Review Article

The treatment of resectable gastric cancer: a literature review of an evolving landscape

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Background and Objective: Gastric cancer carries a poor prognosis despite advances in treatment. Despite curative-intent surgery, the risk of recurrence is high. Perioperative treatment may improve rates of complete surgical resection and reduce the rate of recurrence. Treatment practices vary worldwide, while perioperative treatment is considered standard-of-care practice in Western countries, upfront surgery followed by adjuvant therapy is preferred in Asian countries. The current literature is complex to navigate with a plethora of studies available for review. The aim of this review is to summarise current evidence regarding the role of perioperative treatment in resectable gastric cancer and to explore future directions in research.

Methods: We searched the PubMed database for peer-reviewed original articles from phase III trials, published between 2002 to 2021 with regard to the treatment of resectable gastric cancer. Current active clinical trials regarding the use of targeted therapy and immune checkpoint inhibitors in perioperative and adjuvant therapy were identified using the ClinicalTrials.gov database from the US National Library of Medicine.

Key Content and Findings: Compared to surgery alone, the use of perioperative chemotherapy prior to resection of gastric cancer and the use of adjuvant chemotherapy after upfront surgery both improve survival in those with resectable gastric cancer. However, treatment practices vary worldwide. In clinical practice, patient factors such as functional status should be considered when considering treatment approach. Many current clinical trials explore the role of targeted therapy and immune checkpoint inhibitors in the perioperative setting, which appear to be promising.

Conclusions: Gastric cancer continues to carry a poor prognosis. The addition of targeted agents and immune checkpoint inhibitors in the perioperative setting appear to be promising although further research is required in this area to assess efficacy. Further clinical research is required to identify new agents and approaches to treatment to improve the survival of these patients.

Keywords: Gastric cancer; resectable; perioperative; neoadjuvant treatment; adjuvant treatment; literature review

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Introduction

Gastric cancer is the fifth most commonly diagnosed cancer worldwide and carries a poor prognosis, with a 5-year survival rate of 30% (1,2). The incidence of gastric cancer varies worldwide and is highest in Eastern Asia (1). Risk factors of gastric cancer include *Helicobacter pylori* infection, obesity, smoking and alcohol consumption (3). Over 90% of gastric cancers are adenocarcinomas, which may arise anatomically proximally from the cardia, adjacent to the

Table 1 The search strategy summary

Items	Specification
Date of Search	3rd November 2021
Databases and other sources searched	PubMed
	ClinicalTrials.gov
Search terms used	Gastric cancer, perioperative, neoadjuvant
	Adjuvant, resectable, targeted therapy
Timeframe	2002 to 2021
Inclusion and exclusion criteria	Inclusion Criteria:
	Peer reviewed original articles
	Phase III clinical trials
	English language only
	Exclusion Criteria:
	Studies published before 2022
	Phase I or II clinical trials
	Other language
Selection process	Conducted by author IT

gastro-oesophageal junction or distally from the non-cardia region in the distal stomach (4). Proximal gastric cancers share some biological and pathological features with distal gastro-oesophageal junction adenocarcinomas (4).

In those with resectable gastric cancer, perioperative treatment may improve survival by downstaging disease and improving rates of complete pathological response. Where upfront surgery has been performed, adjuvant treatment may consist of chemotherapy alone or with concurrent radiotherapy (CRT), which may improve survival by reducing the risk of disease recurrence. However, despite advances in surgical technique and the advent of perioperative therapy, the prognosis of gastric cancer remains poor. This review summarises current evidence, ongoing clinical trials and future research directions to guide the treatment of resectable gastric cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-721/rc).

Methods

The PubMed database was used to search for peer-reviewed original articles that consisted of results from phase III clinical trials, published from 2002 to 2021 with the key words gastric cancer, perioperative, neoadjuvant, adjuvant, resectable and targeted therapy (*Table 1*). The ClinicalTrials.gov database from the US National Library of Medicine was used to search for current active phase II and III clinical trials that recruited patients with resectable gastric cancer and explored the role of targeted therapy or immune checkpoint inhibitors. Phase II and III clinical trials that investigated the efficacy of perioperative chemoradiotherapy versus chemotherapy alone were also included.

Current evidence

The role of perioperative chemotherapy

The use of perioperative chemotherapy in resectable gastric cancer has become standard-of-care practice in many Western countries. It has been demonstrated across multiple clinical trials that perioperative chemotherapy improves survival in non-Asian populations., summarised in *Table 2*.

