Perioperative therapy improves gastro-oesophageal cancer survival

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A randomised phase III study has reported significant improvements in R0 resection rate and overall survival associated with perioperative cisplatin and 5-fluorouracil treatment compared with surgery alone in patients with gastro-oesophageal adenocarcinoma. These data support the results of the randomised phase III MAGIC study that reported a 13% five-year survival benefit from perioperative chemotherapy.

In 2008, the estimated worldwide incidence of gastro-oesophageal cancer was 1.47 million, accounting for 11.6% of all cancer diagnoses. Perhaps more importantly, the estimated number of deaths in that year attributable to gastro-oesophageal cancer was more than 1.1 million, making this the second most common cause of cancer death after lung cancer.[1] Due to the aggressive nature of these cancers, most of the patients have inoperable disease at presentation. However, even in the context of locally-confined disease, the five-year survival rates with surgery alone are less than 25%.[2,3] A study recently published by Ychou et al.[2] supports the use of perioperative chemotherapy as a combined modality therapy in this disease setting with a 14% improvement in five-year overall survival compared with surgery alone.

This approach has been widely practiced throughout Europe since the publication of the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in 2006.[3] The MAGIC study reported a clinically and statistically significant improvement in progression-free survival (PFS) and overall survival with the addition of perioperative ECF (epirubicin, cisplatin and 5-fluorouracil (5-FU)) to surgery. As a result of these data, perioperative chemotherapy became the standard of care in most European and Australasian countries. By contrast, patients in North America are routinely treated with primary resection followed by post-operative 5-FU-based chemoradiotherapy. As reported by MacDonald et al.,[4] this approach also

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CROSS-TRIAL COMPARISON BETWEEN MAGIC AND FFCD/FNCLCC TRIALS[2,3]

Trial (*n*)	Site of tumour (% patients)	Tumour stage to be eligible	Chemotherapy regimen	Tolerance to chemotherapy (% patients completing)	Curative resection (% patients)		OS benefit (HR)
					Peri-op chemo	Surgery alone	
MAGIC[3] (503)	LO 14.5 GEJ 11.5 Stomach 74.0	> Stage II Resectable	Epirubicin=50 mg/m^2 Cisplatin=60 mg/m^2 5-FU=200 mg/m^2/day for 21 days	Preoperative: 86% (3 cycles) Perioperative: 42% completed 6 cycles	67.6	65.6	13% (0.74)
FFCD[2] (224)	LO 11.2 GEJ 64.3 Stomach 24.5	Not staged Suitable for curative resection	Cisplatin=100 mg/m^2 5-FU=800 mg/m^2/day for 5 days	Preoperative: 87% (2 cycles) Perioperative: 23% completed 6 cycles	84.1	73.0	14% (0.69)

GEJ – gastro-oesophageal junction, LO – lower oesophagus, OS – overall survival

improves overall survival compared with surgery alone, and a recent update with long-term follow-up confirmed ongoing benefit for survival (HR=1.32, *P*=0.04).[4] Nevertheless, the two approaches have never been compared in a randomised trial, and cross-trial comparison cannot establish superiority of either strategy due to important differences in the populations. In particular, whereas the MAGIC trial[3] required patients to have potentially resectable tumours, the Intergroup 0116 trial[4] required a completed curative resection for eligibility.

Another geographical variation in the treatment of gastro-oesophageal adenocarcinoma exists in Japan, where the prevalence and natural history of these tumours differ greatly from those in Western populations. S-1, an oral fluoropyrimidine, has become the standard of care in the adjuvant setting in Japan following the results of a Japanese study that demonstrated a significant improvement in three-year overall survival.[5] However, this approach has not been adopted as a standard approach outside of Japan as S-1 is not licensed in many countries and globally capecitabine is the most established oral fluoropyrimidine. A recent meta-analysis of studies on gastric cancer, with individual data from 3838 patients treated within European, American and Asian trials, supports the use of adjuvant chemotherapy with a 5.7% overall improvement in five-year survival.[6] Notably, this overall survival benefit with adjuvant chemotherapy seems to be less than the 13–14% benefit reported with the use of a perioperative approach.[2,3]

