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Overview

Role of Chemoradiotherapy in Oesophageal Cancer — Adjuvant and Neoadjuvant Therapy

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Abstract

Despite low postoperative mortality rates, the long-term outcomes from surgical-based treatment for oesophageal cancer remain poor. Chemoradiotherapy (CRT), either given before surgical resection as neoadjuvant therapy or after resection as adjuvant therapy, has been postulated to improve these outcomes. This systematic review examines the evidence for these approaches. The evidence for postoperative radiotherapy is limited and conclusions are difficult, but it may have a role in patients at high risk of local relapse (positive margins). The addition of chemotherapy is recommended when possible. Patient selection is important due to the associated toxicities. The evidence for neoadjuvant treatment is stronger and based on the current evidence neoadjuvant CRT can be recommended as a treatment approach in T2–T4, N1–3 oesophageal cancer for both adenocarcinoma and squamous cell carcinoma, but further work is needed to establish its superiority over neoadjuvant chemotherapy alone, particularly for adenocarcinoma. We recommend that further studies divide the two histologies and they should be treated as two separate diseases.

Key words: Adjuvant; chemoradiotherapy; neoadjuvant; oesophagus

Statement of Search Strategies Used and Sources of Information

A review of published studies and conference abstracts was conducted using Medline, Embase, SCOPUS, Web of Science and Cochrane Collaboration. Key words were oesophageal, neoplasm, chemoradiotherapy, adjuvant, neoadjuvant, randomised controlled trial. No date limits were set, but the search was limited to the English language. The published studies were assessed for relevance by a single investigator (SG). Only randomised controlled trials and meta-analyses were included. Further relevant studies were identified by reviewing references contained in the meta-analyses.

Introduction

Despite low postoperative mortality rates, the long-term outcomes from surgical-based treatment for oesophageal cancer remain poor [1], due to both systemic relapse and locally advanced disease at presentation resulting in a 30% risk of R1 resection (positive circumferential margin) [2]. Chemoradiotherapy (CRT), either given before surgical resection, as neoadjuvant therapy, or after resection, as adjuvant therapy, has been postulated to improve on these outcomes. Another strategy is to apply chemotherapy alone in these settings, again with the aim of reducing the locoregional recurrence rate and improve survival.

There are differences in practice around the world, with regards to neoadjuvant and adjuvant therapy. In 2009, 250 participants representing 41 countries across six continents were surveyed regarding their management of oesophageal cancer [3]. Neoadjuvant therapy was routinely given by 33%, occasionally by 63% and never by 4%, being more commonly used in Europe and North America than in Asia. It was also

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found that as a surgeon's experience increases the less likely he/she would use a neoadjuvant therapy. In the UK, where adenocarcinoma predominates, neoadjuvant chemotherapy remains the standard of care following the OE02 study [4], which found a survival benefit to two cycles of cisplatin and 5-fluorouracil pre-oesophagectomy. Historically, neoadjuvant CRT was not favoured in the UK, primarily because of concerns over surgical morbidity and mortality [5], but has been identified as a priority for the UK oesophageal radiotherapy community [2] after publication of the CROSS trial [6].

NeoSCOPE, funded to start in early 2013, is a randomised UK phase II study in 85 patients of two neoadjuvant CRT regimens (two cycles of oxaliplatin and capecitabine followed by radiotherapy, 45 Gy in 25 fractions with either concurrent oxaliplatin and capecitabine or paclitaxel and carboplatin), before surgery, for resectable adenocarcinoma of the oesophagus/oesophagogastric junction. It is an opportunity to establish the safety of neoadjuvant CRT while evaluating a number of components of oesophageal radiotherapy planning and the effects of these on treatment outcome, including pathological response. The aim of the overview is to detail where we are to date and to make recommendations for both current practice and future research.

Methods

A review of published studies and conference abstracts was conducted using Medline, Embase, SCOPUS, Web of Science and Cochrane Collaboration. Key words were oesophageal, neoplasm, chemoradiotherapy, adjuvant, neoadjuvant, randomised controlled trial. No date limits were set, but the search was limited to the English language. The published studies were assessed for relevance by SG. Only randomised controlled trials (RCTs) and meta-analyses were included. Further relevant studies were identified by reviewing references contained in the meta-analyses.

Results

Studies Evaluating Adjuvant Radiotherapy

Six RCTs were identified. Four studies used radiotherapy alone [7–10] and two used CRT [11,12]. One of the latter compared adjuvant radiotherapy with adjuvant CRT [12]. Details are given in Table 1.

Studies Evaluating Neoadjuvant Chemoradiotherapy

Ten RCTs were identified. Nine studies looked at neoadjuvant CRT versus surgery [6,13–20], one looked at neoadjuvant CRT versus neoadjuvant radiotherapy versus neoadjuvant chemotherapy [21]. Details are given in Table 2. Table 3 gives the details of the three most recent meta-analyses in this area [22–24].

Discussion

Adjuvant Radiotherapy

A postoperative approach to adjuvant therapy has the advantage of patient selection based on pathological findings, but there are issues with patient fitness after oesophagectomy, tolerability and difficulties in target volume delineation (TVD) as gross disease has been removed and the anatomy has changed. These issues have resulted in the role of adjuvant treatment being relatively neglected compared with neoadjuvant CRT, as evidenced by the heterogeneity of the study type and the relative lack of large RCTs [22]. Much of the data is retrospective and non-randomised, resulting in a difficulty to draw firm conclusions around the benefit in overall and disease-free survival with this approach. This has certainly hindered attempts at meta-analyses, a limitation acknowledged by the authors [22].

The literature on this topic was reviewed by Malthaner *et al.* in 2004 [25]. The studies included [7–10] were mainly adjuvant radiotherapy rather than adjuvant CRT. They concluded that the evidence did not support the use of adjuvant treatment when a curative resection had been achieved. Xiao *et al.*'s study [10] is the only one to show a statistically significant survival benefit in stage III patients, with a non-statistically significant survival benefit also seen in the node-positive group. Only one study has compared radiotherapy with CRT in this setting [12] and showed a survival benefit to the addition of chemotherapy. However, as only 24/30 patients in the radiotherapy arm completed the planned course, compared with 30/30 in the CRT arm and with two patient deaths in the radiotherapy arm during the treatment period, the conclusion from this study is not clear.

The most recent meta-analysis is by Zheng *et al.* 2013 [22]. They included seven studies of adjuvant CRT [11,12,26–30] (only two RCTs [11,30], the rest were retrospective or non-randomised prospective studies) with a total of 600 patients. They concluded that there was a survival benefit for the use of adjuvant CRT, but acknowledged that they had less than 600 patients and were therefore limited in the conclusions that could be drawn. Adjuvant CRT was found to be associated with a higher rate of complications. Reported common grade 3–4 toxicities were leucocytopenia 90–32%), anaemia (0–16.7%), thrombocytopenia (0–6.5%), nausea/vomiting (0–18.2%) oesophagitis (0–19.4%) and stomatitis (0–4.5%) [22]. The RCTs only included patients with squamous cell (SCC) histology. Zheng's meta-analysis [22] included three studies that had enrolled patients with either SCC or adenocarcinoma, but did not comment on any difference in outcome between the two histologies.

At the current time no definite recommendations can be made on the basis of the evidence available. With the increasing focus on neoadjuvant CRT it is unlikely that further studies to examine the role of adjuvant CRT will ever be conducted. It may have a role in patients who have

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