The phase III trial, MAGIC recruited 503 patients, of which 74% had gastric adenocarcinoma. Patients in the intervention arm received 3 cycles of preoperative epirubicin, cisplatin and fluorouracil (ECF) prior to surgery

Table 2 Summary of key clinical trials investigating the role of perioperative therapy in resectable gastric cancer

Trial name	Phase	Tumour location	Histology	Intervention	Control	DFS/PFS	OS	R0 resection rate
MAGIC, 2006 (5)	III	- Stomach 74% - Lower oesophagus 14% - GOJ 11%	Adenoca only	3x ECF→Surgery→3x ECF Doses: Epirubicin 50 mg/m^2, Cisplatin 60 mg/m^2, Infusional fluorouracil 200 mg/m^2; Every 21 days	Surgery only	HR 0.66, 95% CI: 0.53–0.81, P<0.001	5-year: 36% *vs.* 23%; HR 0.75, 95% CI: 0.60–0.93; P=0.009	Not reported
EORTC 40954, 2010 (6)	III	- Gastric 53% - Oesophageal: Middle third 26%, Lower third 21%	Adenoca only	2x CF→Surgery Doses: Cisplatin 50 mg/m^2, Infusional fluorouracil 2,000 mg/m^2; Every 48 days	Surgery only	HR 0.76, 95% CI: 0.49–1.16, P=0.2	HR 0.84, 95% CI: 0.52–1.35; P=0.466	81.9% *vs.* 66.7%, P=0.036
FNCLCC & FCCD, 2011 (7)	III	- Stomach 25% - Lower oesophagus 11% - GOJ 64%	Adenoca only	2–3x CF→Surgery→3-4x CF Doses: Cisplatin 100 mg/m^2, Infusional fluorouracil 800 mg/m^2; Every 28 days	Surgery only	HR 0.65, 95% CI: 0.48–0.89, P=0.03	5-year: 38% *vs.* 24%; HR 0.69, 95% CI 0.50–0.95, P=0.02	84% *vs.* 74%, P=0.04
FLOT4, 2019 (8)	II/III	- Stomach 44% - GOJ Siewert 1 24% - GOJ Slewart 2/3 32%	Adenoca only	4x FLOT→Surgery→4x FLOT Doses: Docetaxel 50 mg/m^2, Oxaliplatin 85 mg/m^2, Leucovorin 200 mg/m^2, Infusional fluorouracil 2,600 mg/m^2; Every 14 days	3x ECF/ECX→ Surgery→3x ECF/ECX Doses: Epirubicin 50 mg/m^2, Cisplatin 60 mg/m^2, Infusional fluorouracil 200 mg/m^2 or Capecitabine 1,250 mg/m^2; Every 21 days	HR 0.75, 95% CI: 0.62–0.91, P=0.0036	5-year: 45% *vs.* 36%; HR 0.77, 95% CI: 0.63–0.94, P=0.012	85% *vs.* 78%, P=0.0162
PRODIGY, 2021 (9)	III	- Gastric 94% - GOJ 6%	Adenoca only	3x DOS→Surgery→8x S-1 Doses: Docetaxel 50 mg/m^2, Oxaliplatin 100 mg/m^2, S-1 40 mg/m^2, Every 21 days S-1 40–60 mg BD, D1-28 every 6 weeks	Surgery→S–1	HR 0.7, 95% CI: 0.52–0.95, P=0.0227	HR 0.8, 95% CI: 0.60–1.19, P=0.3383	95% *vs.* 84%, P<0.0001

Table 2 (*continued*)

Table 2 (*continued*)

Trial name	Phase	Tumour location	Histology	Intervention	Control	DFS/PFS	OS	R0 resection rate
RESOLVE, 2021 (10)	III	- Gastric 64% - GOJ 36%	Adenoca only	Arm C: 3x SOX→Surgery→5x SOX→3x S-1 Doses: S-1 40–60 mg BD D1–14 & Oxaliplatin 130 mg/m^2, Every 3 weeks	Arm A: Surgery→8x CAPOX Doses: Capecitabine 1,000 mg/m^2 BD D1–14 & Oxaliplatin 130 mg/m^2; Every 3 weeks Arm B: Surgery→ 8x SOX Doses: S-1 40–60 mg BD D1–14, Oxaliplatin 130 mg/m^2 every 3 weeks	Arm C *vs.* A: HR 0.77, 95% CI: 0.61–0.97, P=0.028 Arm B *vs.* A: HR 0.86, 95% CI: 0.68–1.07, P=0.17	Not reported	Arm C *vs.* A: 93% *vs.* 87%, P=0.0075 Arm A *vs.* B: 87% *vs.* 88%

GOJ, gastro-oesophageal junction; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival.

and 3 cycles of postoperative ECF (5). Patients who received perioperative chemotherapy had a significantly greater progression-free survival (HR 0.66; 95% CI: 0.53–0.81, P<0.001) and overall survival (HR 0.75; 95% CI: 0.60–0.93, P=0.009) compared to the control arm, with a 5-year survival rate of 36.3% *vs.* 23% respectively. 86% of patients who were randomised to the intervention arm completed 3 cycles of preoperative chemotherapy and 65.6% completed another 3 cycles of chemotherapy after surgery. The most common cause of treatment discontinuation was disease progression. Common chemotherapy-related toxicities included neutropenia, thrombocytopenia, anaemia, nausea and vomiting, which were manageable during the trial. The extent of resection achieved was determined by the surgeon's perception of whether a curative resection has occurred rather than measured by an objective outcome. Nonetheless, a curative resection was thought to be achieved in 69.3% and 66.4% of patients in the intervention and control arms respectively. This study was practice-changing in supporting the use of perioperative chemotherapy in resectable gastric cancer rather than surgery alone.

