-year DFS rate (RR 0.68; P = 0.006), whereas the three-year DFS between the two groups was not significantly different (RR 0.97; P = 0.84). Further analysis showed that postoperative chemotherapy could improve the three-year OS of stage III–IV patients (RR 0.43; P = 0.00001) and the five-year DFS of N^+ patients (RR 0.97; P = 0.04). The results suggested that a specific subpopulation could benefit from postoperative chemotherapy, and that pathological stage and/or lymph node status should be taken into consideration.

Both meta-analyses shared the common limitations of confounders and poor data quality. Additionally, the sample sizes of the two meta-analyses were relatively small, with 1001 and 2047 cases, respectively. After 2012, four retrospective studies on postoperative chemotherapy for esophageal cancer have been published, and most have confirmed the value of postoperative chemotherapy. In 2014, Hashiguchi *et al.* from Japan evaluated the efficacy of postoperative docetaxel, cisplatin, and 5-Fu (DCF) chemotherapy for 139 stage II/III N1/N2 ESCC patients, and showed that patients with lymph node metastasis could possibly benefit from postoperative chemotherapy.[8] In the same year, Lyu *et al.* from China retrospectively evaluated 349 cases treated between 2008 and 2010 and demonstrated that postoperative chemotherapy could improve survival in stage II–III pN^+ ESCC patients after R0 resection.[9] In 2015, Pasquer *et al.* from France conducted a retrospective analysis of 104 patients from multiple centers in Europe, and showed that postoperative chemoradiation could not elicit any survival benefit for esophageal cancer patients with positive lymph nodes.[10] In 2016, Qin *et al.* from China assessed the efficacy of adjuvant chemotherapy in 434 stage II–III ESCC patients with positive lymph nodes confirmed by postoperative pathology and concluded that adjuvant chemotherapy could improve DFS of pN1 ESCC patients and those with tumors < 4.5 cm, as well as OS in patients with positive lymph nodes.[11]

As a result of this emerging data, it is rational and necessary to conduct an updated meta-analysis. Our meta-analysis comprising nine studies and 1684 patients showed that postoperative chemotherapy could improve OS (HR 0.78, 95% CI 0.66–0.91; P = 0.002) and DFS (HR 0.72, 95% CI 0.6–0.86; P < 0.001) of ESCC patients. Although the total number of cases in our meta-analysis was smaller than the cases used in the meta-analysis published in 2014, the quality of the included articles and newly added cases was superior. With a stricter retrieval strategy, the coverage of mainstream data from three major databases, and an extensive search with strict inclusion criteria, the accuracy and completeness of the included data are ensured, making the conclusions of this meta-analysis more credible.

No consensus reached on the role of postoperative chemotherapy

The 2018 National Comprehensive Cancer Network guidelines for the diagnosis and treatment of esophageal cancer and gastroesophageal junction carcinoma recommend that regardless of pT or pN staging, no additional treatment other than regular follow-up is needed for patients who have undergone R0 resection.[18] If the surgery is an R1 or R2 resection, then adjuvant chemoradiation or palliative care is feasible. In 2016, the updated European Society for Medical Oncology Clinical Practice Guidelines for esophageal cancer failed to provide any clear recommendations for adjuvant treatment of patients after surgery.[19] In 2012, the St. Gallen International Expert Consensus on the primary therapy for gastric, gastroesophageal, and esophageal cancer advised that postoperative adjuvant treatment should not be offered to ESCC patients, even those who have undergone R1 resection.[20] In 2011, the guidelines for the management of esophageal and gastric cancer jointly drafted by the Associations of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical

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Oncology also noted that there was no evidence to support routine postoperative chemotherapy for ESCC (Grade Ia evidence).[21] Similarly, the 2014 Society of Thoracic Surgeons guidelines from the United States and the 2010 guidelines from Canada offered no clear recommendation for adjuvant therapy for ESCC.[22,23]

