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# Pharmacotherapy for Oesophagogastric Cancer

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## Abstract

Gastric cancer is the seventh and oesophageal cancer the ninth most common cancer in the UK, and >50% of patients present with locally advanced or metastatic disease. The incidence of oesophageal and oesophagogastric junctional tumours is increasing, making these important disease entities to understand and research. Despite improvements in surgical and peri-operative supportive care, 3-year overall survival with surgery alone for resectable disease is still poor. Outcomes in localised oesophageal cancer are improved with pre-operative chemotherapy, and in gastric cancer with peri-operative treatment or post-operative chemoradiotherapy. Oesophageal squamous cell carcinoma can be treated with definitive chemoradiotherapy as an alternative to surgery. While survival in patients presenting with metastatic disease is improved with the

addition of systemic chemotherapy, median survival remains <1 year. Patients who are otherwise fit can be offered chemotherapy and this is superior to best supportive care. Regimens including a platinum and an anthracycline agent are favoured by the results of randomised trials. No standard second-line therapy has emerged. New research into taxanes has shown promising anti-cancer activity, and novel areas of investigation include incorporation of agents targeting vascular endothelial growth factor or epidermal growth factor receptor into standard regimens. This review focuses on the clinical trial evidence that dictates the optimal management of localised and advanced oesophagogastric cancer, focusing on pharmacotherapy. We examine areas of current research and highlight future therapeutic directions.

Oesophagogastric cancer is common, associated with significant morbidity, and most individuals who are diagnosed will eventually die of their disease. There is an ever-increasing array of treatment options and modalities available to the practicing clinician who must understand the complexities of both the disease and the patient in order to offer the greatest degree of palliation to those with advanced disease and to increase the prospect of cure in those with operable disease.

Oesophageal cancer is the ninth most common cancer in the UK, with >7500 people diagnosed each year and an all-stage 5-year survival of 8%.[1] The two predominant histological subtypes are adenocarcinoma (AC) and squamous cell carcinoma (SCC). There is an overall male : female ratio of 3 : 2, but the occurrence of AC is 5-fold higher in males. The incidence is increasing, with rates of 7.8 per 100 000 men in 1971 and 13.2 per 100 000 men in 2004, due to an increasing frequency of AC of the lower third of the oesophagus and oesophagogastric junction (OGJ), while the incidence of tumours of the upper two-thirds of the oesophagus has remained static.[2] Cancers of the OGJ are defined as those tumours that arise within 5cm of the anatomical cardia, and are further classified as type I, II or III. Type I tumours arise from the oesophagus and infiltrate distally, type II tumours have their origin at the true cardia or within 2cm, and type III tumours arise from below and infiltrate upwards to the OGJ and oesophagus (table I).[3] The incidence of gastric cancer is declining, but there are still >9000 cases diagnosed in the UK each year, making it the seventh most common cancer in the UK.[4] A shift in the pattern of disease has also been observed, with a reduction in the number of distal tumours but a rise in the incidence of tumours of the gastric cardia and OGJ.[5] While the mortality rates for gastric cancer have reduced from ≈22.3 per 100 000 in 1971 to 6.7 per 100 000 in 2004, unfortunately nearly two-thirds of individuals diagnosed with gastric cancer will eventually die of their disease.

The high rate of local and distant failure after complete surgical resection has stimulated interest in a multi-modality approach to the treatment of localised oesophagogastric cancer, incorporating radiotherapy, chemotherapy and surgery. In advanced disease, chemotherapy has been shown to reduce symptoms and prolong life, and the advent of therapies aimed at specific molecular targets offers new options to palliate an aggressive disease.

Treatment approaches differ depending on the location of the primary tumour, histology, degree of local invasion, presence of metastases, and patient characteristics and co-morbidities. Conventional strategies include surgery alone, definitive chemoradiotherapy, pre- or peri-operative chemotherapy, pre-operative chemoradiotherapy and post-operative chemoradiotherapy.

**Table I.** Characteristics of tumours of the oesophagogastric junction[3]

| Characteristics | Type I | Type II | Type III | p-Value |
|---|---|---|---|---|
| Mean age (y) | 60.1 | 60.4 | 62.6 | NS |
| Male : female | 9.0 : 1 | 5.4 : 1 | 2.1 : 1 | <0.01 |
| Associated Barrett's oesophagus | 76.9% | 9.8% | 2.0% | <0.01 |
| Grade 3/4 tumours | 51.0% | 55.4% | 71.6% | <0.01 |

**NS** = not statistically significant.

## 1. Treatment of Localised Oesophageal Cancer

### 1.1 Surgery Alone

Surgical resection of the primary tumour has previously been considered to be the only modality to offer the prospect of cure, but this is increasingly challenged by effective chemoradiation strategies. The two most common surgical approaches are a transthoracic oesophagogastrectomy and a transhiatal approach. An Australian single-centre review reported similar survival rates with both procedures in experienced hands.[6] A large series prior to 1980 found a peri-operative mortality rate of 13% and a 5-year survival rate of 4%.[7] Despite a reduction in peri-operative mortality, the 3-year survival is still only 6–12%.[8,9] This provides the backdrop against which other modalities are compared.

### 1.2 Radiotherapy Alone

Radiotherapy as a single modality is not generally used because of the lack of efficacy compared with chemoradiotherapy and with surgery alone.[10] However, poor performance status, medical co-morbidity or other contra-indications to chemotherapy sometimes necessitate its use.

### 1.3 Pre-Operative Radiotherapy

Five randomised trials and one meta-analysis have shown little benefit to the addition of pre-operative radiotherapy to surgery. A meta-analysis of trials including 1147 patients, mostly with SCC, randomised to pre-operative radiotherapy or surgery alone, found a hazard ratio (HR) for death of 0.89 (95% CI 0.78, 1.01) favouring pre-operative radiotherapy. This equates to a non-significant reduction in death of 3% at 2 years and 4% at 5 years.[11] On the basis of these data, single-modality pre-operative radiotherapy is not recommended.

### 1.4 Pre-Operative Chemotherapy

The use of neo-adjuvant chemotherapy is attractive as it may increase the chance of a microscopically complete (R0) resection by reducing the size of the tumour, demonstrate chemo-sensitivity of the tumour, and help eliminate micro-metastatic disease that is responsible for distant failure. Its use has been supported by positive results from large randomised controlled trials.