The phase III trial, EORTC 40954 aimed to evaluate the benefit of neoadjuvant chemotherapy alone but without planned postoperative chemotherapy in resectable gastric cancer (6). However, this trial was ceased early due to poor recruitment. Those in the intervention arm received 2 cycles of preoperative chemotherapy with cisplatin and fluorouracil. Although the R0 resection rate was significantly higher in the intervention arm (81.9% *vs.* 66.7%, P=0.036) compared to the control arm, there was no progression-free or overall survival benefit observed in the intervention arm. Findings from this trial were limited by limited statistical power due to small sample size.

The FNCLCC and FCCD multicentre phase III trial recruited 224 patients, of which 25% had gastric adenocarcinoma (7). Patients who received 2 to 3 cycles of preoperative cisplatin and fluorouracil had a significantly higher disease-free survival (HR 0.65, 95% CI: 0.48–0.89, P=0.03) and overall survival (HR 0.69, 95% CI: 0.50–0.95, P=0.02) with 5-year survival rates of 38% *vs.* 24% respectively (7). R0 resection rates were significantly higher in the intervention arm compared to the surgery alone arm (84% *vs.* 74%, P=0.04). Despite 38% of patients experienced grade 3 or higher toxicity including neutropenia, nausea and thrombocytopenia, 87% completed at least 2 cycles of preoperative chemotherapy and 50% of patients who received preoperative chemotherapy proceeded to have

post-operative chemotherapy.

More recently, findings from the phase II/III trial, FLOT4 established a new standard-of-care perioperative treatment regimen in resectable gastric cancer (8). This trial recruited 716 patients, of which 44% had gastric adenocarcinoma. Patients in the intervention arm received 4 cycles of preoperative chemotherapy with docetaxel, oxaliplatin, leucovorin and infusional fluorouracil (FLOT), followed by 4 cycles of postoperative FLOT, whereas those in the control arm received perioperative ECF or ECX. Overall, 90% of patients in both arms completed preoperative chemotherapy. However, only 60% and 52% of patients completed postoperative FLOT and ECF/ECX respectively. Both groups proceeded to surgery at similar rates but patients in the FLOT group had a significantly higher rate of completion of tumour surgery compared to the control arm (94% *vs.* 87%, P=0.001). The R0 resection rate was significantly higher in the FLOT group (85% *vs.* 78%, P=0.0162) compared to the control arm. Further, disease-free survival (HR 0.75, 95% CI: 0.62–0.91, P=0.0036) and overall survival (HR 0.77, 95% CI: 0.63–0.94, P=0.012) were both significantly higher in the FLOT group, compared to the ECF/ECX group, with 5-year survival rates of 45% *vs.* 36% (P=0.012) respectively. Rates of dose delay and hospitalisation were similar between the two groups. FLOT and ECF/ECX had different toxicity profiles, grade 3 or above nausea, thromboembolism and anaemia were more commonly reported in the ECF/ECX group whereas infection, neutropenia, diarrhoea and neuropathy were more common in the FLOT group. Findings from this trial resulted in the establishment of FLOT as the new standard-of-care perioperative chemotherapy regimen used in resectable gastric adenocarcinoma.

Treatment practices in resectable gastric cancer vary worldwide. Despite the use of perioperative chemotherapy is the accepted standard-of-care treatment in Europe and Australia, this practice is much less common in Asia. Moreover, the availability of chemotherapy agents varies worldwide. S-1 is a combination oral fluoropyrimidine drug, which is non-inferior to infusional fluorouracil in efficacy and has less gastrointestinal toxicity, hence this drug is widely used in Asia (11). The phase III trial, PRODIGY randomised 530 Korean patients, of which over 90% had gastric adenocarcinoma (9). Patients in the intervention arm received neoadjuvant chemotherapy with 3 cycles of docetaxel, oxaliplatin and S1 (DOS) prior surgery, followed by adjuvant S-1 after surgery, while those in the control arm received upfront surgery followed by adjuvant S-1. 90% of patients in the intervention arm completed all cycles of chemotherapy. The most common grade 3 and above chemotherapy-related toxicities included neutropenia, febrile neutropenia and diarrhoea. The rate of R0 resection was significantly higher in the intervention arm compared to the control arm (95% *vs.* 84%, P<0.0001). Further, there was a significantly higher rate of complete pathological response in the intervention arm of 10.4% compared to the control arm (P<0.0001). Over 83% of patients in both groups completed all cycles of adjuvant S-1 treatment. Neoadjuvant chemotherapy with DOS in the intervention arm significantly prolonged progression-free survival (HR 0.7, 95% CI: 0.52–0.95, P=0.0227), however there was no overall survival benefit observed but this study was not statistically powered to detect a significant overall survival difference. The rate of completion of adjuvant chemotherapy was much higher in this trial compared to the FLOT4 trial, this may be due to the use of single agent S-1, which is more well tolerated compared to the FLOT regimen. Moreover, the dose of docetaxel used in the PRODIGY trial is lower than that in the FLOT4 trial, which tends to cause more myelosuppression in Asian patients due to genetic predisposition.

