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Adjuvant therapy for gastric cancer: Current and future directions

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Abstract

The management of gastric cancer continues to evolve. Whilst surgery alone is effective when tumours present early, a large proportion of patients are diagnosed with loco-regionally advanced disease, resulting in high loco-regional and distant relapse rates, with subsequent poor survival. Early attempts at improving outcomes following resection were disappointing; however, randomized trials have now established either post-operative chemoradiotherapy (INT0116) or peri-operative chemotherapy as standard adjuvant therapies in the Western world. There remain, however, significant differences in the approach to management between the West and East. In Asia, where there is the highest incidence of gastric cancer, extended resection followed by adjuvant chemotherapy represents the standard of care. This review discusses current standard adjuvant therapy in gastric adenocarcinoma, as well as recent and ongoing trials investigating novel (neo)adjuvant approaches, which hope to build on the successes of previous studies.

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Core tip: Surgery remains the cornerstone of curative therapy in gastric cancer. However, a large proportion of patients are diagnosed with locally advanced disease, resulting in poor survival. Randomized trials have now established either post-operative chemoradiotherapy or perioperative chemotherapy as standard adjuvant therapies in the Western world. There remain, however, significant differences in the approach to management between the West and East. In Asia, extended resection followed by adjuvant chemotherapy represents the standard of care. This review discusses the evidence supporting current standard adjuvant therapy in gastric cancer, as well as recent and ongoing trials investigating novel (neo)adjuvant approaches.

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INTRODUCTION

Gastric cancer represents the second leading cause of cancer death worldwide and is the fourth most common malignancy in the world, with an estimated 988000 new cases diagnosed in 2008, and accounting for 736000 cancer-related deaths^[1].

Surgery provides high rates of cure in the early stages; however less than 25% of patients present with early stage disease. The survival of the remaining patients with potentially curable, non-metastatic disease falls below 50% and 20% when the tumour invades through the

Table 1 American Joint Committee on Cancer 6th vs 7th edition staging of gastric cancer

AJCC 6 th		AJCC 7 th	
T1	Tumour invades lamina propria or submucosa	T1a	Invades Lamina propria or muscularis mucosae
		T1b	Invades Submucosa
T2a	Invades Muscularis propria	T2	Invades Muscularis propria
T2b	Invades Subserosa		
T3	Penetrates Serosa (visceral peritoneum), without invasion of adjacent structures	T3	Penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Invades adjacent structures	T4a	Tumor invades serosa (visceral peritoneum)
		T4b	Tumor invades adjacent structures
N1	1-6 nodes involved	N1	1-2 nodes involved
N2	7-15 nodes involved	N2	3-6 nodes involved
N3	> 15 nodes involved	N3a	7-15 nodes involved
		N3b	> 15 nodes involved

AJCC: American Joint Committee on Cancer.

muscularis propria and involves regional lymph nodes, respectively^[2], prompting much effort to improve patient outcomes following gastrectomy.

The publication of two landmark trials in 2001 and 2006 established both post-operative chemo-radiotherapy (CRT) and perioperative chemotherapy (CT) as effective adjuvant treatment options, and both are currently accepted standards of care in the Western world^[3,4]. However, debate continues concerning the applicability of these trials to the Asian population, where there is the highest incidence of gastric cancer.

The staging of gastric cancer has recently undergone revision, with the 7th edition of the American Joint Committee on Cancer classification amending the T-stage definition of serosal and subserosal invasion, as well as the extent of lymph node involvement (Table 1)^[2,5]. It also addresses the classification of tumours arising at the gastro-oesophageal junction. Though there continues to be wide variation and imprecise definitions of gastro-oesophageal junction (GOJ) tumours (including gastric cardia), the current staging system classifies tumours that arise in the gastric cardia, or within 5 cm of the GOJ and extending into the oesophagus, as oesophageal cancers.

This review will examine current standard adjuvant therapies in resectable gastric adenocarcinoma, and will focus predominantly on tumours arising in the stomach, rather than the GOJ. In addition, newer strategies and trials, which aim to build on the successes of current adjuvant and neoadjuvant approaches will be discussed.

