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Review

A systematic review and network meta-analysis of neoadjuvant therapy combined with surgery for patients with resectable esophageal squamous cell carcinoma

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HIGHLIGHTS

- Esophageal squamous cell carcinoma (ESCC) accounts for most cases of esophageal carcinoma worldwide.
- Evidence from randomized controlled trials (RCTs) for improved effects of neoadjuvant therapy is inconsistent.
- Traditional meta-analysis cannot integrate all the evidence from different therapeutic methods at the same time.
- A network meta-analysis was used to simultaneously combine both direct and indirect evidence from RCTs for ESCC.

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ABSTRACT

Background: The role of neoadjuvant therapy combined with surgery for treating esophageal squamous cell carcinoma (ESCC) remains controversial. We performed a network meta-analysis to synthesize direct and indirect evidence to identify the optimal therapeutic method for ESCC.
Methods: We identified 15 randomized controlled trials that compared any of the following 4 therapeutic measures: surgery alone (S), preoperative chemotherapy followed by surgery (CTS), preoperative radiotherapy followed by surgery (RTS), and preoperative chemoradiotherapy followed by surgery (CRTS). The main outcomes were 5-year survival, rate of radical resection, operative mortality and postoperative complications.
Results: Network meta-analysis showed that CRTS was associated with improved survival as compared with S (OR = 1.50 [95% CI 1.21 to 1.97]) and decreased occurrence of complications as compared with RTS (OR = 0.50 [95% CI 0.22 to 0.99]). Direct evidence revealed CRTS associated with improved survival (OR = 1.61 [95% CI 1.01 to 2.57]) and radical resection (OR = 4.01 [95% CI 1.66 to 9.69]) as compared with S. In terms of radical resection, CTS was more effective than S (OR = 1.73 [95% CI 1.09 to 2.76]). Findings for CTS and RTS did not differ for 5-year survival, operative mortality and postoperative complications.
Conclusions: Overall, CRTS might be the best choice for resectable ESCC because it could increase the radical resection rate and lower the occurrence of complications, thereby prolonging survival time.

1. Introduction

Esophageal carcinoma is an aggressive malignancy that has the eighth highest incidence and is the sixth leading cause of tumor-related deaths worldwide, causing approximately 400,000 deaths annually [1,2]. Esophageal squamous cell carcinoma (ESCC) accounts for most cases of esophageal carcinoma worldwide [3]. The survival rate of patients with ESCC is 15%–20% at 5 years [4]. Resectable ESCC is a treatable disease but has little prospect for cure.

Surgery is a standard treatment for patients with operable ESCC [5], and surgical results have improved in the past few years, but the improvement is mostly due to advances in preoperative staging (More accurate staging has improved selection of appropriate patients for surgery and who should benefit from combined treatments) and postoperative care and rarely to the effectiveness of the

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surgery itself [6,7]. As a solitary treatment method, surgery remains unsatisfactory because it is associated with postoperative complications and recurrence. Therefore, neoadjuvant therapy combined with surgery appears to be preferable rather than surgery alone in patients with ESCC. However, evidence from randomized controlled trials for improved effects is inconsistent [8,9]. A comprehensive clinical summary of neoadjuvant therapy would be a significant contribution.

Traditional pair-wise meta-analysis cannot integrate all the evidence from different therapeutic methods at the same time. Therefore, we used a network meta-analysis, also known as multiple-treatment meta-analysis or mixed-treatment comparison meta-analysis, to simultaneously combine both direct and indirect evidence from randomized controlled trials [10,11] to evaluate the relative efficacy of neoadjuvant therapy combined with surgery for ESCC.

2. Materials and methods

2.1. Literature search

We identified relevant trials published up to February 2016 by a systematic search of MEDLINE via PubMed using the MeSH terms "esophageal neoplasms" and the search line [(esophag* or oesophag*) and (cancer* or tumour* or tumor* or neoplasm* or carcinoma)]. In addition, we manually searched reference lists of included articles.