The role of upfront surgery followed by adjuvant chemotherapy

In Asia, upfront surgery followed by adjuvant chemotherapy is considered the standard-of-care treatment of resectable gastric cancer, as multiple clinical trials have demonstrated improvement in survival using this approach in an Asian population (*Table 3*). However, these outcomes were not found in trials that recruited non-Asian patients, which may be explained by biological differences in the populations and variable rates of D2 lymphadenectomy across these trials. The efficacy of adjuvant treatment may be difficult to ascertain because traditionally overall survival (OS) is considered to be the only gold standard endpoint used to confirm the benefit of adjuvant chemotherapy after surgery in gastric cancer. However, OS is an endpoint that requires extended follow up over years. Currently, there is meta-analysis data to support the use of DFS as a surrogate endpoint for OS given most relapses in gastric cancer occurs within 3 years after surgery (19).

The phase III trial, ACTS-GC recruited 1,059 Japanese patients with resected gastric cancer, who received a R0 resection, of which over 93% received a D2

Table 3 Summary of key clinical trials investigating the role of upfront surgery followed by adjuvant therapy in resectable gastric cancer

Trial name	Phase	Intervention	Control	DFS/PFS	OS	R0 resection rate
INT-0116, 2001 (12)	III	Surgery→CRT (4,500 cGy RT with Fluorouracil 425 mg/m^{2}over 5 weeks	Surgery→None	30 *vs.* 19 mo; HR 1.52, 95% CI: 1.23–1.86; P<0.001	36 *vs.* 27 mo; HR 1.35, 95% CI: 1.09–1.66; P=0.005	Not reported
ACTS-GC, 2007 (13,14)	III	Surgery→S-1 40 mg/m^2, 6-weekly cycle of 4 weeks on, 2 weeks off for 1 year	R0 Surgery→None	5-year: 65.4% *vs.* 53.1%	5-year: 71.7% *vs.* 61.1%	100%
ARTIST, 2011 (15)	III	Surgery→2x XP→XRT (45 Gy RT with capecitabine 1,650 mg/m^2 for 5 weeks)→2x XP	Surgery→6x XP Doses: Capecitabine 2,000 mg/m^2 D1–14, Cisplatin 60 mg/m^2; Every 3 weeks	3-year: 78.2% *vs.* 74.2%, P=0.0862	Not reported	100%
CLASSIC, 2012 (16,17)	III	Surgery→8x CAPOX Doses: Capecitabine 1,000 mg/m^2 BD D1-14, Oxaliplatin 130 mg/m^2; Three weekly	R0 Surgery→None	5-year: 68% *vs.* 53%; HR 0.58, 95% CI: 0.47–0.72; P<0.0001	5-year: 78% *vs.* 69%; HR 0.66, 95% CI: 0.51–0.85; P=0.0015	100%
ARTIST II, 2020 (18)	III	Arm C: Surgery→CRT (45 Gy RT + SOX)	Surgery→Arm A: S-1 40-60 mg daily, 4 weeks on, 1 week off every 6 weeks for 1 year or Arm B: SOX for 6 months (S1 2 weeks on/ 1 week off) + oxaliplatin 130 mg/m^2)	3-year: SOXRT *vs.* SOX *vs.* S1; 72.8% *vs.* 74.3% *vs.* 64.8%	Not reported	100%

DFS, disease-free survival; PFS, progression-free survival; OS, overall survival.

lymphadenectomy (13). Patients who received 1 year of adjuvant S-1 had a significantly longer relapse-free survival (72.2% *vs.* 59.6%; HR 0.62, 95% CI: 0.50–0.77; P<0.001) and 3-year overall survival rate compared to those who did not receive any adjuvant treatment (80.1% *vs.* 70.1%; HR 0.68, 95% CI: 0.52–0.87; P=0.004). The survival benefit secondary to adjuvant therapy persisted upon 5 years of follow up (14); 65.8% of patients in the intervention arm completed 1 year of adjuvant treatment as planned. The most common reason for treatment discontinuation is treatment-related toxicity. The incidence of grade 3 or higher adverse events such as nausea, anorexia, diarrhoea and leucopenia were higher in the intervention arm. Findings from this study support the use of adjuvant chemotherapy in resected gastric cancer.

Similarly, the phase III trial, CLASSIC recruited 1,035 Asian patients with resected gastric cancer, who all received D2 lymphadenectomy, with R0 resection (16,17). Patients who received adjuvant chemotherapy with 8 cycles of capecitabine and oxaliplatin (CAPOX) had a significantly prolonged disease-free survival (68% *vs.* 53%; HR 0.58, 95% CI: 0.47–0.72, P<0.0001) and overall survival (78% *vs.* 59%; HR 0.66, 95% CI: 0.51–0.85, P=0.0015) at 5 years of follow up. 67% of patients in the intervention arm received all cycles of chemotherapy as planned. The most common grade 3 or above adverse effects in the intervention arm included neutropenia, thrombocytopenia, nausea and vomiting. Peripheral neuropathy was reported in over 50% of patients who received chemotherapy. Findings from both the ACTS-GC and CLASSIC trials support the use of adjuvant chemotherapy in resected gastric cancer. However, favourable outcomes observed for this study population may also be partially attributed to high rates of D2 lymphadenectomy and all patients received a R0 resection.

