Oesophageal cancer: preoperative chemotherapy

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Introduction

The optimal management of localised oesophageal cancer remains controversial. Indeed, currently utilised strategies are clearly unsatisfactory, given that most randomised trials report overall 5-year survivals of 20% or less for patients undergoing surgical resection. The rationale behind preoperative chemotherapy is two-fold: (i) to downstage or downsize the primary tumour in order to ensure complete surgical resection; and (ii) to pre-emptively destroy any distant foci of micrometastatic disease. This preoperative chemotherapy paradigm is increasingly being used in a number of other areas in gastrointestinal oncology, but has yet to become generally accepted for oesophageal cancer.

The current issues that need to be addressed include the fundamental question of whether preoperative chemotherapy is superior to surgery alone; identification of the optimal chemotherapy regimen; defining the optimal duration of preoperative chemotherapy; and assessing tumour response to such therapy. This article will address these issues, focusing on preoperative and perioperative chemotherapy approaches to the management of localised adenocarcinomas and squamous cell carcinomas (SCC) of the oesophagus and oesophago-gastric junction (EGJ).

Preoperative chemotherapy versus surgery alone

The potential benefits of preoperative chemotherapy have been tested in a number of randomised trials over the past 20 years. Unfortunately, most of these trials were small and inadequately powered to show differences in overall survival. Additionally, in practically all these trials, SCC was the dominant histology enrolled. This is a critical point, as the incidence of lower oesophageal and EGJ adenocarcinomas is rising rapidly in Western countries [1]. The most useful data are contained in two larger randomised trials, one European and one North American, both of which included significant proportions of patients with adenocarcinoma.

The UK Medical Research Council (MRC) OE02 study randomised 802 patients with SCC (31%) and adenocarcinoma (66%) to preoperative therapy with two cycles of cisplatin and 5-fluorouracil (5-FU) followed by surgery, or to surgery alone [2]. The microscopic complete resection rate was higher in patients who received preoperative chemotherapy (60% versus 54%; P<0.0001). Overall survival was also superior in the preoperative chemotherapy arm [hazard ratio (HR) 0.79; 95% confidence interval (CI) 0.67–0.93; P=0.004]. Patients who received chemotherapy demonstrated an absolute improvement in 2-year survival of 9% over patients who proceeded directly to surgery (43% versus 34%). The rate of post-operative complications was the same in both treatment arms.

The second-largest randomised study was the US National Cancer Institute (NCI)-sponsored Intergroup trial 0113, which comprised 440 patients with SCC (46%) and adenocarcinoma (54%) [3]. Patients were entered in a randomised study of three cycles of preoperative cisplatin and 5-FU followed by surgery, or surgery alone. Two cycles of post-operative chemotherapy were recommended for patients who had stable or responding disease on preoperative treatment; however, this was only completed in 38% of patients. The probability of microscopic involvement of the resection margin was higher in the surgery-alone arm (15% versus 4%; P=0.001). However, there was no difference in overall survival between the two treatment groups (HR 1.07; 95% CI 0.87–1.32; P=0.53). Two-year survival was 35% for patients who received preoperative chemotherapy, and 37% for patients who had surgery alone. Fatal and non-fatal post-operative complication rates were similar for both arms.

The apparent discrepancy between the results of these two large studies has yet to be resolved. There are several factors that might have masked detection of a treatment effect in the Intergroup 0113 study. Possibly the most important of these is the relatively low proportion (80%) of patients who went on to curative surgery following preoperative chemotherapy. In contrast, 92% of patients in the preoperative chemotherapy arm of the OE02 study proceeded to surgery. Also, some have speculated that the longer duration of preoperative chemotherapy in the 0113 study might have allowed non-responders to develop micrometastatic disease before surgery. This might have led to a bias towards poorer survival in the preoperative chemotherapy group.

Some commentators have taken the nihilistic view that even if there is an advantage to preoperative chemotherapy, it must be small in magnitude, given the lack of consensus between the two randomised studies. It is therefore important to consider results from related clinical trials, in order to avoid missing clinically significant benefits due to preoperative chemotherapy. In fact, there is further strong evidence of improved patient outcome associated with perioperative chemotherapy as demonstrated by the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) study [4]. In this study,
503 patients with adenocarcinoma of the stomach, EGJ or lower esophagus were randomised to receive perioperative chemotherapy and surgery or surgery alone. Twenty-six per cent of the study population had oesophageal or EGJ tumours. The perioperative chemotherapy consisted of epirubicin, cisplatin and infusional 5-FU (ECF), on the basis of randomised data showing survival benefit associated with this regimen in patients with advanced esophago-gastric cancer [5]. Perioperative chemotherapy was divided into three preoperative and three post-operative cycles. Resected tumours were smaller in the perioperative chemotherapy group (mean maximal diameter 3 versus 5 cm; \( P < 0.001 \), Mann–Whitney \( U \)-test). After a median follow-up of 2 years, a significant improvement in progression-free survival was demonstrated in the perioperative chemotherapy arm (HR 0.70; 95% CI 0.56–0.88; \( P = 0.002 \)). There was a trend towards improved overall survival, which at the time of analysis had not yet reached statistical significance. These benefits were seen despite only 88% of patients randomised to perioperative chemotherapy completing the preoperative phase, and only 40% of patients completing all six cycles. As with the OE02 and 0113 studies, there was no difference in post-operative complications or deaths between the treatment arms.