The largest study of pre-operative chemotherapy in oesophageal cancer is the UK Medical Research Council (MRC) OE02 trial reported in 2002.[8] A total of 802 patients, which included both AC and SCC (31%) as well as type I and II tumours of the OGJ, were randomised to receive either: (i) two cycles of cisplatin (80 mg/m$^2$ day 1, day 22) and fluorouracil (5-FU) [1000 mg/m$^2$/day continuous intravenous infusion (CIVI) days 1–4, days 22–25] followed by surgery (CS group); or (ii) to immediate surgery (S group). Of these patients, 9% received pre-operative radiotherapy in both the CS and S groups. In the S group, 97% received surgery compared with 92% in the CS group, because of mainly disease progression or death. Of those randomised to chemotherapy, 87.5% received both treatment cycles. R0 resection was achieved in 60% of patients in the CS group compared with 54% in the S group. There were no differences in peri-operative complications. Overall survival (OS) at 2 years favoured the CS group (43% vs 34%, HR 0.79; 95% CI 0.67, 0.93). Quality-of-life (QOL) outcomes were comparable. On the basis of these data, pre-operative chemotherapy has become the standard approach in the UK.

The recently published MAGIC (MRC Adjuvant Gastric Infusional Chemotherapy) trial showed the benefit of peri-operative chemotherapy in patients with tumours of the stomach (74%), OGJ (11%) and lower third of the oesophagus (15%),[12] and is discussed in detail with respect to localised gastric cancer in section 3.3.

A conflicting result was found in the US Intergroup INT0113 trial, in which 467 patients with resectable AC or SCC (46%) of the oesophagus were randomised to receive either surgery or three cycles of chemotherapy followed by surgery.[13] The chemotherapy consisted of cisplatin 100 mg/m$^2$ on day 1 and 5-FU by CIVI 1000 mg/m$^2$ on days 1–5, every 28 days for three cycles, with three further cycles administered post-operatively in those patients who responded or remained stable on pre-operative chemotherapy. Radiotherapy was permitted for positive margins at clinician discretion. The primary outcome measure was OS. Only 71% of

those in the chemotherapy arm received all three pre-operative cycles, predominantly because of patient/physician choice, disease progression or death. In the CS group, 80% proceeded to surgery compared with 96% in the S group. There was a death rate of 2% due to toxicity with chemotherapy. After a median study time of 55.4 months, OS was similar in the two groups (1-year OS 59% for CS vs 60% for S; 2-year OS 35% for CS vs 37% for S), and median survival was also similar (14.9 months in CS vs 16.0 months in S; p = 0.51), with no significant differences in local or distant failure rates. There was no difference observed between histological subtypes.

A Cochrane meta-analysis has also examined the role of pre-operative chemotherapy in resectable thoracic oesophageal cancer. Data was examined for 2051 patients from 11 trials. Data from the MAGIC trial were not included. Both histological subtypes were examined. The meta-analysis concludes that there is a small but statistically non-significant benefit of pre-operative chemotherapy (HR 0.88; 95% CI 0.75, 1.04; p = 0.15).[14] The researchers acknowledge the heterogeneity of trials included and the different chemotherapy regimens used. Also, data from the MRC OE02 and INT0113 studies contributed 72% of the data available for calculation of OS.

Because the largest two trials (MRC OE02 and INT0113) yielded conflicting results, it is important to consider them in more detail. Although cross-trial comparison should be done with caution, a number of observations can be made. The survival in the surgery groups of both trials is similar, indicating that the differences lie within the chemotherapy arm. The total chemotherapy doses were higher in the INT0113 study, yet more participants in the MRC OE02 trial completed chemotherapy than in the INT0113 study, so dose intensity may have been important. Alternatively, greater toxicity may have counteracted benefit. Also, considerably fewer patients in the CS arm of the INT0113 study had surgery than was the case in the MRC OE02 trial. In the MRC OE02 trial, the treatment effect was most pronounced for OGJ tumours and potentially fewer numbers of these in the INT0113 study may have contributed to a negative result.

The MRC OE02 and MAGIC studies have established the utility of pre-operative chemotherapy in localised oesophageal cancer. The optimal regimen and number of cycles is the subject of the ongoing MRC OE05 trial.

### 1.5 Pre-Operative Chemoradiotherapy

Although pre-operative radiotherapy does not offer additional benefit over surgery alone, the synergistic properties of chemotherapy and radiotherapy (CT-RT) have been trialled in an attempt to improve R0 resection rates, local and distant failure, and OS (table II).

A trial of sequential chemoradiotherapy with cisplatin and 5-FU followed by surgery (CT-RT-S) compared with surgery alone in 86 patients with resectable SCC demonstrated a non-significant trend in favour of CT-RT-S over surgery alone (disease-free survival [DFS] 7.6 vs 5.0 months, p = 0.10; 3-year OS 19.2 vs 13.8%, p-value not reported, but not statistically significant).[15] Another trial with concurrent cisplatin plus 5-FU and radiotherapy in patients with AC found a median survival of 16 months compared with 11 months for surgery alone, and a 3-year survival of 32% compared with 6% (p = 0.01).[9] However, this trial has been criticised for its poor 3-year survival in the surgery-only group, which is lower than that found in comparable trials.

An EORTC (European Organisation for Research and Treatment of Cancer) and FFCD (Federation Francophone de Cancerologie Digestive Group) trial of two cycles of cisplatin plus 5-FU in combination with radiotherapy followed by surgery compared with surgery alone found identical 3-year survival between study arms.[16] The peri-operative mortality rate was 12.3% in the combination treatment arm compared with 3.6% in the surgery-only group (p = 0.012), which is considerably higher than in comparable trials. This was influenced by a higher number of severe complications in this group, including pneumonia, respiratory insufficiency, mediastinal infections and anastomotic leakage. There was no difference in morbidity or mortality according to study centre, and the high dose of radiotherapy per fraction (3.7Gy) was thought to contribute to morbidity.