More recently, the phase III trial, RESOLVE investigated the role of perioperative chemotherapy versus upfront surgery followed by adjuvant chemotherapy in a Chinese population (10). 1,000 Chinese patients were recruited, of which over 60% had gastric adenocarcinoma. Patients in the intervention arm received 3 cycles of preoperative S1 and

oxaliplatin (SOX) and post-operative treatment including 5 cycles of SOX, followed by 3 cycles of S-1 alone. The other two arms received upfront surgery with either adjuvant CAPOX or adjuvant SOX. The rate of R0 resection was significantly higher in patients who received perioperative SOX compared to those who received upfront surgery followed by adjuvant CAPOX (93% *vs.* 87%, P=0.0075). Three-year disease-free survival was significantly higher in the intervention arm compared to the adjuvant CAPOX only arm (59.4% *vs.* 51.1%, HR 0.77, 95% CI: 0.61–0.97, P=0.028). There was no difference in R0 resection rate or disease-free survival between the adjuvant CAPOX and adjuvant SOX arms. Haematological toxicity was common across all arms but the incidence of grade 3 or above thrombocytopenia and anaemia was significantly higher in the intervention arm (P=0.013). Although perioperative SOX appears to offer promising disease-free survival, overall survival data remains immature.

The role of upfront surgery followed by adjuvant chemoradiotherapy (CRT)

The use of adjuvant CRT in resected gastric cancer became widely adopted in the United States (US) in the 2000s as a result of findings from the phase III trial, INT-0116 (12). This trial recruited 275 patients from the US with resected gastric adenocarcinoma. Patients who received adjuvant chemoradiotherapy with fluorouracil had significantly longer relapse-free survival and overall survival compared to those who did not. However, only 10% of patients in this trial received a D2 lymphadenectomy.

Findings from the phase III trial, ARTIST prompted re-evaluation of the role of adjuvant CRT in resected gastric cancer (15). 458 Korean patients were included in this study and all received D2 lymphadenectomy with R0 resection. Patients in the intervention arm received adjuvant treatment with 2 cycles of capecitabine and cisplatin (XP) followed by CRT with capecitabine and another 2 cycles of XP whereas those in the control arm only received 6 cycles of XP. There was no significant difference in 3-year disease-free survival (DFS) between the two arms. However, 3-year DFS was significantly prolonged in the intervention arm in the subgroup of patients with node-positive disease (77.5 *vs.* 72.3%, HR 0.69, 95% CI: 0.474–0.995, P=0.0365).

More recently, the phase III trial, ARTIST-II investigated the role of adjuvant chemotherapy versus adjuvant CRT (18). 546 Korean patients who underwent D2 lymphadenectomy with R0 resection were recruited. Patients were randomised to receive either adjuvant S-1, adjuvant SOX or CRT with SOX. The addition of radiotherapy to SOX did not improve DFS (72.8% *vs.* 74.3%; HR 0.97, 95% CI: 0.66–1.42, P=0.879). However, patients who received adjuvant SOX had significantly longer DFS compared to those who received S-1 only (64.8% *vs.* 74.3%; HR 0.69, 95% CI: 0.41–0.99, P=0.042) but this study was not designed to compare the efficacy between S-1 and SOX. Nonetheless, findings from this trial does not support the use of adjuvant CRT in resected gastric cancer, in which D2 lymphadenectomy and R0 resection have already been achieved.

The approach to selecting treatment for resectable gastric cancer

Although the treatment of resectable gastric cancer varies worldwide, as Western countries such as Europe, Australia and the United States favour perioperative therapy whereas Asian countries such as Japan and Korea favour upfront surgery followed by adjuvant therapy. Both approaches prolong survival compared to surgery alone, as demonstrated across multiple clinical trials. One additional advantage that may favour perioperative therapy is the downstaging of tumour to increase the rate of complete surgical resection and allows for assessment of tumour biology, when assessing pathological and treatment response on histopathology post-operatively. Moreover, patients tend to be fitter prior to surgery and are more likely to complete pre-operative chemotherapy, whereas completion rates of adjuvant treatment post-operatively tend to be lower. Further, extent of surgery is an important factor to consider. Whereas all patients in CLASSIC received D2 lymphadenectomy and R0 resection prior to adjuvant chemotherapy, only 57% of patients who received FLOT in the FLOT4 trial received a D2 lymphadenectomy and 85% received R0 resection. Moreover, there are likely intrinsic biological differences between Asian and non-Asian patients with gastric cancer, that may not be captured across clinical trials. Currently, the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines both recommend perioperative chemotherapy with doublet or triplet chemotherapy with a fluoropyrimidine in the treatment of resectable Stage IB to III gastric cancer (20,21). Perioperative CRT is not recommended for the treatment of gastric cancer. For patients who had upfront surgical resection without any perioperative

Table 4 Current clinical trials comparing the role of perioperative chemotherapy versus CRT in resectable gastric and gastro-oesophageal cancer