“EAST VS WEST” APPROACH TO GASTRIC CANCERS

There continues to be differences between Western and

Asian countries, both in terms of approach to management of gastric cancer, as well as efficacy of therapy. Whereas a D1 or less lymph node dissection has been common practice amongst Western surgeons, Japanese surgeons in particular consider an adequate lymphadenectomy to at least include the D2 echelon of nodes (described below). There are also frequently observed differences in outcomes, where reported survival rates are consistently higher in Asian studies^[6-8]. It is not clear whether the extent of surgery can solely be responsible for this. Numerous hypotheses have been suggested to explain this observation, the first of which relates to the issue of stage migration, where a more extensive nodal dissection leading to more accurate prognostic stratification and inevitable upstaging in a proportion of patients may in fact falsely suggest a treatment benefit^[9]. Other factors may also contribute, including inherent biological differences in the disease between the two populations^[10], as well as differing tolerance and sensitivity to chemotherapeutic agents.

EXTENT OF LYMPH NODE DISSECTION

The extent of lymphadenectomy remains a major area of controversy in gastric cancer management. Though a comprehensive discussion of lymphadenectomy is beyond the scope of the current review, a brief discussion follows, as it puts into context some of the difficulties with interpreting and comparing results of older vs newer studies, as well as Asian vs Western trials.

Although there are slight variations in definition, in general, a D1 lymphadenectomy entails removal of perigastric lymph nodes as well as those around the left gastric artery (stations 1-7), whereas a D2 dissection removes additional lymph nodes around the hepatic, celiac, splenic, as well as splenic hilar and hepatoduodenal (stations 8-12) nodes^[11]. Comprehensive guidelines describing the extent of lymphadenectomy according to primary tumour location are detailed by the Japanese Research Society for Gastric Cancer (JRS GC)^[12]. Extended dissections beyond D2 are not routinely performed, as these lymph nodes are often regarded as distant metastases^[2]. Japanese surgeons consider a D2 dissection the standard of care, whilst less extensive dissections are still commonplace amongst Western surgeons.

There have been at least five randomised controlled trials (RCT's) comparing D1 vs D2 dissection, of which the Dutch and United Kingdom Medical Research Council (MRC) trials were the largest^[13-17]. In addition, multiple reviews of these trials have been reported. In summary, most of these trials suggested higher rates of mortality and morbidity with D2 dissection, with no convincing overall survival benefit^[18-20]. This was confirmed in a recent meta-analysis published in 2012, of five RCT's where overall hospital mortality was higher in D2 patients (RR = 2.02; 95%CI: 1.30-3.14, P = 0.002); however, overall survival at 5 years reported in three trials was similar at 43.5% and 44.9% for D1 and D2 patients, respectively

(RR = 1.06; 95%CI: 0.85-1.33, $P = 0.58$)^[21]. It is interesting to note that in a recent 15-year update of the Dutch RCT, the authors reported a reduction in gastric cancer-related deaths, although there was still no difference in overall survival (OS)^[16].

There is evidence that at least some of the morbidity associated with D2 dissection may relate to the requirement for spleen and pancreas resection. The most recent results from the Italian RCT, which show no difference in morbidity or mortality between D1 and D2 certainly suggests there may be a contribution and benefit from advances in modern surgical technique and perioperative care^[17]. Despite a lack of clear evidence of benefit, there is growing consensus amongst Western surgeons that D2 dissection should be performed whenever possible.

STANDARD OF CARE IN THE WEST-POSTOPERATIVE CRT AND PERIOPERATIVE CT

The role of locoregional radiation is based on the fact that a significant proportion of relapses following curative gastrectomy occur in the upper abdomen^[22]. In fact, early evidence suggested that these recurrences are likely occult and exceeded clinically detected events, thereby providing further rationale for adjuvant radiotherapy^[23,24].

Initial efforts to improve outcomes after surgery alone, however, were disappointing. Earlier trials of pre- and post-operative radiotherapy, which individually did not demonstrate any benefit, were hampered by small numbers, toxicity, and heterogeneous dose-fractionation schedules^[25-28].

In 2001, the INT0116 trial was reported by MacDonald *et al*^[4] and demonstrated a major survival advantage for the use of postoperative adjuvant chemoradiotherapy. This trial randomly assigned 556 patients with stage IB-IV gastric cancer following surgery to either observation or adjuvant therapy with 4 monthly cycles of bolus 5-fluorouracil (5-FU) and leucovorin combined with radiation to 45 Gray in 25 fractions. With a median follow-up period of 5 years, the 3-year survival rate was 50% in the CRT group *vs* 41% in the surgery alone group ($P = 0.005$). The 10-year update demonstrated persistent median OS benefits of 35 mo *vs* 27 mo, with a HR of 1.32 (95%CI: 1.10-1.60; $P = 0.046$)^[29].