Hyper-fractionated radiotherapy combined with cisplatin, 5-FU and vinblastine followed by surgery was compared with surgery alone in a study that

**Table II.** Trials of pre-operative chemoradiotherapy

| Study | Histology | n | Median survival (mo) | 3-Year OS (%) | p-Value |
|---|---|---|---|---|---|
| **Le Prise et al.**[15] | | | | | |
| Cis/5-FU → 20Gy RT→ Cis/5-FU | SCC | 41 | 7.6[a] | 19.2 | |
| Surgery alone | | 45 | 5.0 | 13.8 | 0.10 |
| **Walsh et al.**[9] | | | | | |
| 40Gy RT + Cis/5-FU → Cis/5-FU | AC | 58 | 16 | 32 | |
| Surgery alone | | 55 | 11 | 6 | 0.01 |
| **Bosset et al.**[16] | | | | | |
| Cis + 18.5Gy RT → Cis + 18.5Gy RT | SCC | 143 | 18.6 | 37 | |
| Surgery alone | | 139 | 18.6 | 37 | 0.78 |
| **Urba et al.**[17] | | | | | |
| CVF + 45Gy RT (bid dose) | All | 50 | 16.9 | 30 | |
| Surgery alone | | 50 | 17.6 | 16 | 0.15 |
| **Lee et al.**[18] | | | | | |
| Cis/5-FU + 45.6Gy RT (bid dose) → Cis | SCC | 51 | 28.2 | 55[b] | |
| Surgery alone | | 50 | 27.3 | 57 | 0.93 |
| **Chiu et al.**[19] | | | | | |
| Cis/5-FU + 50–60Gy RT | SCC | 44 | NR | 58.3[b] | |
| Surgery alone | | 36 | NR | 54.5 | 0.45 |
| **Burmeister et al.**[20] | | | | | |
| Cis/5-FU+ 35Gy RT | All | 128 | 22.2 | 16[c] | |
| Surgery alone | | 128 | 19.3 | 12 | NS |

a Disease-free survival.

b 2-Year OS.

c Time to progression.

**5-FU** = fluorouracil; **AC** = adenocarcinoma; **bid** = twice daily; **Cis** = cisplatin; **CVF** = cisplatin, vinblastine, fluorouracil; **NR** = not reported; **NS** = not statistically significant; **OS** = overall survival; **RT** = radiotherapy; **SCC** = squamous cell carcinoma.

found a greater 3-year OS with CT-RT, although this did not reach statistical significance (30% vs 16%; p = 0.15).[17] A similar trial demonstrated comparable median survival and OS between groups, but results may have been influenced by 31% of patients in the CT-RT-S group not undergoing surgery, predominantly because of patient choice.[18]

In the recent TROG (Trans-Tasman Radiation Oncology Group) study,[20] 256 patients with either AC or SCC were randomised to receive either one cycle of cisplatin and CIVI 5-FU with concurrent radiotherapy followed by surgery or to receive surgery alone. Although there was no difference in outcome between treatments in patients with AC, there was a significant improvement in progression-free survival (PFS) for those with SCC treated with CT-RT-S (HR 0.47; 95% CI 0.25, 0.86; p = 0.014). The OS curve followed a similar pattern but numbers were small and the result not statistically significant (HR 0.69; 95% CI 0.42, 1.15; p = 0.15).

The CALGB (Cancer and Leukaemia Group B) 9781 trial closed to accrual having only recruited 56 of a planned 500 patients with resectable AC or SCC of the oesophagus, or with type I and II OGJ tumours. Participants were randomised to either surgery alone or to trimodal therapy consisting of 5-FU 1000 mg/m$^2$ on days 1–4 and cisplatin 100 mg/m$^2$ on day 1 both repeated in week 5 with radiotherapy 50.4Gy in 28 fractions given concurrently. With a median follow-up of 6 years, a median survival of 4.5 years versus 1.8 years favoured trimodal therapy (p = 0.02), as did 5-year survival (39%, 95% CI 21, 57 vs 16%, 95% CI 5, 33).[21] Although the results reached statistical significance, the low number of patients and slow accrual of this trial raises ques-

tions over validity of the data, especially regarding potential selection bias.

A 2003 meta-analysis[22] combined data from nine randomised controlled trials involving a total of 1116 patients with AC and SCC, and found an overall benefit for neo-adjuvant CT-RT in terms of 3-year survival that was most pronounced for schedules with concurrent CT-RT (odds ratio 0.45; 95% CI 0.26, 0.79; p = 0.005). The meta-analysis was unable to detect an effect of histological subtype but was performed without the data from the TROG study.

In comparison with the MRC OE02 and INT0113 pre-operative chemotherapy-only trials, the pre-operative CT-RT trials are all much smaller with less power to detect small but potentially meaningful differences in outcome. A few small trials show a benefit for trimodal therapy and this is confirmed by meta-analysis. Concurrent schedules are favoured, and one trial suggests that SCC may benefit more from multi-modal treatment strategies.

### 1.6 Chemoradiotherapy as Definitive Treatment

Patients with oesophageal cancer often have co-morbidities precluding surgery. In addition, SCC is highly sensitive to chemoradiotherapy with some studies reporting pathological complete response rates of 30%, raising interest in chemoradiotherapy as definitive treatment.

The CURE (Chinese University Research Group for Esophageal Cancer) trial enrolled 80 patients with SCC and randomised them to either cisplatin and CIVI 5-FU with radiotherapy or to surgery, and found no significant difference in OS at 2 years.[19] In a study of 172 patients with SCC of the oesophagus, patients were randomised to receive either CT-RT alone (consisting of induction chemotherapy with three courses of bolus 5-FU, folinic acid (leucovorin), etoposide and cisplatin on days 1–3 every 3 weeks, followed by concurrent chemoradiation with cisplatin and etoposide and 40Gy in 20 fractions), or CT-RT followed by surgery (CT-RT-S). Those not proceeding to surgery received an additional 20Gy radiotherapy. OS was the same between the groups, which was partly the result of a lower disease-related mortality in the CT-RT-S arm but a higher treatment-related mortality (12.8% vs 3.5%; p = 0.03). This was reinforced with a longer PFS in the arm involving surgery (2-year PFS 64.3% vs 40.7%, HR 2.1; 95% CI 1.3, 3.5; p = 0.003).[23]

In patients who are not fit for surgery, chemoradiotherapy has also been shown to be superior to radiotherapy alone. The RTOG (Radiation Therapy Oncology Group) 85-01 study randomised 129 patients with localised AC or SCC of the thoracic oesophagus to either four cycles of cisplatin and CIVI 5-FU concurrent with radiotherapy, or to radiotherapy alone. Five-year survival was 26% in the CT-RT arm compared with 0% in the radiotherapy arm. Only 68% of patients could receive all of the prescribed chemotherapy and 10% of patients experienced life-threatening toxicity with CT-RT compared with 2% with radiotherapy alone.[24,25]

A Cochrane review of CT-RT versus radiotherapy alone showed an HR for OS of 0.73 (95% CI 0.64, 0.84) in favour of combined treatment. The absolute reduction in mortality was 9%. Disease-free survival had a HR of 0.5 (95% CI 0.4, 0.78) and the overall rate of local recurrence was 12% lower with multi-modal therapy. Toxicity was predictably higher, with 17% of patients experiencing grade 3/4 toxicity.[26]

These trials provide evidence for the use of chemoradiotherapy as the definitive treatment in patients with SCC. The trials also demonstrate the superiority of chemoradiotherapy over radiotherapy alone as treatment for those not fit to undergo surgery.