2.2. Study selection

We included only randomized controlled trials published in English that compared any of the following 4 treatment strategies: surgery alone (S), preoperative chemotherapy followed by surgery (CTS), preoperative radiotherapy followed by surgery (RTS), and preoperative chemoradiotherapy followed by surgery (CRTS). Patients were confirmed to have resectable ESCC without metastasis. Resectable was defined as the tumor was clinically confined to the locoregional area (Stage IIA, IIB, and III; T2–T3N0M0 and T1–T3N1M0) according to tumor-node-metastasis (TNM) classification system. Resection was deemed curative/radical when the tumor was limited to the esophagus and the adjacent lymph nodes were uninvolved. Both the primary tumor and the adjacent lymph nodes were removed completely. "Down staging" was determined by computed tomography (CT). The included studies reported at least one of the outcomes mentioned below. If the results of a study were published in duplicate, we chose the latest published.

We excluded articles with (1) a non-randomized controlled trial design; (2) including patients who received chemotherapy, radiotherapy or chemoradiotherapy without surgery; and (3) lacking information.

Three authors (YH, HW and YZ) identified studies independently, and disagreements were resolved by consensus, or a third arbitrator, if necessary.

2.3. Data extraction

Three authors (YH, LW and GL) independently reviewed the full text of eligible studies and extracted the following data by using standardized data-abstraction form: first author, year of publication, sample size, treatment schedule, tumor type and stage, and outcomes of interest. Disagreements were resolved by discussion.

Outcomes of interest were 5-year survival, rate of radical resection, operative mortality (defined as death within 30 days after operation) and postoperative complications. The intent-to-treat analysis was used to calculate the number of events, with analysis based on total number of randomly assigned patients.

2.4. Quality assessment

All included articles were assessed for quality according to the Jadad scale [12], a five-point scale measuring the following key points: (1) description of randomization, (2) description of blinding, and (3) description of withdrawals and drop outs. Scores >3 were considered high quality.

2.5. Statistical analysis

First, we performed conventional pair-wise meta-analysis to synthesize data for trials that compared the same intervention. We used a random-effects model, which was conservative in that it incorporated the assumption that different studies assessed different yet related treatment effects [13,14]. The Higgins I-squared statistic was used to test for statistical heterogeneity among studies, with $I^2 < 50\%$ considered low heterogeneity and $I^2 > 50\%$ high heterogeneity [15,16].

Second, we used Bayesian network meta-analysis to synthesize direct and indirect evidence for estimating the therapeutic effect between any given pair of treatments and ranked these results [17,18]. We used a random-effects model with Markow chain Monte Carlo methods in WinBUGS (MRC Biostatistics Units, Cambridge, UK) and determined whether the residual deviance approximated the number of data points by posterior mean [10]. We calculated odds ratios (ORs) and their 95% confidence intervals (95% CIs) to assess treatment effects [19]. We also assessed the probability of the first, second, third, etc. best preoperative therapy in terms of the outcome of interest by calculating the ORs for each treatment compared with the control [18].

Third, we estimated inconsistency in all closed loops; the underlying assumption of the network meta-analysis was that the consistency between direct and indirect evidence would indicate that data from both sources were similar enough for incorporation [20,21]. The Bucher method was used to check this assumption [22]. Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CI excluding 0 [23].

Finally, we performed a sensitivity analysis according to the main computations by using a fixed-effect model. Analyses involved use of STATA 12.0 (pair-wise meta-analysis and I^2 calculations), R 3.2.0 (estimation of consistency, ranking) and WinBUGS 1.4.3 (network meta-analysis models).

3. Results

3.1. Characteristics of included trials

We identified 3740 clinical trials from the electronic search, with 103 potentially eligible articles retrieved for more detailed analysis. We excluded 88 articles that did not meet inclusion criteria. Ultimately, 15 reports of randomized controlled trials [24–38] (published from 1989 to 2011) were used for the network meta-analysis (Fig. 1). Most trials (13/15) were two-arm studies, and the rest were four-arm studies (2/15).

A total of 2208 patients were randomly assigned to one of the 4 treatment strategies (Table S1). The chemotherapy schemes in most trials were based on cisplatin and 5-fluorouracil, and most trials used conventional fractionation in a radiation therapy scheme. The tumor stage of most patients ranged from I to III by the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system [39]. The trials did not differ in preoperative stage of tumors. Quality assessment resulted in 13 trials with a Jadad score of 2 and 2 trials with a score of 3. The methods of randomization were not specified in most trials.