However, the guidelines from Asian countries differ from those of Europe and the Americas with regard to recommending adjuvant chemotherapy for ESCC. The Japanese Esophageal Society issued their latest guidelines in 2015 for the diagnosis and treatment of esophageal cancer, which recommended that patients with positive lymph nodes, especially those who did not receive neoadjuvant therapy, should undergo adjuvant chemotherapy after radical esophagectomy.[24] In 2011, the guidelines from the Chinese Anti-Cancer Association recommended: for T3-4N0 or N^+ patients after R0 resection, observation or chemotherapy based on platinum/5-Fu or radiation should be applied; for esophageal cancer patients after R1 resection, chemotherapy based on 5-Fu or radiation is appropriate; and for esophageal cancer patients after R2 resection, a combination regimen of chemotherapy based on 5-Fu and radiation or palliative therapy should be adopted.[25]

Usefulness of additional postoperative chemotherapy for patients after neoadjuvant chemotherapy

Presently, the efficacy of preoperative treatment of esophageal cancer has been suggested and gradually generalized, leading to an increase in the number of patients undergoing preoperative therapy. However, it remains unclear which group of patients require additional therapy and which type of treatment is superior. In 2016, Brescia *et al.* evaluated the efficacy of postoperative chemotherapy for pN^+ esophageal cancer patients after preoperative treatment, and the results showed that adjuvant chemotherapy may improve survival in this subset of patients.[26] However, this conclusion requires further validation in prospective clinical trials. In 2017, Saeed *et al.* demonstrated that postoperative chemotherapy did not improve prognosis in esophageal cancer patients after neoadjuvant chemotherapy.[27] Sisic *et al.* also concluded that adjuvant treatment did not improve prognosis in esophageal cancer patients after neoadjuvant chemotherapy.[28] Nevertheless, in the same year, Saunders *et al.* reported that adjuvant treatment ($n = 70$) could elicit a significant survival benefit ($P = 0.045$) in patients who achieved good efficacy from neoadjuvant chemotherapy ($n = 129$).[29]

As some scholars believe that postoperative chemotherapy should be offered to patients with a heavy tumor burden after neoadjuvant therapy while others believe that postoperative chemotherapy should be administered to patients with a good response to neoadjuvant therapy, it is currently difficult to reach a consensus. We also note that there is no research evaluating postoperative chemotherapy for the treatment of ESCC patients after neoadjuvant therapy. Future studies are expected to answer this question to provide references for clinical practice.

Limitations

This meta-analysis has the following limitations. The data we summarized and analyzed were derived from the whole group in each study instead of from the individual patients; therefore, further analysis according to different patient characteristics could not be performed. The total sample size of the nine studies was low, and high-quality randomized controlled trials/publications are lacking, the latter of which is associated with the research status regarding this topic. Some of the studies did not provide HRs and 95% CIs of OS or DFS, which prevented us from evaluating the efficacy of postoperative chemotherapy on patient prognosis on a more accurate scale.

Conclusion

The current meta-analysis demonstrated that postoperative chemotherapy is an independent, favorable prognostic factor for both OS and DFS for patients with advanced ESCC. Our results support postoperative chemotherapy as a supplementary treatment after surgery, especially for esophageal cancer patients not administered neoadjuvant therapy before surgery.

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Disclosure

No authors report any conflict of interest.

References

1 Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D *et al.* The global burden of cancer 2013. (Published erratum appears in JAMA Oncol 2015; 1: 690). *JAMA Oncol* 2015; **1**: 505–27.
2 Chen W, Zheng R, Baade PD *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
3 Pouliquen X, Levard H, Hay JM, McGee K, Fingerhut A, Langlois-Zantin O. 5-Fluorouracil and cisplatin therapy after