### 1.7 Newer Chemotherapy Agents

A number of early phase studies have been performed testing the use of paclitaxel and cisplatin or carboplatin with or without 5-FU in the radical management of oesophagogastric cancer. A neo-adjuvant study of 129 patients tested paclitaxel 200 mg/m$^2$ on day 1 and day 22, 5-FU 225 mg/m$^2$ CIVI on days 1–42 and radiotherapy 45Gy in 25 fractions followed by surgery. The rate of complete pathological response was 38% and median survival was 22 months. A total of 57% of patients required hospitalisation because of toxicity, but there were no pre-operative deaths. Three-year OS was 41%.[27] The outcomes of this regimen compare favourably

with earlier regimens but toxicity is considerable. Another study testing induction chemotherapy followed by chemoradiotherapy with paclitaxel and cisplatin followed by surgery had similar efficacy, but 76% of patients experienced grade 3/4 toxicity, which is far in excess of other studies.[28] Therefore, these regimens require further exploration prior to being incorporated into routine clinical practice.

## 2. Treatment of Localised Gastric Cancer

Treatment options for patients with localised gastric cancer include adjuvant chemoradiotherapy and peri-operative chemotherapy, the latter being the favoured approach in the UK. When surgery is used as a single modality in Western populations, 5-year survival for resectable gastric cancer is ≈25%.[12,29,30]

### 2.1 Adjuvant Chemotherapy

Trials of adjuvant chemotherapy for resected gastric cancer have shown either no additional benefit or small benefit only. The approach has been largely superseded by either peri-operative chemotherapy or post-operative chemoradiotherapy because of the larger treatment effects.

Early trials using older agents such as semustine[31] and regimens such as 5-FU, doxorubicin and methotrexate[32] or mitomycin,[33] showed no benefit over surgery alone. A trend in favour of adjuvant cisplatin-based chemotherapy was shown in later trials, which were underpowered to detect a significant increase in survival.[29]

Five meta-analyses have pooled data to overcome the problem created by a small sample size. In an attempt to limit trial heterogeneity,[29,34-37] one meta-analysis excluded trials using intra-peritoneal chemotherapy, immunotherapy or those that included patients with post-operative residual disease. An overall odds ratio for death of 0.80 favoured chemotherapy (95% CI 0.66, 0.97) equating to an OS benefit of ≈4%. Benefit appears to be greater in patients with node-positive disease.[37] A later meta-analysis that included less methodologically robust trials still found a similar degree of benefit with a HR of 0.82 (95% CI 0.75, 0.89; $p < 0.001$) for OS.[34]

A Japanese trial of adjuvant chemotherapy with the novel oral fluoropyrimidine S-1 was reported recently in abstract form. A total of 1059 patients with D2 or greater resections for stage II/ III gastric cancer (Japanese classification) were randomised to receive either 12 months of S-1 or observation alone. Overall, 27% of patients did not complete the 12-month course of treatment because of adverse events. Three-year OS was 70.1% in the surgery-only group and 81.1% in the group that received adjuvant therapy, principally due to a reduction in nodal and peritoneal relapse.[38] Results from trials in Japanese patients are often not reproduced in Western populations; therefore, these results will need to be replicated before being generalised to other groups.

Overall, the meta-analyses suggest a small positive benefit for post-operative chemotherapy. However, other treatment approaches are favoured because of the positive results of randomised trials.

### 2.2 Adjuvant Chemoradiotherapy

In the INT0116 study, 556 patients with completely resected AC of the stomach or OGJ were randomised to either post-operative chemoradiotherapy or standard post-operative surveillance only.[30] The type of surgical procedure or degree of lymph-node dissection (D0, D1 or D2) was not specified, although a D2 procedure was recommended (achieved in only 10% of participants).

Patients randomised to chemoradiotherapy had one cycle of Mayo-clinic schedule 5-FU (5-FU 425 mg/m$^2$ and folinic acid 20 mg/m$^2$ intravenously per day for 5 days), followed on day 28 by chemoradiotherapy (45Gy in 25 fractions over 5 weeks to a treatment area including the tumour bed, regional lymph nodes and a 2cm margin, with 5-FU 400 mg/m$^2$ and folinic acid 20 mg/m$^2$ on days 1–4 and 28–30 of radiotherapy). This was followed by a 1-month break followed by two further cycles of 5-FU and folinic acid.

With a median follow-up period of 5 years, the median survival was 36 months in the chemoradiotherapy group compared with 27 months in the surgery-only group. Relapse-free survival was 30 months versus 19 months, respectively, ($p < 0.001$), and 3-year OS was 50% versus 41% in

favour of the adjuvant treatment arm (p = 0.005). There were three treatment-related deaths (1%), 54% of patients experienced grade 3–4 haematological toxicity and 34% experienced grade 3–4 gastrointestinal toxicity. These results were preserved when the 7-year follow-up results were presented in 2004.[39] This approach has become the preferred treatment for these patients in the US.