The criticisms of adjuvant CRT in the MacDonald study included the substantial rates of acute toxicity (33% had \geq grade 3 gastro-intestinal toxicity), lower rates and extent of nodal dissection (54% had a D0 dissection and only 10% had a formal D2 dissection), the relatively simple (and now outdated) radiotherapy techniques used, and the choice of chemotherapy regimen, the latter two of which are further discussed below.

The publication of the MAGIC trial in 2006 provided a new option for the treatment of gastric cancer^[3]. This trial randomly assigned 503 patients with resectable stage

IB-IV gastric cancer to either perioperative chemotherapy [three preoperative and three postoperative cycles of epirubicin cisplatin, 5-FU (ECF)] and surgery or surgery alone. With a median follow-up of 4 years, the 5-year survival rate was 36% in the perioperative chemotherapy group *vs* 23% in the surgery alone group (HR = 0.75; 95%CI: 0.6-0.93; $P = 0.009$).

Therefore, in Western countries there are two standards of care for patients with resectable gastric cancer^[30-32], leaving clinicians with the dilemma of which strategy to employ. There are difficulties in delivering post-operative therapy in patients who are deconditioned following surgery, and this was highlighted in both INT0116, where only 64% of patients randomized to the CRT arm completed all protocol treatment, as well as MAGIC, where less than half of patients completed the post-operative component of protocol chemotherapy. In contrast, pre-operative therapy is far better tolerated: in the MAGIC study, 86% of patients completed all three neo-adjuvant cycles of ECF, with haematological toxicity being the most common toxicity (24%-28% grade 3-4 granulocytopenia), and grade 3-4 nausea and vomiting occurring in only 6.4% and 5.6%, respectively. In addition, the rates of post-operative complications, deaths within 30 d and median hospital stay were similar in both arms of the MAGIC trial.

It is obviously difficult to directly compare absolute outcomes across both trials as the patient cohorts were dissimilar, in that MAGIC included a slightly higher proportion of node-negative patients (28% *vs* 15%), as well as patients with distal oesophageal primaries (15% *vs* 0%). In addition, approximately 66% of patients in MAGIC underwent a curative resection (according to the operating surgeon), whereas in INT0116, all patients underwent an R0 resection. This is likely a reflection of the fact that the MAGIC trial recruited patients pre-operatively, whereas patients in INT0116 were randomised 20-40 days following R0 gastrectomy.

Despite the issues with INT0116 described above, there are other lines of evidence to support a benefit for radiotherapy in gastric cancer, including several meta-analyses and a large population-based database, all of which consistently demonstrate a survival benefit for the addition of radiotherapy to surgery. The four meta-analyses of radiotherapy published since 2006 are summarized in Table 2^[33-36]. One of the more recent meta-analysis was reported by Ohri *et al*^[33] and included 13 trials with 2811 patients^[37-42]. Their results were consistent with those from previous meta-analyses, suggesting that the addition of radiotherapy to surgery (with or without CT) improves OS [HR = 0.78 (0.70-0.86), $P < 0.001$]. Inclusion of the three more recent Asian trials, which compared adjuvant CT with adjuvant CRT, also showed improvements in DFS [HR = 0.77 (0.91-0.65), $P = 0.002$], as well as OS [HR = 0.83 (0.67-1.03), $P = 0.087$], though the latter did not reach statistical significance.

An analysis of the Surveillance, Epidemiology, and

Table 2 Meta-analyses of adjuvant chemo-radiotherapy trials after 2006

Ref.	Year	Number of trials	Number of patients	HR	P value
Ohri <i>et al</i> ^[33]	2013	13	2811	HR = 0.78 [0.70-0.86]	< 0.001
Guo <i>et al</i> ^[36]	2011	9	1548	OR = 0.57 [0.34-0.95]	0.03
Valentini <i>et al</i> ^[35]	2009	9	2025	RR = 1.26 [1.08-1.48]	0.004
Fiorica <i>et al</i> ^[34]	2007	9	1694	OR = 0.54 [0.43-0.68]	< 0.00001

