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Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: A comprehensive review and network meta-analysis

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ABSTRACT

Background: Surgery is the mainstay of treatment for oesophageal squamous-cell carcinoma (OSCC) but with poor results. Attempts to improve patient outcome have been made by introducing chemotherapy (CT), radiotherapy (RT), or both (CRT). However, randomized comparisons for all these strategies are not always available.
Patients and methods: We conducted an extensive literature search for studies comparing surgery with multimodality treatment (*i.e.* [neo-]adjuvant CT or RT or CRT or definitive CRT). Network meta-analysis was performed in a Bayesian framewor and node-split models were built to assess inconsistency.
Results: Twenty-five trials including a total of 3866 OSCC patients were included. Neoadjuvant CRT was associated with the most robust survival advantage across different multimodality treatment options (HR 0.73; 95% credible interval [CrI] 0.63–0.86). Definitive CRT was also significantly more effective than surgery but with greater uncertainties (HR 0.62; 95%CrI 0.41–0.96). Neoadjuvant CT (HR 0.90; 95%CrI 0.76–1.07) and adjuvant CRT (HR 1.00; 95%CrI 0.70–1.40) are associated with a non-significant benefit.
Conclusions: To date, neoadjuvant CRT seems to represent the best approach to maximize the benefit of a multimodality approach.

1. Introduction

Oesophageal tumour is a major cause of cancer-related mortality worldwide and oesophageal squamous cell carcinoma (OSCC) is

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the most common histological subtype. Long-term outcome results for OSCC patients are disappointing, and even in resectable cases 5-year overall survival (OS) rates are in the range of 15%–35% (Pennathur et al., 2013). Surgical resection is feasible only in a minority of patients, and it is weighed down by potentially severe complications and not negligible mortality rates. Attempts to improve OS have been made by adding chemotherapy (CT), radiotherapy (RT) or both (chemoradiotherapy, CRT) in the adjuvant or neoadjuvant setting or as a definitive treatment instead of surgery.

A multidisciplinary team individualising the therapeutic strategy in each patient is now regarded as mandatory in locally advanced OSCC (Stahl et al., 2013), as the optimal approach beyond surgical resection is yet to be defined due to several reasons. Indeed, many trials conducted in the past were underpowered to show OS differences among different multimodality treatments. Moreover, RT techniques were less advanced compared to currently available facilities, as well as staging work-up is now more precise and reliable. Finally, systemic therapies and supportive measures have been improved and are now often delivered in dedicated oncology units.

Guidelines from the European Society for Medical Oncology (ESMO) recommend preoperative platinum-based CRT or CT and definitive CRT as acceptable treatment modalities for locally advanced T3 or more, N0/N+ OSCC (Stahl et al., 2013). These conclusions are mainly derived from conventional meta-analyses, demonstrating a survival benefit for neoadjuvant CRT and, apparently to a lower extent, neoadjuvant CT compared to surgery alone (Sjoquist et al., 2011; Kranzfelder et al., 2011). However, results were not consistent across trials and any head-to-head study or meta-analysis definitively proved the superiority of preoperative CRT compared to CT, or that of a multimodality approach comprising surgery compared to definitive CRT.

Network meta-analyses offer the opportunity to perform indirect treatment comparisons among randomized studies without breaking randomization, as long as specific assumptions regarding heterogeneity and inconsistency are fulfilled (Caldwell et al., 2005). We sought to compare the results of different treatment modalities, *i.e.* (neo-)adjuvant CT, RT or CRT and definitive CRT: due to the lack of conclusive trials and the difficulties in the conduction of adequately dimensioned studies, Bayesian methods may be useful to estimate the impact of different treatment strategies in locally advanced OSCC.

2. Materials and methods

2.1. Search strategy and data extraction

We carried out a systematic search of available literature and results were reported in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Liberati et al., 2009).

No language restriction has been used. Pubmed and EMBASE were searched for randomized controlled trials, using different combination of the following terms: "[o]esophageal cancer" AND one of the following terms per time: "squamous cell", "chemotherapy", "radiotherapy", "chemoradiotherapy", "radiochemotherapy" or "chemoradiation", "neoadjuvant", "adjuvant", "preoperative", "postoperative" and "definitive". Search was performed in the presence and absence of the "randomized controlled trial" filter. Meta-analyses and systematic reviews have also been looked for with the same terms. References of the retrieved publications were screened for additional eligible studies. Abstracts and posters presented at international meetings (*i.e.* American Society of Clinical Oncology [ASCO] Annual Meeting and Gastrointestinal Cancers Symposium, ESMO Congress and World Congress on Gastrointestinal Cancer) have been checked, too, starting from 1990 and using the previously aforementioned keywords.

Studies enrolling oesophageal cancer patients independently of tumour histology were included if the following criteria were respected: *i*) the study design provided for patient stratification according to histology; *ii*) sufficient data for the OSCC subgroup were reported.

The first two authors performed the literature search independently and screened all retrieved publications at the title or abstract level. Full publications were then obtained for all relevant studies, while for unpublished studies data were extracted from the abstracts. Studies enrolling less than 25 OSCC patients were not included in the meta-analysis, as well as studies testing biologic agents either alone or in combination with CT or CRT.

2.2. Risk of bias assessment

We assessed the risk of bias for each study by the use of the Cochrane tool (available at: http://methods.cochrane.org/bias/home). The first two authors independently assessed the risk of bias for each included study, while the last author acted as referee in case of controversies. Considering the nature of the treatments tested, formal allocation concealment in the included trials was clearly impossible: however, it is unlikely that the chosen endpoint of OS is influenced by such bias. Publication bias was assessed by visual inspection of funnel plots.

Results for the analyses of the risk of bias, heterogeneity and inconsistency are reported in the Supplementary Material (online only).

2.3. Statistical methods

The primary end point of our network meta-analysis was OS, defined from the time of randomization or the start of treatment to death from any cause. Hazard ratios (HRs) and their 95% confidence intervals (95%CIs) were used to estimate treatment effects. The model for the network meta-analysis was fit as previously suggested (Woods et al., 2010). Data were extracted from the publications. If enough data were not reported, we estimated HR and 95%CI as proposed by Parmar et al. (Parmar et al., 1998). Treatment effects were estimated by posterior means and 95% credible intervals (95% CrIs). Random effect was used. We used identity link function and non-informative prior distributions (uniform and normal) to fit the model, yielding 25,000 iterations with burn-in number of 5000 iterations and a thin interval of 20 to obtain the posterior distributions of model parameters. Convergence was assessed using the Brooks–Gelman–Rubin method. Posterior distributions were used to assess the probability of each treatment to be the best, second best and so on. Node-split models were fit to evaluate inconsistency. To assess heterogeneity we performed standard pairwise meta-analyses and looked at the results of I2 and Cochran Q tests. Significant heterogeneity was deemed to be present for $I2 > 50\%$ or p-value > 0.10. Der Simonian and Laird method and random effect were used. All the analyses were made with the R packages "Metaphor" and "Gemtc" (https://www.r-project.org/).

3. Results

3.1. Search results

Fig. 1 summarizes the selection process and reasons for exclusion. Twenty-five studies, published between 1988 and 2014 and including a total of 3866 OSCC patients, were finally included in the meta-analysis (Roth et al., 1988; Schlag, 1992; Nygaard et al., 1992; Apinop et al., 1994; Maipang et al., 1994; Le Prise et al., 1994; Ando