### 2.3 Peri-Operative Chemotherapy

The MAGIC trial examined peri-operative chemotherapy in patients with AC of the stomach (74%), OGJ (11%) or lower third of the oesophagus (15%).[12] A total of 503 patients were randomised to either peri-operative chemotherapy and surgery, or to surgery alone. Peri-operative chemotherapy consisted of three cycles of pre-operative and three cycles of post-operative epirubicin, and cisplatin both on day 1 of a 21-day cycle and CIVI 5-FU (the ECF regimen) given throughout the chemotherapy treatment. This combination was selected because of its greater activity and tolerability in advanced disease compared with other regimens.[40] With a median follow-up of 4 years, 5-year OS was 36.3% for the ECF-group versus 23.0% for the surgery-only group (HR for death 0.75; 95% CI 0.60, 0.93; p = 0.009). The benefit in survival was the same regardless of tumour location. PFS was also improved (HR for progression, 0.66; 95% CI 0.53, 0.81; p < 0.001). A higher proportion of patients in the ECF-group had resections which were considered to be curative, and examination of the resected specimens showed that chemotherapy was associated with tumour downsizing and downstaging. Peri-operative mortality was not greater with chemotherapy.

The type of surgery, whether D1 or D2, was not specified by the protocol, which instead required surgeons to dissect particular lymph-node groups depending on the location of the primary tumour. However, nearly 70% of the patients who underwent gastrectomies had procedures that were considered D2 by the operating surgeon.

The study has been criticised because only 42% of patients received all six cycles of chemotherapy.[41-43] However, reasons for not completing post-operative treatment were disease progression or early death (37 patients), patient choice (11), post-operative complications (10) and Hickman catheter problems (4), reflecting some of the difficulties in using post-operative treatment. Only five patients did not complete treatment as a result of prior toxic effects or lack of response to pre-operative treatment.

The results of the MAGIC trial are supported by the preliminary results of an FFCD trial that randomised 224 patients with resectable AC of the lower oesophagus, OGJ or stomach to receive either two to three cycles of pre-operative cisplatin and 5-FU followed by surgery and three further cycles (in those that responded or had stable disease), or surgery alone. More R0 resections were achieved with pre-operative chemotherapy (84% vs 73%; p = 0.04) and tumours were of lower stage. Three-year DFS was 40% versus 25% (HR = 0.63; 95% CI 0.46, 0.86; p = 0.0018),[44] providing support for the peri-operative approach.

### 2.4 Summary of Treatment of Localised Gastric Cancer

Adjuvant chemotherapy has failed to make a major impact on either disease-free or overall survival and has not become standard practice in Western countries. Instead, the choice of treatment for resectable gastric cancer is between post-operative chemoradiotherapy and peri-operative chemotherapy.

The INT0116 and MAGIC trials cannot be compared directly because there were significant differences in the patients included in each trial. The INT0116 patients had to have survived surgery and achieved an R0 dissection, factors biasing towards a more favourable outcome. By contrast, the MAGIC-trial participants were selected at the time of diagnosis.

The pattern of referral effectively determines the treatment strategy; where referral is made post-operatively, the Intergroup approach would be adopted, whereas in the UK, where patient management is determined at the outset by a multidisciplinary team, there is an opportunity for patients to be considered for peri-operative chemotherapy.

## 3. Treatment of Advanced Oesophagogastric Cancer

Despite greater awareness and timely investigation, ≈50% of patients will still present with locally advanced or metastatic disease.[45] Palliative measures, such as endoscopic stenting, can be employed to relieve dysphagia and for the treatment of fistulas, but the procedure is associated with a high complication rate. One series of 82 patients found a complication rate of stent insertion of 64.6%, including 7.3% fistula/perforation and up to 51% recurrent dysphagia.[46] Intractable pain is also a complication.[47] Recent reports examining self-expandable plastic stents cite an absence of major complications,[48] but still with a 21% re-intervention rate.[49]

There is a paucity of randomised trials in which only patients with advanced oesophageal cancer were included. The treatment of these patients has often been informed by trials which have also enrolled patients with gastric cancer.

### 3.1 Comparison with Best Supportive Care

In metastatic gastric cancer, chemotherapy has consistently demonstrated a survival advantage and increased QOL over best supportive care, with four randomised controlled trials[50-53] and one meta-analysis[54] examining the issue. The regimens initially tested were FAMTX (5-FU, doxorubicin and methotrexate), FEMTX (5-FU, epirubicin and methotrexate) and ELF (etoposide, folinic acid and 5-FU) [figure 1]. This question has never been addressed with oesophageal cancer alone.

Median survival with the addition of chemotherapy was increased by 3–9 months; chemotherapy was well tolerated and QOL data reported in one trial favoured the chemotherapy group. Response rates (RRs) were between 23% and 50%. The most common grade 3/4 adverse effects were alopecia, haematological toxicity, nausea/vomiting (40% with FEMTX), stomatitis and diarrhoea.

These trials demonstrate the activity of chemotherapy in metastatic gastric cancer and set the background for comparison in later trials

### 3.2 Selection of the Most Active Regimen

Cisplatin (100 mg/m$^2$) as a single agent and cisplatin with 5-FU (1000 mg/m$^2$ by CIVI on days 1–5) were compared in a randomised study of 88 patients with metastatic SCC of the oesophagus. The RRs were 19% and 35%, respectively, and the median duration of response was 28 weeks with single-agent therapy compared with 33 weeks with the combination regimen. Toxicity is greater with the combination.[55] This study confirms the superior efficacy of combination treatment over single agents at the expense of greater toxicity. Regimens where treatment is given over 5 days instead of on day 1 have slightly lower activity but toxicity is less.[56]

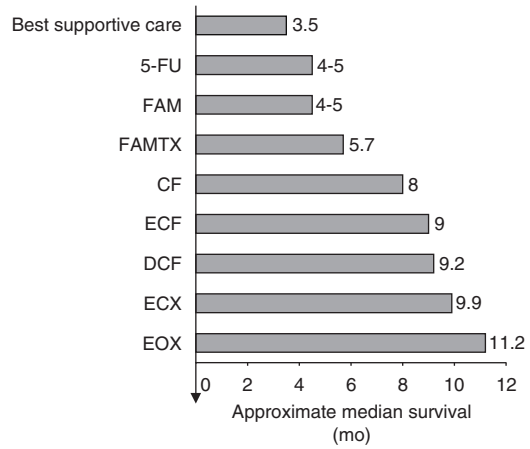


**Fig. 1.** Survival gains with improved treatment of metastatic oesophagogastric cancer. **5-FU** = 5-fluorouracil; **CF** = cisplatin, 5-FU; **DCF** = docetaxel, cisplatin, 5-FU; **ECF** = epirubicin, cisplatin, 5-FU; **ECX** = epirubicin, cisplatin, capecitabine; **EOX** = epirubicin, oxaliplatin, capecitabine; **FAM** = 5-FU, doxorubicin, mitomycin; **FAMTX =** 5-FU, doxorubicin, methotrexate.