Table 3 Meta-analyses of adjuvant chemotherapy after 2006

Author	Year	Number of trials included	Number of patients	HR for OS	P value
GASTRIC	2010	17	3838	HR = 0.82 [0.76-0.90]	< 0.001
Sun <i>et al</i>	2009	12	3809	HR = 0.78 [0.71-0.85]	< 0.001
Zhao <i>et al</i>	2008	15	3212	RR = 0.88 [0.77-0.99]	0.001
Liu <i>et al</i>	2008	19	4599	RR = 0.85 [0.80-0.90]	< 0.00001

GASTRIC: Global Advanced/Adjuvant Stomach Tumor Research International Collaboration; OS: Overall survival.

End Results database, which includes 11630 patients, suggested a benefit for adjuvant radiotherapy predominantly in node-positive patients (5-year OS 30.4% *vs* 21.4%, *P* < 0.0001)^[43]. The survival benefit of CRT was consistently demonstrated when > 15 or > 30 lymph nodes were removed in N1/2 and N3 patients, respectively.

Current consensus and practice guidelines from the National Comprehensive Cancer Network, European Society for Medical Oncology and Canada recommend either perioperative CT or post-operative CRT as standard treatment options for patients with resectable gastric cancer^[30-32].

STANDARD OF CARE IN THE EAST-ADJUVANT CHEMOTHERAPY

Adjuvant CT has been a widely explored approach both in Western and Asian countries since the 1960's, given the propensity for distant and metastatic relapse following curative resection. Various agents have been tested including 5-FU, doxorubicin, mitomycin C, epirubicin, cisplatin and various combinations of these.

Multiple meta-analyses of adjuvant CT have been reported, the most recent of which are summarised in Table 3^[44-48]. These show a modest survival benefit for adjuvant CT, particularly in Asian patients. The GASTRIC meta-analysis was an individual patient-level analysis of 17 trials including 3838 patients^[49]. At a median follow-up of 7 years, adjuvant CT significantly increased OS from 49.6% to 55.3% [HR = 0.82 (0.76-0.90); *P* < 0.001]. Similar statistically significant effects were seen with DFS.

Although adjuvant CT is not used routinely in the West, it represents standard practice in the East, following the reporting of two large RCT's in Asian patients, namely the CLASSIC trial from East Asia and the Japanese ACTS-GC trial, both of which used different CT regimens^[50-52].

The ACTS-GC trial randomized 1059 patients with stage II or III gastric cancer following D2 gastrectomy to observation or S-1, an oral fluoropyrimidine CT preparation containing tegafur, gimeracil and oteracil, for 1 year after surgery. Initial results were published in 2007^[50], and 5-year follow-up data have recently been reported^[51]. There is a persistent OS benefit of S-1 from 61% to 71% [HR = 0.669 (0.54-0.828)]. S-1 appears well tolerated with < 5% of patients reporting grade 3 or higher toxicities. S-1, however, is not widely available in Western countries.

The CLASSIC trial randomized 1035 patients with stage II or III gastric cancer following D2 gastrectomy to observation or eight cycles of capecitabine and oxaliplatin^[52]. Patients in the CT arm had improved 3-year disease-free survival, from 59% to 74% (*P* < 0.0001). Overall survival was also improved (78% *vs* 83%, *P* = 0.0493). However, more than half the patients in the CT arm experienced grade 3 or 4 toxicities.

As a result of these two trials, the current standard of care for adjuvant therapy of gastric cancer in the East is postoperative CT with either S-1 or capecitabine/oxaliplatin.

BEYOND MAGIC AND INT0116

Since the reporting of the MAGIC trial in 2006, a new generation of adjuvant gastric studies have been reported that include more recent RCT's, and studies of novel neoadjuvant approaches.

Perioperative chemotherapy

The MAGIC study reported that only 49.5% of patients in the perioperative CT arm completed all post-operative treatment, prompting some investigators to question the relative contribution of the post-operative cycles of CT.