Trial	Phase	Tumour location	Histology	Arm A	Arm B	Primary endpoint	Secondary endpoints	Status
TOPGEAR (24,25), (NCT01924819)	II/III	Stomach GOJ	Adenoca only	3x ECF/ECX→Surgery→3x ECF/ECX Doses: Epirubicin 50 mg/m^2 & Cisplatin 60 mg/m^2 & Infusional flurouracil 200 mg/m^2 or Capecitabine 625 mg/m^2 D1–14 Over 21 days	2x ECF/ECX→CRT→ Surgery→3x ECF/ECX Doses: CRT: Infusional fluorouracil 200 mg/m^2 or capecitabine 825 mg/m^2 with RT 45 Gy	OS	- PFS - Pathological response rate - Toxicity	Active, completed recruitment
CRITICS II (26), (NCT02931890)	II	Gastric GOJ	Adenoca only	Arm A: 4x DOC→Surgery Arm B: 2x DOC→CROSS→Surgery Doses: DOC: Docetaxel 50 mg/m^2 Oxaliplatin 100 mg/m^2 Capecitabine 850 mg/m^2 BD, every 21 days	Arm C: CROSS→Surgery Doses: CROSS: Carboplatin AUC2 & Paclitaxel 50 mg/m^2 & RT (45 Gy)	EFS	- Time to event - Time to recurrence - Toxicity	Recruiting

GOJ, gastro-oesophageal junction; CRT, chemoradiotherapy; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; EFS, event-free survival.

therapy, adjuvant chemotherapy or chemoradiotherapy is recommended post-operatively. In contrast, the Japanese Gastric Cancer Association and Korean Gastric Cancer Association guidelines both recommend upfront surgical resection followed by adjuvant chemotherapy consisting of a fluoropyrimidine and platinum agents (22,23). In clinical practice, treatment approach should be discussed in a multidisciplinary setting and patient factors such as functional status and co-morbidities should be considered.

Future directions

The role of perioperative chemoradiotherapy (CRT)

Although perioperative CRT is currently not recommended for the treatment of resectable gastric cancer, it is hypothesised that the addition of radiotherapy to perioperative chemotherapy may further improve tumour downstaging and rates of R0 resection. As summarised in *Table 4*, TOPGEAR is the first phase III trial (NCT01924819) to evaluate the role of perioperative chemoradiotherapy in the treatment of resectable gastric cancer (24,25). Patients in the intervention arm received 2 cycles of preoperative ECX or ECF followed by CRT with infusional fluorouracil or capecitabine, compared to those in the control arm, who only received perioperative ECX or ECF. Survival data is not available yet but preliminary results from this trial demonstrated high rates of treatment completion as 93% and 98% of patients completed preoperative treatment in the control and intervention arms respectively. The incidence of postoperative complications and chemotherapy-related toxicities including haematological and gastrointestinal side effects were similar across both groups.

The phase III trial, CRITICS investigated the role of post-operative CRT in patients with resected gastric cancer who completed perioperative treatment (27). All patients received perioperative chemotherapy with epirubicin, capecitabine and cisplatin or oxaliplatin. Only 6% of patients received D2 lymphadenectomy and 80% achieved R0 resection. Those in the intervention arm received 5 weeks of adjuvant CRT with cisplatin and capecitabine whereas those in the control arm received postoperative chemotherapy only. The addition of radiotherapy to post-operative chemotherapy did not improve overall survival. However, there was a high patient dropout rate after surgery in this study as less than 50% of patients completed the planned post-operative treatment. Hence, it was hypothesised that CRT may be more well-tolerated and

Table 5 Summary of clinical trials investigating the role of HER2-targeted therapy in HER2-positive resectable gastric cancer

Trial name	Phase	Tumour location	Histology	Intervention	Control	DFS/PFS	OS	R0 resection rate
PETRARCA, 2021 (30)	II	Gastric GOJ	Adenoca only	4x FLOT + T + P→Surgery→4x FLOT + T + P→9x T+P	4x FLOT→Surgery→ 4x FLOT	26 months *vs.* NR; HR 0.58, P=0.14	2-year: 84% *vs.* 77%	93% *vs.* 90%
NEOHX, 2021 (31)	II	Gastric GOJ	Adenoca only	3x XELOX-T→Surgery→3x XELOX-T→12x T	NA	18-month: 71%	5-year: 58%	90%

GOJ, gastro-oesophageal junction; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; T = trastuzumab 8/6 mg/kg; P = pertuzumab 840 mg; CROSS = Carboplatin AUC2 + paclitaxel 50 mg/m^2 + RT 23Gy x 1.8; FLOT = Docetaxel 50 mg/m^2 + Oxaliplatin 85 mg/m^2 + Leucovorin 200 mg/m^2 + Infusional fluorouracil 2,600 mg/m^2; XELOX = Capecitabine 1,000 mg/m^2 BD D1–14 + Oxaliplatin 130 mg/m^2.

more beneficial in the neoadjuvant setting. This gave rise to CRITICS II, a phase II trial (NCT02931890), which is currently recruiting patients and aims to assess the role of neoadjuvant CRT in the treatment of resectable gastric cancer (26). Patients are randomised into three arms to either receive neoadjuvant chemotherapy with DOC alone or neoadjuvant CRT with the CROSS regimen alone or both neoadjuvant DOC and CRT with CROSS. The primary end point of this trial is event-free survival.

The role of targeted agents in perioperative therapy

Cytotoxic chemotherapy is the main form of systemic treatment used in perioperative therapy of resectable gastric cancer. However, the role of targeted agents in perioperative treatment is currently being investigated.