In the 1990s, the ECF regimen was evaluated in phase II trials of patients with locally advanced or metastatic oesophagogastric cancer. RRs of 71% were seen with 12% of patients obtaining a complete response.[57] Median survival was 8.2 months, and toxicity was not notably greater than with other regimens in historical trials. These results were sufficient to warrant direct comparison with other regimens in phase III trials.

In a head-to-head trial, 274 patients were randomised to receive either ECF or FAMTX.[40] ECF demonstrated a RR of 45% compared with 21% for FAMTX, and a median survival of 8.9 versus 5.7 months ($p = 0.0002$) was observed. With the necessity for an indwelling venous access device for protracted venous infusion of 5-FU and the pro-

coagulant properties of both cancer and chemotherapy, line complications necessitated its removal in 19% of trial patients. Toxicities were broadly comparable except that ECF caused more alopecia and nausea and vomiting, but less neutropenia and infection. In a separate randomised comparison between ECF and mitomycin plus cisplatin plus 5-FU, efficacy was similar but QOL was greater with ECF.[58]

The addition of an anthracycline to cisplatin and 5-FU has shown a trend towards benefit in three randomised trials.[58-60] These data were reinforced by a recent Cochrane meta-analysis, which pooled the data from these trials and reported a statistically significant benefit in favour of anthracycline/platinum containing regimens.[54] The survival benefit was estimated to afford an additional 2 months and, of the available agents, epirubicin appeared to be the best tolerated. Therefore, ECF is considered to be the optimal regimen.

The largest clinical trial in the management of locally advanced or metastatic oesophagogastric cancer is the REAL-2 trial presented at the 2006 American Society of Clinical Oncology (ASCO) annual meeting. A $2 \times 2$ factorial design was used to evaluate the non-inferiority of an EOX regimen, in which oxaliplatin was substituted for cisplatin and capecitabine for 5-FU in the ECF regimen. In addition to demonstrating the non-inferiority of both substitutions, the comparison of the individual study arms showed that 1-year and median survivals were higher for EOX (46.8% and 11.2 months) than for ECF (37.7% and 9.9 months). A RR of 47.9% of patients treated with EOX was attained. Treatment was generally well tolerated in all study arms, with grade 3/4 peripheral neuropathy higher in the oxaliplatin arms and a slight increase in grade 3/4 diarrhoea. Thrombotic events were highest in the ECF arm, significantly lower in the oxaliplatin arms, and mainly related to line thromboses. There were no significant differences in QOL. RR and survival were not influenced by primary tumour location or histological subtype. This trial demonstrated the non-inferiority for efficacy when oxaliplatin and capecitabine were substituted for their more traditional counterparts, and underlines the efficacy of these regimens in locally advanced and metastatic oesophagogastric cancer.[61]

A phase III trial presented at ASCO 2006 compared a cisplatin plus 5-FU regimen to an oxaliplatin plus 5-FU regimen. Oxaliplatin was associated with a longer time to progression (5.7 vs 3.8 months) and higher RR (34% vs 27%), although these were non-significant. Non-inferiority for the oxaliplatin regimen was demonstrated, providing further support for the substitution of this agent for cisplatin.[62]

### 3.3 Taxane-Based Regimens

The taxanes exert their anti-cancer effect by stabilising microtubules, thereby inhibiting cellular replication. Paclitaxel has shown activity in many other solid tumours and therefore has been tested in oesophagogastric cancer. Despite showing activity in combination with carboplatin,[63,64] the toxicity is prominent, with 11 of 51 patients in one study requiring hospitalisation because of haematological toxicity.[65] Docetaxel appears to have a lower RR when used as a single agent,[66] and demonstrated an 18% RR when used as first-line therapy and 0% in previously treated patients in one study of advanced oesophageal AC.[67]

In a phase III trial of 457 patients with advanced gastric cancer, patients were randomised to either cisplatin plus 5-FU (CF) or to docetaxel with CF (DCF). RR was greater with the DCF regimen (36.7% vs 25.4%; $p = 0.01$), time to progression was 5.6 versus 3.7 months ($p = 0.004$), median survival was 9.2 versus 8.6 months ($p = 0.02$) and 1-year OS was 40% compared with 32%, all in favour of DCF. Haematological toxicity was prominent with DCF, however, with 82.3% of patients experiencing grade 3/4 neutropenia compared with 56.0% with CF, and febrile neutropenia was experienced by 30% versus 13.5% of patients. QOL analyses favoured DCF.[68] Although toxicity is notable, this trial and others demonstrate the activity of docetaxel, and investigation into weekly regimens and other less toxic regimens that preserve activity are underway.

Irinotecan in combination with docetaxel was tested in 46 patients with gastroesophageal AC and resulted in a RR of 26% limited by grade 4 neutropenia and fevers in 8 of 13 patients.[69] A separate trial at slightly higher doses confirmed similar responses with 71% of patients experiencing grade 4 haematological toxicity and 43% febrile neutropen-

ia, underlining the intense myelosuppression of this combination.[70]

### 3.4 Other Cisplatin-Based Combination Regimens

Cisplatin, 5-FU and interferon α-2a have been tested in a number of phase II trials. In one study, 27 patients with either AC or SCC achieved a RR of 50% at the expense of a 41% occurrence of grade 3/4 haematological toxicity and 26% non-grade 3/4 toxicity.[71] Increasing the dose of interferon can enhance the RR but with greater toxicity.[72] Omitting the cisplatin markedly lowers the RR.[73,74] Later, interferon α-2a and 13-cis-retinoic acid were tested with no objective responses recorded.[75]

Etoposide and cisplatin achieved RRs of 40–48% with myelosuppression and neutropenic fever being the major toxic adverse effects. The addition of radiotherapy has resulted in the relief of dysphagia in up to 89% of patients.[76-78]

Despite a lack of single-agent activity, gemcitabine has been studied with cisplatin because of their synergistic activity. A SWOG (Southwest Oncology Group) phase II trial did not report a RR but recorded 1-year OS of 20% and a median survival of 7.3 months.[79] A second trial of 36 patients, the majority of whom had AC, achieved a RR of 41% and a median survival of 9.8 months. Grade 3/4 anaemia occurred in 81% of patients and dose delays in 63%.[80] Therefore, moderate activity is noted with manageable mainly haematological toxicity.