Two European RCT's have evaluated pre-operative CT *vs* surgery alone. The ACCORD-07/FFCD 9703 trial reported by Ychou *et al*^[53] which closed early because of poor accrual, randomized 224 patients to surgery alone

Table 4 Trials of adjuvant chemo-radiotherapy *vs* adjuvant chemotherapy in gastric cancer after 2006

Ref.	Year	Surg	Postop CRT arms	No. of patients	% having D2 dissection	Survival Outcome	P value	Outcome	P value
Lee <i>et al</i> ^[37]	2012	Surg	Cape/Cis x2 - 45Gy/ Cape - Cape/Cis x2	458	100%			3-yr DFS 78.2% <i>vs</i> 74.2%	0.862
Yu <i>et al</i> ^[42]	2012	Surg	Cape/Cis - x6 FU/LV - 45Gy/FU/LV - FU/LV	404	100%	5-yr OS 48% <i>vs</i> 41.8	0.122 (for median OS)	5-yr RFS 45.2% <i>vs</i> 35.8%	0.029 (for median OS)
Kim <i>et al</i> ^[39]	2012	Surg	5-FU/LV x5	90	100%	54.6% <i>vs</i> 65.2%	0.67		
Bamias <i>et al</i> ^[40]	2010	Surg	x1 5-FU/LV - 45Gy/5-FU - x2 5-FU/LV	147	44% D1-2	OS/DFS no difference			
Yu <i>et al</i> ^[42]	2012	Surg	Docetaxel/Carboplatin + 45Gy	68	69%	3yr OS 68% <i>vs</i> 44%	< 0.05	3-yr DFS 56% <i>vs</i> 29%	< 0.05
Kwon <i>et al</i> ^[41]	2010	Surg	INT-0116 5-FU/Cis x6	61	100%	5-yr OS 70.1% <i>vs</i> 70%	0.814	5-yr DFS 80% <i>vs</i> 75%	0.887
		Surg	FPx1 - 45Gy/Cape - FP x3						

Cape: Capecitabine; Cis: Cisplatin; FU/LV: Fluorouracil/leucovorin; FP: Fluorouracil/cisplatin; OS: Overall survival; DFS: Disease-free survival; RFS: Relapse-free survival.

vs two to three cycles of pre-operative cisplatin and 5-FU CT. This study included predominantly patients with gastro-oesophageal junction adenocarcinomas, with stomach primaries allowed later in the study and comprising 25% of the patients enrolled. At a median follow-up of 5.7 years, pre-operative CT improved the R0 resection rate from 74% to 84% ($P = 0.004$), as well as increasing 5-year OS and DFS from 24% to 38% ($P = 0.02$), and 19% to 34% ($P = 0.003$), respectively. The EORTC 40954 trial, which also closed early because of poor accrual, randomized 144 patients (of a planned 360) to surgery alone *vs* two cycles of pre-operative cisplatin and 5-FU CT. Although this trial allowed the inclusion of Siewert I and II GOJ tumours, 47.2% of patients had primary tumours in the middle and lower third of the stomach. At a median follow up of 4.4 years, despite an improvement in RO resection rate from 66.7% to 81.9%, there was no difference in overall survival between the two arms^[54].

The reasons for the negative result in the EORTC trial are not clear. Possible explanations include poor accrual, higher reported rates of postoperative complications and lower proportion of patients completing the full protocol of pre-operative CT. In addition, the trial has also highlighted some of the difficulties with accurate pre-operative staging, where 50% of patients in the surgery alone arm had pT1-2 tumours, despite inclusion criteria requiring endoscopic ultrasound (EUS) stage T3-4 tumours only, suggesting a degree of over-staging with EUS.

Postoperative chemoradiotherapy

An important question, particularly for Asian surgeons, is the relative and incremental benefit of postoperative radiation above and beyond that of CT, in the context of extended lymphadenectomy.

There have been at least six recent trials examining the addition of postoperative CRT to CT, five of which have been conducted in Asian patients. These are outlined in Table 4, with the ARTIST trial from South Korea being the largest^[37-42]. This Phase III RCT randomized 458 patients following D2 gastrectomy to adjuvant CT alone with six cycles of capecitabine and cisplatin (XP) *vs* adjuvant CRT comprising 2 cycles of XP, then 45Gy CRT with Capecitabine, followed by two further cycles of XP. At a median follow up of 53 mo, the primary endpoint was not met, with no difference in 3-year DFS. However, an unplanned subgroup analysis of node-positive patients (comprising 86% of patients), showed significant improvement in 3-year DFS (77.5% *vs* 72.3%; $P = 0.0365$). It is worth noting that the final analysis of the study was performed earlier than initially planned, as there were fewer events than expected. This was likely related to the fact that almost 60% of patients had early stage disease (*i.e.*, IB/IIA), of which more than 20% had T1 or T2 primaries.