HER2-targeted therapy

Up to 30% of gastric and gastro-oesophageal adenocarcinomas express HER2 amplification, but the prognostic role of HER2 is controversial due to the heterogeneity of overexpression in HER2-positive gastric cancer (28). The addition of HER2-targeted treatment trastuzumab to chemotherapy improves overall survival in those with advanced HER2-positive gastric cancer (29). However, the role of HER2-targeted therapy in resectable disease remains unclear as there is a lack of randomised data to guide the treatment of resectable HER2-positive gastric cancer. Clinical trials that assess the role HER2-targeted therapy in resectable gastric cancer are summarised in *Table 5*.

The phase II trial, PETRARCA assessed the efficacy of adding HER2-targeted therapy trastuzumab and pertuzumab to perioperative FLOT chemotherapy in resectable gastric cancer (30). Complete pathological response rates were significantly higher in those who received HER2-targeted therapy in the perioperative setting (35% *vs.* 12%, P=0.02) but the rates of R0 resection were similar across both groups. Peri-operative HER2-targeted therapy did not improve disease-free survival or overall survival. Investigators did not proceed with a phase III trial on review of these findings.

The phase II trial, NEOHX included 45 patients in a single arm, who received 3 preoperative and 3 postoperative cycles of XELOX-T consisting of capecitabine, oxaliplatin and trastuzumab followed by 12 cycles of maintenance trastuzumab (31). The R0 resection rate was 90% and complete pathological response was 9.6%. Common toxicities included diarrhoea, nausea and vomiting. The median 5-year overall survival was 58%. Results from this trial appear promising, but the role of trastuzumab in perioperative treatment requires further investigation in a randomised phase III setting.

The randomised phase II trial, INNOVATION (NCT02205047), is currently recruiting patients with resectable HER2-positive gastric cancer (32). Patients are randomised into 3 arms to either receive perioperative chemotherapy alone, chemotherapy with trastuzumab or chemotherapy with trastuzumab and pertuzumab. Chemotherapy regimens that could be given include CAPOX, FOLFOX, FLOT, cisplatin and platinum with a fluoropyrimidine. The primary endpoint is major pathological response rate, defined as less than 10% of vital residual tumour cells. Secondary endpoints include R0 resection rate, complete pathological response rate, progression-free and overall survival.

Anti-VEGF targeted therapy

Vascular endothelial growth factors (VEGF) play an

important role in angiogenesis to promote tumour proliferation in gastric cancer (33). Hence, anti-VEGF agents were thought to be crucial in the treatment of these cancers. The ST03 phase II/III trial randomised patients with resectable gastric and gastro-oesophageal junction cancers to receive either perioperative chemotherapy with epirubicin, cisplatin and capecitabine or perioperative chemotherapy together with the anti-VEGF monoclonal antibody, bevacizumab (34). However, the addition of bevacizumab to perioperative chemotherapy did not improve overall survival. Moreover, patients who received bevacizumab had higher rates of post-operative anastomotic leak, which resulted in the study being terminated early.

Ramucirumab is a monoclonal antibody that targets the anti-VEGF2 receptor and is efficacious in the second-line treatment of advanced gastric cancer (35). However, the role of ramucirumab in resectable disease is unclear. RAMSES is a phase II/ III clinical trial (NCT02661971) that is investigating the role of ramucirumab in addition to perioperative chemotherapy with FLOT in resectable gastric cancer (36). Patients in the intervention arm received post-operative treatment with 4 cycles of FLOT and 4 cycles of ramucirumab, followed by 16 cycles of ramucirumab alone. Preliminary results show that the R0 resection rate is significantly higher in the intervention arm (97% *vs.* 83%, P=0.0049) compared to the control arm. However, survival data is not available yet.

Immune checkpoint inhibitor therapy

PD-1 is expressed on activated T cells and when bound to PD-L1 and PDL-2 expressed on tumour cells, T cell anergy and suppression of anti-tumour immune response occurs (37). PD-L1 is often overexpressed in gastric cancers (38). Immune checkpoint inhibitors such as pembrolizumab and nivolumab are monoclonal antibodies that block the interaction between PD-1 and PDL-1, thereby improving anti-tumour response (37). Treatment with immune checkpoint inhibitor in conjunction with chemotherapy improves survival in patients with advanced gastric cancer (39). However, the role of immune checkpoint inhibitor combined with chemotherapy in perioperative treatment of resectable gastric cancer remains unclear and is currently being investigated in various phase II and III trials (*Table 6*).

The phase II trial, DANTE investigated the role of atezolizumab in perioperative treatment of gastric cancer. Patients in the intervention arm received perioperative FLOT and atezolizumab (40). This trial has completed recruitment recently and preliminary results from data analysis of 40 patients showed that the addition of atezolizumab to perioperative chemotherapy is a feasible treatment regimen that is safe to deliver. Final results are pending. Similarly, the phase III trial, KEYNOTE-585 aims to assess the role of adding pembrolizumab to perioperative chemotherapy (41). Patients in the intervention arm will receive perioperative pembrolizumab in conjunction with chemotherapy with FLOT or cisplatin with a fluoropyrimidine. This trial is aiming to recruit 800 patients. The primary endpoints include overall survival, event-free survival and complete pathological response rate. Similarly, the phase III trial, MATTERHORN is aiming to recruit 900 patients with resectable gastric cancer (42). Patients in the intervention arm will receive durvalumab in addition to perioperative chemotherapy with FLOT. The primary endpoint is event-free survival.