While the population studied in the MAGIC trial comprised mainly patients with gastric tumours, there was also a significant proportion with oesophageal or junctional adenocarcinomas. ECF is active in patients with advanced esophago-gastric cancer, and represents a reasonable regimen to test in the perioperative setting. While less than half of patients assigned to perioperative chemotherapy received all of the planned three post-operative cycles, advantages in progression-free and possibly also overall survival were still demonstrable, compared with surgery alone. It is therefore probable that the majority of the survival benefit gained from perioperative chemotherapy was actually due to the preoperative component. Mature data from this trial are eagerly awaited.

At least three meta-analyses addressing the issue of perioperative chemotherapy for oesophageal cancer have been conducted. A systematic review of perioperative chemotherapy versus surgery alone conducted for the Cochrane collaboration was recently updated [6]. Eleven randomised trials comprising 2051 patients were analysed. While at 1 and 2 years the risk ratios showed no difference in overall survival, at 3 and 4 years there appeared to be a trend towards increased survival in the preoperative chemotherapy patients. This culminated in a statistically significant survival advantage at 5 years (relative risk 1.44; 95% CI 1.05–1.97; \( P = 0.02 \)).

Another meta-analysis including 11 randomised trials and 1976 patients found no advantage to preoperative chemotherapy over surgery alone [7]. However, survival estimates were available only at 1, 2 and 3 years. The most recent meta-analysis examined 11 randomised trials of perioperative chemotherapy or chemoradiotherapy and included 2311 patients [8]. Seven trials of perioperative chemotherapy versus surgery alone (1683 patients) were analysed separately. This analysis demonstrated improved 2-year survival of patients treated with perioperative chemotherapy compared with surgery alone. The absolute difference was 4.4% (95% CI 0.3% to 8.5%). The results of these meta-analyses lend additional weight to a perioperative chemotherapy strategy for oesophageal cancer.

On the basis of these data, UK investigators have proposed a trial seeking to further refine the perioperative chemotherapy paradigm for oesophageal/EGJ cancer. The proposed experimental chemotherapy arm consists of a variant of ECF used in the MAGIC trial; however, capecitabine is substituted for infusional 5-FU, for ease of administration. Hence, the next-generation randomised MRC OE05 study will examine whether the combination of epirubicin, cisplatin and capecitabine (ECX) given preoperatively is superior to perioperative 5-FU and cisplatin in patients with adenocarcinoma of the esophagus or EGJ.

### New agents

Various newer agents have been tested in the setting of advanced oesophageal cancer, including paclitaxel, docetaxel and irinotecan (Table 1). Preclinical and early phase clinical data have demonstrated single-agent activity of these compounds against oesophageal cancer [9–11]. Combinations of these agents with the established drugs of cisplatin and/or 5-FU have also been studied in patients with advanced disease [12–14]. Encouraging response rates of up to 57% for combination treatment have been reported.

Several recently published phase I/II trials have evaluated paclitaxel and cisplatin-based combinations in the preoperative setting. A phase II study enrolled 50 patients with resectable oesophageal SCC who were treated with paclitaxel and cisplatin on a 2-weekly schedule for between three and six cycles, depending on response [15]. The overall response rate was 59%, with a histopathological complete response rate of 14%. Seventy-one per cent of patients experienced grade 3/4 neutropenia; however, only 4% had neutropenic fever. A similar, but less dose-dense, approach using paclitaxel and carboplatin was evaluated in a phase II study of 26 patients with SCC or adenocarcinoma of the esophagus [16]. The overall response rate was 61%, with a histopathological complete response rate of 11%.

Sixty-six assessable patients with resectable SCC of the esophagus were entered into two phase I trials of neo-adjuvant chemotherapy with mitomycin, ifosfamide and cisplatin [17]. Patients received between two and four cycles of chemotherapy preoperatively. Sixty-one per cent of patients had a radiological response, and the complete histopathological response rate was 13.6%. The median overall survival was 12.4 months (CI 9.6–18.8). In this paper, haematological and other toxicities were reported to be low. These combinations show promise in terms of efficacy and tolerability; however, they have yet to be tested in a randomised fashion against standard cisplatin/5-FU-based perioperative therapy.