In terms of treatment tolerability, only three of 203 patients that started CRT did not complete radiotherapy, and the majority completed two further protocol cycles of chemotherapy. In contrast to the INT0116 study, where 33% of patients experienced grade 3 or higher GI toxicity, the incidence of grade 3 or higher nausea, vomiting, diarrhoea, stomatitis or constipation was approximately 19%, compared with 19.9% in the chemotherapy only arm. It is also interesting to note the incidence of Grade 2 nausea and vomiting seemed lower in the CRT arm (18.9% and 4.8%) compared with the chemotherapy alone arm (27.9% and 8.4% respectively).

An analysis of failure pattern data from INT0116 showed minimal effect of 5-FU/LV on distant failure,

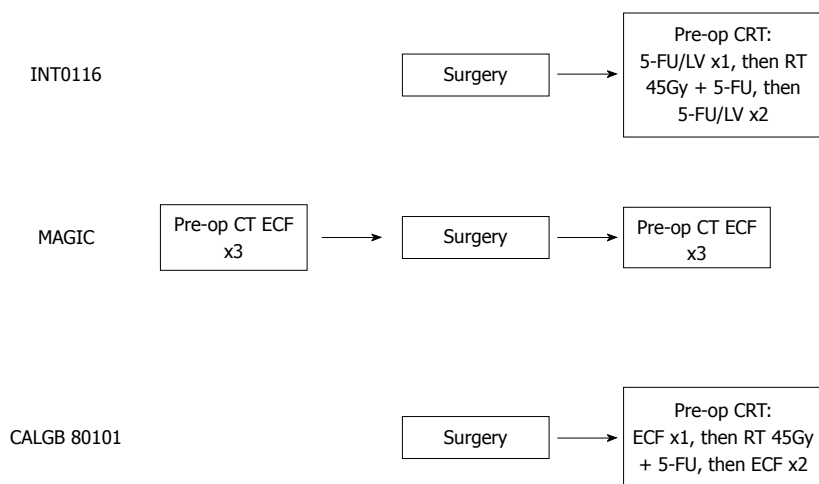


Figure 1 Experimental arms for INT0116, MAGIC and CALGB 80101 study. ECF: Epirubicin, cisplatin, 5-fluoro-uracil; LV: Leucovorin; FU/LV: Fluorouracil/leucovorin; CT: Chemotherapy; CRT: Chemo-radiotherapy.

suggesting that the improvement noted in the study entirely reflected an improvement in local control, with little effect on distant metastases. This strongly suggests that the 5-FU/LV combination delivered in this study produced its effect through radiosensitisation to assist radiation therapy in obtaining local control. With the aim of improving distant disease control, the US Intergroup have recently completed a phase III RCT, which attempted to build on the results from INT0116 by incorporating a potentially more active chemotherapy regimen using ECF^[55]. This study randomised 546 patients to post-operative CRT using the INT0116 regimen with 5-FU/LV *vs* post-operative CRT sandwiched between cycles of ECF (Figure 1). Preliminary results, which have only been reported in abstract form, suggest no difference in survival outcomes, although the toxicity profile favoured the ECF arm.

FUTURE DIRECTIONS/ONGOING TRIALS

A number of ongoing RCT's are examining various neoadjuvant and adjuvant strategies.

In Asian countries, ongoing trials aim to define the optimum postoperative strategy. The SAMIT trial from Japan has recruited 1495 patients and will examine the addition of paclitaxel to fluoropyrimidine adjuvant CT following gastrectomy^[56]. The addition of post-operative CRT to CT is being further evaluated in the ARTIST2 trial from South Korea. This trial aims to build on the first ARTIST trial by limiting eligibility to patients with node-positive tumours only, thus randomizing patients to adjuvant CT *vs* adjuvant CRT. It will incorporate S1 and oxaliplatin CT regimens in a 4-arm design with radiotherapy.