Vinorelbine in combination with cisplatin was shown to be active in metastatic SCC of the oesophagus. In a trial of 71 patients, a RR of 33.8% was observed, with grade 3/4 neutropenia being the major toxicity occurring in 41% of patients. QOL was improved in the majority of participants.[81] Vindesine has lower activity.[82]

Irinotecan with cisplatin achieved a RR of 57% in a trial of 35 patients. Symptomatic dysphagia and QOL were improved in 90% of participants in this study; 37% of patients experienced grade 3 and 9% grade 4 neutropenia, and 11% grade 3 diarrhoea (0% grade 4).[83] Schedule amendment to a regimen of administration on day 1 and day 8 every 21 days preserved anti-tumour activity with a reduction in grade 3/4 haematological toxicity to 22%.[84]

### 3.5 Platinum-Taxane Combinations

Cisplatin and paclitaxel have been combined in a number of single-arm phase II studies with varying schedules. RRs of 40–49% have been achieved, but with frequent toxicity. In one trial, 50% of patients required hospitalisation for toxicity and four died from toxic effects.[85-87]

In a trial of docetaxel and cisplatin in 16 chemotherapy-naive patients, a RR of 31.3% was achieved, and a median OS of 29 weeks with lower haematological toxicity than the paclitaxel regimen.[88] A bimonthly schedule tested in a phase II trial achieved a response in 46% of patients and median survival of 11.5 months, which is one of the best reported. In addition, four patients (11%) had complete responses to chemotherapy without substantially increased toxicity.[89]

### 3.6 Regimens without Cisplatin or Taxanes

Substitution of cisplatin for carboplatin is often done on the presumption that efficacy will be relatively preserved with less toxicity. However, in a single-arm study of 17 patients with both histological subtypes treated with carboplatin and 5-FU in combination with split-course accelerated radiation therapy, a RR of only 25% was found,[90] considerably lower than that seen in trials of cisplatin and 5-FU. Although there are no randomised comparisons of carboplatin regimens with cisplatin regimens, cross-trial comparisons show lower RRs with carboplatin combinations than in trials utilising cisplatin-containing regimens.[91,92] Where a substitute for cisplatin is required, the results of the REAL-2 study suggest that oxaliplatin is the best of available alternatives.

The FOLFIRI regimen, comprising irinotecan, folinic acid and a bolus of 5-FU followed by a 48-hour infusion of 5-FU is active in metastatic colorectal cancer and was studied in 40 patients with relapsed or refractory SCC or AC of the oesophagus, gastroesophageal junction or stomach who had been previously treated with a platinum plus 5-FU combination. In a group of patients who were likely to show chemotherapy resistance, a RR of 29% was observed with an additional 34% attaining stable disease. Improvement in dysphagia occurred in 78.6% of patients. Haematological toxicity was

most prominent and grade 3/4 neutropenia occurred in 26.4% of patients. Median OS was 6.4 months.[93]

In a phase III trial limited to patients with metastatic gastric cancer, 337 patients were randomised to a regimen of either irinotecan, folinic acid and a 22-hour infusion of 5-FU (IF group), or to cisplatin and a 5-day continuous infusion of 5-FU (CF group).[94] The primary endpoint was time to progression, and there was a non-significant trend in favour of the IF regimen (5.0 vs 4.2 months). Grade 3/4 diarrhoea was higher in the IF group (21.6% vs 7.2%), but grade 3/4 stomatitis (2.4% vs 16.9%), neutropenia (25% vs 52%) and febrile neutropenia (4.8% vs 10.2%) were all lower in the IF compared with the CF group. This shows that the activity of the IF regimen is preserved when compared with CF with a more favourable adverse-effect profile, presenting an alternative regimen for selected patients.

A novel platinum derivative, nedaplatin was tested in combination with 5-FU in 17 patients with metastatic or unresectable oesophageal cancer, and an RR of 60% was observed in 15 assessable patients without significant neutropenia, nausea, neuropathy or renal impairment.[95] Three grade 3 toxicities were seen in this small cohort, specifically allergy, reduced haemoglobin level and thrombocytopenia.

### 3.7 Regimens Containing the Oral Fluoropyrimidine S-1

S-1 (TS-1) is a combination of tegafur (ftorafur) and two modulators; gimeracil (CDHP) and potassium oxonate, in a molar ratio of 1 : 0.4 : 1.[96] It has been tested extensively in Japanese populations as a single agent, and in combination with both platinum and taxane regimens. Most trials have been single-arm phase I/II trials. However, RRs and median survival appear comparable to those seen in trials of similar fluoropyrimidine-combination regimens.[97-99] A European randomised phase III trial comparing S-1 plus cisplatin with 5-FU plus cisplatin in advanced gastric cancer is currently recruiting.[100]

### 3.8 Explorations of Single-Agent Activity

The anti-neoplastic antibiotic bleomycin was an early agent to be investigated, but its pulmonary toxicity, especially in patients with underlying lung disease and when combined with radiotherapy, has limited its usefulness.[101]

Gemcitabine has shown activity in pancreatic and cholangiocarcinoma, but achieved no measurable responses in a cohort of 17 patients with metastatic oesophageal carcinoma.[102]

Vinorelbine, which belongs to the vinca alkaloid family of anti-neoplastics, binds to tubulin resulting in inhibition of microtubule formation and cell replication. It has been tested in both pretreated and untreated patients with SCC, [103,104] and objective tumour RRs of 20–25% were obtained with only one patient experiencing grade 4 non-haematological toxicity.

Irinotecan alone has shown modest activity in both AC and SCC,[105] with one report of nine patients, including pre-treated patients, reporting two partial responses and two patients with stable disease. Diarrhoea and neutropenia were the major toxicities.[105]

### 3.9 Second and Subsequent Lines of Treatment

There are no randomised trials comparing second-line chemotherapy with best supportive care in oesophagogastric cancer. Most trials are single-arm studies that report RR and PFS as their endpoints, with few data on QOL. Many different regimens have been tested in early phase studies including docetaxel, paclitaxel, paclitaxel and cisplatin, docetaxel and capecitabine, irinotecan, cisplatin and irinotecan, FOLFIRI, gefitinib[67,93,105-110] and many of these are discussed in the previous sections. RRs ranging from 0% to 52% have been reported, with variation as a result of heterogeneity of trial design, patient population, regimens previously used and degree of pre-treatment. No standard second-line therapy has emerged. If there has been a long disease-free interval, a prior response to treatment and the patient has a good performance status, the patient can be re-treated with the regimen used initially. Recruitment into well designed clinical trials is recommended.