Oxaliplatin is an active agent in colorectal cancer, and has been evaluated in patients with gastric cancer. A recently published study of 37 assessable patients with metastatic gastric cancer reported a 43% response rate with a regimen of
biweekly oxaliplatin, 5-FU (24-h infusion) and leucovorin (LV) [18]. An earlier study of 49 assessable patients with metastatic gastric cancer reported a similar 45% response rate with the oxaliplatin and bolus/infusional 5-FU/LV (de Gramont) regimen (FOLFOX6) [19]. It remains to be seen whether oxaliplatin has comparable activity in oesophageal cancer; however, evidence from previous studies suggests that response rates to combination chemotherapy are similar for patients with gastric or oesophageal primary sites [20]. Indeed, an ongoing randomised study is evaluating ECF and the substitution within this regimen of oxaliplatin for cisplatin and capecitabine for infused 5-FU in a 2×2 factorial design for patients with advanced gastric, EGJ and oesophageal cancer [21]. This study, which is now planned to accrue 1000 patients, should help to address the issue of oxaliplatin efficacy in advanced oesophageal cancer. A phase I trial showed preliminary efficacy and tolerability of oxaliplatin, infused 5-FU and radiotherapy in patients with stages II–IV oesophageal cancer, some of whom went on to surgical resection. Oxaliplatin may yet become a candidate for incorporation into preoperative chemotherapy regimens for localised oesophageal cancer.

Table 1. Selected studies illustrating the development of newer agents for the preoperative treatment of oesophageal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>Setting</th>
<th>Assessable patients</th>
<th>Treatment regimen</th>
<th>Response rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agents (advanced disease)</td>
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<tr>
<td>Kelsen et al. [9]</td>
<td>(1994)</td>
<td>Adenocarcinoma and SCC</td>
<td>Phase II advanced disease</td>
<td>Paclitaxel 250 mg/m² over 24 h every 3 weeks</td>
<td>28</td>
<td>Paclitaxel identified as an active agent</td>
</tr>
<tr>
<td>Heath et al. [10]</td>
<td>(2002)</td>
<td>Adenocarcinoma</td>
<td>Phase II advanced disease</td>
<td>Docetaxel 75 mg/m² every 3 weeks</td>
<td>18</td>
<td>Response rate is for chemotherapy naive patients—pretreated patients did not respond</td>
</tr>
<tr>
<td>Muhr-Wilkenshoff et al. [11] (2003)</td>
<td>SCC and adenocarcinoma</td>
<td>Phase II advanced disease</td>
<td>13</td>
<td>Irinotecan 125 mg/m² weekly for 4 weeks out of 6</td>
<td>15</td>
<td>Modest activity demonstrated for single-agent irinotecan</td>
</tr>
<tr>
<td>Combinations (advanced disease)</td>
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<tr>
<td>Ilson et al. [12]</td>
<td>(1999)</td>
<td>Adenocarcinoma and SCC</td>
<td>Phase II advanced disease</td>
<td>Cisplatin 30 mg/m² and irinotecan 65 mg/m² weekly for 4 weeks out of 6</td>
<td>57</td>
<td>Similar response rates in adenocarcinoma and SCC</td>
</tr>
<tr>
<td>Ilson et al. [13]</td>
<td>(2000)</td>
<td>Adenocarcinoma and SCC</td>
<td>Phase II advanced disease</td>
<td>Paclitaxel 200–250 mg/m² over 24 h day 1; cisplatin 75 mg/m² day 2 with G-CSF; every 3 weeks</td>
<td>44</td>
<td>50% required hospitalisation for toxicity; regimen considered too toxic for general use</td>
</tr>
<tr>
<td>Polee et al. [14]</td>
<td>(2002)</td>
<td>Adenocarcinoma and SCC</td>
<td>Phase II advanced disease</td>
<td>Paclitaxel 180 mg/m² over 3 h and cisplatin 60 mg/m² every 2 weeks</td>
<td>43</td>
<td>Durable remissions in 4 patients receiving subsequent surgery/ radiotherapy suggested feasibility as a neo-adjuvant regimen</td>
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<tr>
<td>Preoperative combinations</td>
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<tr>
<td>Polee et al. [15]</td>
<td>(2003)</td>
<td>SCC</td>
<td>Phase II localised disease</td>
<td>Paclitaxel 180 mg/m² and cisplatin 60 mg/m² every 2 weeks for 3–6 cycles preoperatively</td>
<td>59</td>
<td>90% of patients had surgical resection; 7 patients had pathological complete responses</td>
</tr>
<tr>
<td>Keresztes et al. [16]</td>
<td>(2003)</td>
<td>Adenocarcinoma and SCC</td>
<td>Phase II localised disease</td>
<td>Paclitaxel 200 mg/m² and carboplatin AUC 6 on day 1 and day 22 preoperatively</td>
<td>61</td>
<td>77% of patients had surgical resection; 11% of all patients had pathological complete responses</td>
</tr>
<tr>
<td>Darnton et al. [17]</td>
<td>(2003)</td>
<td>SCC</td>
<td>Phase II localised disease</td>
<td>Mitomycin C 6 mg/m²; ifosfamide 3 g/m² and cisplatin 50 mg/m² every 3 weeks for 2–4 cycles preoperatively</td>
<td>61</td>
<td>79% of patients had surgical resection; 9 patients had pathological complete responses</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma; G-CSF, granulocyte colony-stimulating factor; AUC, area under the curve.
therapy with agents such as cetuximab [22]. There are ongoing trials studying the role of monoclonal antibodies in this disease, and there may be a role in the future as a component of preoperative therapy. Likewise, ~50% of oesophageal cancers express VEGF and therefore may be susceptible to therapy with VEGF-targeting monoclonal antibodies such as bevacizumab [23].