Lymphocyte Activation Gene-3 (LAG-3) is often co-expressed with PD-1 and contributes to T cell anergy and suppression of anti-tumour response (37). The inhibition of both LAG-3 and PD-1 appear to contribute to anti-tumour response in *in vivo* studies (43). The phase II trial, IMAGINE (NCT04062656) aims to investigate the role of nivolumab and the anti-LAG3 monoclonal antibody, relatlimab, in perioperative treatment of resectable gastric cancer. Patients in the intervention arm will receive 2 cycles of nivolumab and relatlimab whereas those in the control arm will receive nivolumab alone. If no tumour response occurs after 2 cycles of treatment, 4 cycles of FLOT chemotherapy is added to perioperative treatment. The primary endpoint is complete pathological response rate.

The phase III trial, ATTRACTION-5 (NCT03006705) aims to investigate the role of adjuvant immune checkpoint inhibitor, nivolumab in patients with resected gastric cancer, who received D2 lymphadenectomy. Patients in the control arm will receive either 1 year of adjuvant S-1 or 6 months of adjuvant CAPOX. Those in the intervention arm will also receive adjuvant nivolumab in addition to chemotherapy. The primary end-point is relapse-free survival.

Conclusions

The advent of perioperative and adjuvant chemotherapy has improved the prognosis of patients with resectable gastric cancer. Nonetheless, treatment practices vary worldwide and the optimal treatment strategy remains unclear. The addition of targeted therapy and immune checkpoint inhibitor to chemotherapy in the perioperative and adjuvant

Table 6 Current clinical trials investigating the role of immune checkpoint inhibitor in the treatment of resectable gastric cancer

Trial	Phase	Tumour location	Histology	Intervention	Control	Primary endpoint	Secondary endpoints	Status
KEYNOTE 585 (NCT03221426)	III	- Gastric - GOJ	Adenoca only	3x CP or FP or FLOT & Pembrolizumab→Surgery→3x CP or FP or FLOT & Pembrolizumab→11x pembrolizumab	3x CP or FP or FLOT→Surgery→ 3x CP or FP or FLOT	OS, EFS, pCR	Toxicity, DFS	Recruiting
MATTERHORN (NCT04592913)	III	- Gastric - GOJ	Adenoca only	2x FLOT + durvalumab→Surgery→2x FLOT + durvalumab→10x durvalumab	2x FLOT→Surgery→2x FLOT	EFS	OS, pCR	Recruiting
DANTE (NCT03421288)	II	- Gastric - GOJ	Adenoca only	4x FLOT + atezolizumab→Surgery→4x FLOT+ atezolizumab→8x atezolizumab	4x FLOT→Surgery→4x FLOT	DFS, PFS	pCR, R0 resection, OS, Immune cell infiltration rate	Active, not recruiting
MONEO (NCT03979131)	II	- Gastric - GOJ	Adenoca only	4x FLOT + avelumab→Surgery→4x FLOT + avelumab→Avelumab for 1 year	NA	pCR	OS, DFS, PFS, R0 resection	Recruiting
ICONIC (NCT03399071)	II	- Gastric - GOJ - Oesophageal	Adenoca only	4x FLOT + avelumab→Surgery→4x FLOT + avelumab→Avelumab for 1 year	NA	pCR	Toxicity, Radiological response rate, PFS, OS	Recruiting
PANDA (NCT03448835)	II	- Gastric - GOJ	Adenoca only	1x atezolizumab→4x capectabine + oxaliplatin + docetaxel→Surgery	NA	Toxicity	Pathological tumour regression grade	Recruiting
IMAGINE (NCT04062656)	II	- Gastric - GOJ	Adenoca only	2x nivolumab + relatlimab→If responding: 4x nivolumab + relatliimab →Surgery→Nivolumab for 1 year If not responding after 2x nivolumab + relatlimab: 4x nivolumab + FLOT→Surgery→4x nivolumab + FLOT→Nivolumab for 1 year	2x nivolumab→If responding: 4x nivolumab→Surgery→Nivolumab for 1 year If not responding after 2x nivolumab: 4x nivolumab + FLOT→Surgery→4x nivolumab + FLOT→Nivolumab for 1 year	pCR	R0 resection, DFS, OS, Toxicity, Perioperative mortality	Recruiting
ATTRACTION-5 (NCT03006705)	III	Gastric	Adenoca only	Surgery→S-1 for 1 year or CAPOX for 6 months + Nivolumab for 1 year	Surgery→S-1 for 1 year or CAPOX for 6 months + Placebo	RFS	OS, Safety	Recruiting

GOJ, gastro-oesophageal; EFS, event-free survival; PFS, progression-free survival; RFS, relapse-free survival; OS, overall survival; pCR, complete pathological response; DFS, disease-free survival.

setting appears to be a promising approach. Nonetheless, more advances must be made to overcome the challenges of high disease recurrence rates and poor long-term survival in patients with resectable gastric cancer.

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Footnote

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