### 3.10 Summary of Advanced Disease

ECF has been established as the standard regimen in the UK and parts of Europe. On the basis of the results of the REAL-2 study, capecitabine should replace 5-FU as it is equally efficacious, and avoids the inconvenience and complications of central venous access devices. The EOX regimen is the first to report a median survival of >11 months in this population in a phase III trial and should be considered a new reference regimen for the disease. The activity of DCF is encouraging (although to date only tested in patients with OGJ and gastric cancer) but has increased toxicity and represents an area of further research. There is no standard of care in second-line treatment and again, recruitment into clinical trials is encouraged.

## 4. Targeted Agents in Oesophageal and Gastric Cancer

Specific molecular targets have offered a new area of investigation in clinical trials. The epidermal growth factor receptor (EGFR) plays an important role in cell proliferation and is overexpressed in many solid tumours including oesophageal and gastric cancers. In those patients with EGFR overexpression, prognosis has been found to be worse.[111]

Cetuximab, a human/murine chimeric monoclonal antibody against EGFR, has activity in metastatic colorectal cancer when used alone and in combination with chemotherapy.[112]

In one trial, 17 patients with resectable AC or SCC of the oesophagus received neo-adjuvant cetuximab in combination with cisplatin and irinotecan with concurrent radiation therapy followed by surgery. In this analysis, two patients achieved pathological complete responses and grade 3/4 toxicities were prominent with diarrhoea in nine patients, neutropenia in nine, febrile neutropenia in five and anorexia in five.[113] The RR here was lower than that observed in other trials. In combination with paclitaxel and carboplatin and concurrent radiotherapy, 18 of 27 evaluable patients with oesophageal and gastric cancer attained a clinical complete response and 7 of 16 who underwent surgery had a pathological complete response. Modest toxicity only was noted.[114]

In 38 EGFR-positive patients with metastatic gastric or OGJ AC who were chemotherapy naive, treatment with FOLFIRI plus cetuximab was administered. Of 25 assessable patients, 3 showed complete response, 11 showed partial response, and 11 had stable disease, with 53.6% of patients experiencing grade 3/4 neutropenia and 17.8% grade 3 cutaneous toxicity.[115]

The high-affinity humanised monoclonal antibody against EGFR, matuzumab, has been evaluated in phase I studies in advanced oesophagogastric AC. Used in combination with epirubicin, cisplatin and capecitabine (ECX) in patients with EGFR-positive tumours, the maximum tolerated dose was not reached; partial response or stable disease was attained in six of seven patients at a matuzumab dose of 400mg, and five of six patients at a dose of 800mg. Tolerability was similar to that described with ECX with the addition of the expected skin toxicity associated with anti-EGFR agents.[116] In a second study in combination with cisplatin, 5-FU and folinic acid, six of eight patients had a partial response and one patient had stable disease.[117]

The orally active EGFR-tyrosine kinase inhibitor gefitinib has demonstrated limited utility to date in oesophageal cancer. In one phase II trial involving 34 patients unresponsive to first-line therapy, and with unspecified histology, three had a partial response and six had stable disease. Diarrhoea and rash were the prominent toxicities.[118] Another phase II trial involving patients with either metastatic or recurrent oesophageal or OGJ AC or SCC, demonstrated similar poor RRs, with only 3 of 20 patients showing a partial response and 3 of 20 achieving stable disease.[119] In another trial in the second-line setting involving 36 patients, one patient had a partial response and ten had stable disease. Female patients, those with SCC and patients with EGFR overexpression were associated with a higher disease-control rate ($p = 0.002$). Toxicity was manageable.[120] Another abstract has presented results on gefitinib combined with celecoxib in 13 chemotherapy naive patients with advanced oesophageal AC and found no activity.[121]

The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab has been shown to increase tumour RRs and prolong duration of response in metastatic colorectal cancer

in combination with chemotherapy.[122] A proportion of patients with oesophageal cancer overexpress VEGF, and this appears to correlate with degree of invasion.[123] However, its exploration in oesophagogastric cancer has been limited. In one report, 47 patients with previously untreated metastatic gastric or OGJ AC received cisplatin, irinotecan and bevacizumab. The primary end-point was time to progression. Overall RR was 65%, time to progression was 8.3 months and median survival was 12.3 months. Toxicity of the cisplatin plus irinotecan was not increased. Bevacizumab-related toxicities included gastric perforation in two patients, two cardiac events and one peri-rectal fistula. Ten patients experienced grade 3/4 hypertension, which was manageable.[124,125]

On the basis of encouraging early data in advanced gastric cancer, a trial of bevacizumab in localised disease is planned. In a follow-up to the MAGIC trial, patients with gastric or OGJ AC are to be randomised to either six cycles of peri-operative ECX or the same treatment with the addition of bevacizumab. Recruitment to this trial has now commenced.

## 5. Summary and Recommendations

The optimal treatment of oesophagogastric cancer is complex and is influenced by tumour histology, whether the tumour is localised or disseminated and patient co-morbidity. In patients with localised SCC of the oesophagus who are otherwise healthy, definitive chemoradiotherapy is undertaken, with surgery reserved for those who have demonstrated residual disease at the end of treatment. For patients with AC of the lower third of the oesophagus or OGJ, clinical trials support the use of pre- or peri-operative chemotherapy using the MRC OE02 or MAGIC approach. In North America, chemoradiotherapy followed by surgery is often used for oesophageal tumours, in line with the results from the CALGB 9781 study. For tumours of the lower oesophagus, OGJ and stomach, peri-operative ECX can be employed. An alternative approach for localised gastric cancer is definitive surgery followed by adjuvant chemoradiation, based on the results of the INT0116 study.

In metastatic disease, a platinum-based combination regimen is used in the first-line setting. Of the available regimens, EOX should be considered as a new reference regimen on the basis of the longest median survival reported in a phase III study and a number of tolerability benefits. The incorporation of anti-VEGF and anti-EGFR agents remains a promising area of research for the future and should provide further progress in the optimal management of oesophagogastric cancer.

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