**Therapeutic response monitoring**

Another important issue in the administration of preoperative chemotherapy for oesophageal cancer is that of therapeutic response monitoring. This is crucial, especially as there is evidence that non-responders have poorer outcomes, and therefore different strategies may need to be employed for this group. Several modalities for response monitoring have been evaluated, including computed tomography (CT), endoscopic ultrasound (EUS), and positron emission tomography (PET). While useful for initial staging, CT has been found to have limited sensitivity and specificity in assessing residual tumour following preoperative chemotherapy [24].

EUS is well established as a pretreatment staging investigation for patients with oesophageal cancer [25]. Several studies have assessed the role of EUS in response monitoring to preoperative chemoradiotherapy, although none has looked specifically at patients only receiving chemotherapy [26, 27]. One study enrolled 59 patients with oesophageal or EGJ cancer who received preoperative platinum-based chemotherapy and radiotherapy [28]. EUS was performed at baseline and before surgery, with response defined as >50% reduction in primary tumour cross-sectional area. EUS responders were found to have improved overall survival compared with non-responders (17.6 versus 14.5 months; P<0.005). This suggests that EUS does have an important role to play in response monitoring, as well as initial staging for patients undergoing preoperative therapy.

[18F]Fluorodeoxyglucose (FDG) is the most common metabolite used for PET imaging, and has been assessed both for initial staging of oesophageal cancer and for monitoring of response to preoperative chemoradiotherapy [29]. In one study, 40 patients with locally advanced EGJ adenocarcinoma were evaluated with FDG-PET before and 14 days after starting cisplatin-based preoperative chemotherapy [30]. Reduction of tumour FDG uptake (metabolic response) correlated with tumour response as assessed by endoscopy and CT. In addition, metabolic response was predictive of histopathological complete or near-complete response (53% versus 5%; P=0.001). Patients who had a metabolic response had a significantly increased time to progression and overall survival compared with metabolic non-responders. Other studies of therapeutic metabolic monitoring in patients receiving preoperative chemoradiotherapy have shown similar predictive ability of FDG-PET [31].

While the optimal investigation(s) for assessing response to preoperative chemotherapy has yet to be defined, both EUS and FDG-PET currently appear to be the tools of choice. Magnetic resonance imaging is another imaging modality that is being studied at present, and could potentially give additional structural information on tumour response.

**Conclusions**

Preoperative chemotherapy for oesophageal cancer has been a contentious issue for some time. This has been fuelled by the apparently contradictory results from the MRC OE02 and US Intergroup 0113 studies. However, pooled analyses incorporating these and other studies have suggested improved overall survival in patients treated with preoperative chemotherapy. In addition, gastro-oesophageal data from the MAGIC study reinforce the preoperative chemotherapy paradigm in patients with oesophageal and EGJ tumours. The upcoming OE05 study will add significantly to our knowledge base in this area. New agents and combinations that are currently in early phase trials may make an impact in the future. Therapeutic response monitoring is a rapidly developing area, with EUS and PET playing an increasing role. Our ability to maximise the benefits of preoperative chemotherapy may be significantly improved by identifying non-responders early in their course of chemotherapy. While progress may appear slow, advances in the preoperative management of oesophageal cancer are definitely being made.

**References**