Both the MAGIC trial[3] and the study by Ychou et al.[2] included patients with adenocarcinoma of the lower oesophagus, gastro-oesophageal junction and stomach, although the recruited patient populations in the two studies differ greatly in terms of the distribution of tumour sites. Selected demographics and the results of these two studies are shown in the table. Of particular note, in the MAGIC trial, 42% of the patients completed six cycles of perioperative chemotherapy whereas only 23% of the patients completed chemotherapy in the trial by Ychou et al. Although preoperative chemotherapy was completed successfully in most of the patients, postoperative treatment delivery was limited by factors that included disease progression, postoperative complications, and treatment toxicity. As oncological and surgical expertise continue to improve with the perioperative approach, successful completion of therapy should become possible in most of the cases.

The 36% five-year survival rate reported with ECF in the MAGIC study is similar to the 38% rate reported in the study by Ychou et al. that used CF (cisplatin and 5-FU). This inevitably raises the question as to whether epirubicin is necessary in this setting. To address this question, differences between the populations in the two studies must be examined. The study by Ychou and collaborators did not formally stage patients at trial entry and included a predominance of tumours of the gastro-oesophageal junction,[2] which may have improved outcomes, as a subgroup analysis of the MAGIC trial data demonstrated that junctional tumours seemed to benefit most from perioperative

chemotherapy.[3] Furthermore, a meta-analysis from the Cochrane Collaboration carried out in 2010 explored the benefits associated with various chemotherapy regimens in metastatic gastric cancer, based upon data from more than 5000 patients in 35 trials. In subgroup analyses, the researchers demonstrated significant overall survival benefits associated with regimens that included 5-FU, an anthracycline and cisplatin compared with regimens that lacked either the anthracycline or cisplatin.[7] These data support the use of regimens such as ECF in the advanced disease setting, which can be reasonably expected to confer benefit to patients with localised disease.

To improve tolerability and patient convenience, capecitabine is increasingly substituting infused 5-FU in regimens such as ECX (epirubicin, cisplatin and capecitabine), which was confirmed to be non-inferior to ECF in the metastatic setting.[8] The ECX regimen is currently under evaluation as preoperative therapy in the OEO5 study compared with the standard CF regimen for the neoadjuvant therapy of oesophageal cancer (UKCRN trial no. 854).

As therapeutic options for the treatment of gastro-oesophageal cancers expand, clinical trials of multimodality therapy for early-stage disease must incorporate targeted therapies to evaluate the outcome of their addition to perioperative, adjuvant chemotherapy or chemoradiation. In the advanced-disease setting the international randomised phase III ToGA study (n=594) recently demonstrated a significant improvement in response rate, PFS and overall survival when the anti-HER2 monoclonal antibody, trastuzumab, was added to a cisplatin–5-FU doublet in patients with HER2 positive adenocarcinomas of the stomach or gastro-oesophageal junction.[9] Trastuzumab is currently being evaluated in combination with capecitabine and oxaliplatin chemotherapy in a Spanish phase II perioperative gastric cancer study (ClinicalTrials.gov identifier: NCT01130337), and following neoadjuvant chemoradiation and surgery for oesophageal and oesophagogastric junction cancers in the RTOG-1010 trial (ClinicalTrials.gov identifier NCT01196390). The small-molecule inhibitor of HER2 and EGFR, lapatinib, and two monoclonal antibodies targeting EGFR, cetuximab and panitumumab, are currently undergoing evaluation in the first-line advanced-disease setting and, if successful, will likely be evaluated in patients with early-stage disease.

Even though the results of these further studies are awaited, the study by Ychou and collaborators strengthens the current evidence for perioperative chemotherapy with improvements in R0 resection rate, disease-free survival and overall survival in gastro-oesophageal cancer. This study confirms the benefits of this approach and further validates perioperative chemotherapy as a standard treatment option in this disease setting. We expect that the addition of molecularly targeted therapies may further improve patient outcomes in the future.

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Practice points

- Two large randomised phase III trials have now confirmed a 13–14% absolute improvement in overall survival associated with perioperative chemotherapy compared with surgery alone in gastro-oesophageal adenocarcinoma
- Significant geographical variation in practice will continue in the absence of a head-to-head trial to confirm superiority of one approach over another
- Addition of novel targeted agents to perioperative chemotherapy is likely to further improve patient outcomes in the future

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