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palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. *Ann Surg* 1996; **223**: 127–33.
4 Ando N, Iizuka T, Kakegawa T *et al.* A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: The Japan Clinical Oncology Group Study. *J Thorac Cardiovasc Surg* 1997; **114**: 205–9.
5 Heroor A, Fujita H, Sueyoshi S *et al.* Adjuvant chemotherapy after radical resection of squamous cell carcinoma in the thoracic esophagus: Who benefits? A retrospective study. *Dig Surg* 2003; **20**: 229–35.
6 Ando N, Iizuka T, Ide H *et al.* Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: A Japan Clinical Oncology Group Study--JCOG9204. *J Clin Oncol* 2003; **21**: 4592–6.
7 Lee J, Lee KE, Im YH *et al.* Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 2005; **80**: 1170–5.
8 Hashiguchi T, Nasu M, Hashimoto T *et al.* Docetaxel, cisplatin and 5-fluorouracil adjuvant chemotherapy following three-field lymph node dissection for stage II/III N1, 2 esophageal cancer. *Mol Clin Oncol* 2014; **2**: 719–24.
9 Lyu X, Huang J, Mao Y *et al.* Adjuvant chemotherapy after esophagectomy: Is there a role in the treatment of the lymph node positive thoracic esophageal squamous cell carcinoma? *J Surg Oncol* 2014; **110**: 864–8.
10 Pasquer A, Gronnier C, Renaud F *et al.* Impact of adjuvant chemotherapy on patients with lymph node-positive esophageal cancer who are primarily treated with surgery. *Ann Surg Oncol* 2015; 22 (Suppl 3); S1340–9.
11 Qin RQ, Wen YS, Wang WP, Xi KX, Yu XY, Zhang LJ. The role of postoperative adjuvant chemotherapy for lymph node-positive esophageal squamous cell carcinoma: A propensity score matching analysis. *Med Oncol* 2016; **33**: 31.
12 Enziger PC, Mayer RJ. Esophageal cancer. *N Eng J Med* 2003; **349**: 2241–52.
13 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.
14 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.
15 Ando N, Kato H, Igaki H *et al.* A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 2012; **19**: 68–74.
16 Zhang J, Chen HQ, Zhang YW, Xiang JQ. Adjuvant chemotherapy in oesophageal cancer: A meta-analysis and experience from the Shanghai Cancer Hospital. *J Int Med Res* 2008; **36**: 875–82.
17 Zhang SS, Yang H, Xie X *et al.* Adjuvant chemotherapy versus surgery alone for esophageal squamous cell carcinoma: A meta-analysis of randomized controlled trials and nonrandomized studies. *Dis Esophagus* 2014; **27**: 574–84.
18 National Comprehensive Cancer Network. *The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 1.2018)[EB/OL].* NCCN, Fort Washington 2018. [Cited 16 Mar 2018.] Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx#esophageal
19 Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D, ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27 (Suppl 5)**: v50–7.
20 Lutz MP, Zalcberg JR, Ducreux M *et al.* Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer. *Eur J Cancer* 2012; **48**: 2941–53.
21 Allum WH, Blazeby JM, Griffin SM *et al.* Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011; **60**: 1449–72.
22 Malthaner R, Wong RK, Spithoff K, Gatrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Preoperative or postoperative therapy for resectable oesophageal cancer: An updated practice guideline. *Clin Oncol (R Coll Radiol)* 2010; **22**: 250–6.
23 Little AG, Lerut AE, Harpole DH *et al.* The Society of Thoracic Surgeons practice guidelines on the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction. *Ann Thorac Surg* 2014; **98**: 1880–5.
24 Kuwano H, Nishimura Y, Oyama T *et al.* Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. *Esophagus* 2015; **12**: 1–30.
25 Chinese Society of Esophageal Cancer, Chinese Anti-Cancer Association. *Clinical Practice Guidelines for the Diagnosis and Treatment of Esophageal Cancer*. Peking Union Medical College Press, Beijing 2011.
26 Brescia AA, Broderick SR, Crabtree TD *et al.* Adjuvant therapy for positive nodes after induction therapy and resection of esophageal cancer. *Ann Thorac Surg* 2016; **101**: 200–8.
27 Saeed NA, Mellon EA, Meredith KL *et al.* Adjuvant chemotherapy and outcomes in esophageal carcinoma. *J Gastrointest Oncol* 2017; **8**: 816–24.
28 Sisic L, Blank S, Nienhüser H *et al.* The postoperative part of perioperative chemotherapy fails to provide a survival benefit in completely resected esophagogastric adenocarcinoma. *Surg Oncol* 2017. https://doi.org/10.1016/j.suronc.2017.06.001
29 Saunders JH, Bowman CR, Reece-Smith AM *et al.* The role of adjuvant platinum-based chemotherapy in esophagogastric cancer patients who received neoadjuvant chemotherapy prior to definitive surgery. *J Surg Oncol* 2017; **115**: 821–9.

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