In Western countries, ongoing trials aim to build on the results of perioperative ECF as demonstrated in MAGIC, either by adding novel agents or radiotherapy. The MRC ST03 trial from the United Kingdom is a phase III RCT that will examine the addition of bevacizumab (a humanized monoclonal antibody against vascular endo-

thelial growth factor) to perioperative ECF. The Dutch CRITICS trial is a phase III RCT of preoperative chemotherapy using epirubicin, cisplatin and capecitabine (ECC) followed by surgery and further ECC (*i.e.*, MAGIC), or by surgery and CRT (Figure 2)^[57].

Preoperative radiotherapy

The benefit of using radiotherapy in the pre-operative setting has been conclusively demonstrated in a number of other cancer sites^[58-60]. However, there are concerns when adopting a neoadjuvant approach, including potential delay before definitive resection, the possibility of disease progression, and peri- and post-operative morbidity. There are sound radiobiological and practical reasons to support a neoadjuvant RT approach, including a theoretical reduction in hypoxia and, therefore, radioresistance, potential for tumour down-staging and increased R0 resection rate, improved tolerability, as well as improved target and tumour delineation.

A previous RCT in 370 patients with tumours of the gastric cardia demonstrated a survival benefit for preoperative radiotherapy alone^[61]. There has been increasing interest in incorporating concurrent radio-sensitising CT in this preoperative setting. Although no RCT's have yet been reported, several prospective Phase II studies have reported promising results (Table 5), with > 70% of patients undergoing R0 resections, and complete pathological response rates of up to 30%^[62-64]. An ongoing international RCT (TOPGEAR), is examining the addition of this neo-adjuvant CRT strategy to perioperative CT (Figure 2)^[65].

CONCLUSION

The treatment of locally advanced gastric cancer remains a challenge. Whilst there are promising approaches, incorporating novel targeted agents, as well as neo-adjuvant CRT strategies, current evidence suggests postoperative CRT and perioperative CT remain appropriate standard

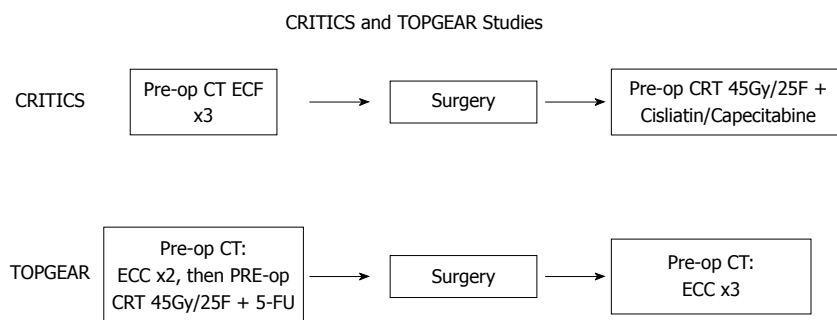


Figure 2 Experimental arms of CRITICS and TOPGEAR trials. ECC: Epirubicin, cisplatin and capecitabine; CRT: Chemo-radiotherapy; FU: Fluorouracil; ECF: Epi-rubicin, cisplatin, 5-FU; LV: Leucovorin; CT: Chemotherapy.

Table 5 Prospective phase 2 trials of preoperative chemo-radiotherapy

Ref.	Year	No. of patients	Induction CT	CRT	Proceeded to surgery	RO resection	pCR
Ajani <i>et al</i> ^[62]	2004	34	x2 FU/Cis/LV	45Gy/FU	85%	70%	30%
Ajani <i>et al</i> ^[63]	2005	41	x2 FU/Cis/Paclitaxel	45Gy/FU/Paclitaxel	98%	78%	20%
Ajani <i>et al</i> ^[64]	2006	49	x2 FU/Cis/LV	45Gy/FU/Paclitaxel	83%	77%	26%

pCR: Pathological complete response; Cis: Cisplatin; CRT: Chemo-radiotherapy; FU: Fluorouracil; CT: Chemotherapy; LV: Leucovorin.

adjuvant treatments in the Western world. Large randomized trials have also established adjuvant CT alone, either with S-1 or Capecitabine/Oxaliplatin, as standards of care in Asian countries, where patients routinely undergo D2 gastrectomy.

The role of postoperative CRT continues to be debated, especially in the setting of D2 gastrectomy. However, based on the current evidence, post-operative chemo-radiotherapy should be considered in high-risk gastric cancer patients who undergo less than a D2 dissection. The ongoing ARTIST II (in the Asian population) and CRITICS (in the Western population) trials will help to clarify the role of postoperative CRT in these settings.

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