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# Multimodality treatment of potentially curative gastric cancer: Geographical variations and future prospects

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## Abstract

After much controversy, multimodality therapy is now accepted worldwide as the gold standard for treatment of resectable bulky localized gastric cancer. There is significant regional variation in the style of multimodality treatment with adjuvant chemoradiation the North American standard, neoadjuvant chemotherapy preferred in Europe and Australasia, whilst adjuvant chemotherapy is preferred in Asia. With further standardization of surgery and D1+/D2 resections increasingly accepted world wide, and in particular in the West, as the surgical standard of care for potentially curable disease, it is timely to reassess the multimodality regimes being used. The challenge in the use of multimodality therapy is how current outcomes can be standardized and improved further. Recent studies indicate that mere intensification of the regime in time, dosage or addition of further agents does not improve localized gastric cancer outcomes. More novel strategies including early commencement of adjuvant therapies, intra-peritoneal chemotherapy or assessing neoadjuvant response with positron emission tomography scanning may give improvements in outcomes. The introduction of targeted

therapies means that the adjuvant use of biological agents needs to be explored. By proper assessment of the patient's co-morbidities, full tumour staging, and a better understanding of the tumour's molecular pathology, multimodality therapy for gastric adenocarcinoma may be individualized to optimize the likelihood of cure.

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**Key words:** Gastric cancer; Gastrectomy; Multimodality; Adjuvant treatment; Neoadjuvant; Targeted therapy; Human epidermal growth factor receptor

**Core tip:** Multimodality therapy targeting occult micro-metastatic disease is now accepted as the standard of care in the curative treatment of gastric cancer. Debate remains as to the best therapeutic regime and there is significant regional variation in the treatments which are routinely used. This review explores the evolution of multimodality treatments and perspectives for future developments including personalization of therapy.

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## INTRODUCTION

Curative treatments for gastric cancer remain a challenge with 988000 new cases and 730000 deaths each year, making it the second most common cause of cancer related death and the fourth most common malignancy worldwide, after lung, breast and colorectal malignancy<sup>[1]</sup>. While its total incidence is declining, particularly with the identification of *Helicobacter pylori* as a major risk factor,

**Table 1** Influential phase III trials for multimodality treatment of gastric cancer

Study name/region	Treatment arms	Total patients	Patients with lower oesophageal tumours	Patients undergoing D2 surgery	Hazard ratio for OS	95%CI	P value	Outcome summary
Intergroup-0116 <sup>[10]</sup> North America	Surgery alone <i>vs</i> adjuvant chemoradiation	556	20%	10%	1.35	1.09-1.66	0.005	Favours surgery plus adjuvant chemoradiation
ARTIST <sup>[14]</sup> Asia	Surgery plus adjuvant chemotherapy <i>vs</i> surgery plus adjuvant chemoradiation	458	0%	100%	Not recorded		0.09	No advantage
MAGIC <sup>[17]</sup> Europe	Surgery alone <i>vs</i> neoadjuvant chemotherapy plus surgery	503	26%	38%	0.75	0.60-0.93	0.009	Favours surgery plus neoadjuvant chemotherapy
FNLCC <sup>[18]</sup> Europe	Surgery alone <i>vs</i> neoadjuvant chemotherapy plus surgery	224	75%	Not recorded but D2 recommended	0.69	0.50-0.95	0.02	Favours surgery plus neoadjuvant
ACTS-GC <sup>[23]</sup> Asia	Surgery alone <i>vs</i> adjuvant S-1 plus surgery	1059	0%	100%	0.68	0.52-0.87	0.003	Favours surgery plus adjuvant chemotherapy
CLASSIC <sup>[24]</sup> Asia	Surgery alone <i>vs</i> postoperative capecitabine and oxaliplatin plus surgery	1035	0%	100%	0.72	0.52-1.00	0.0493	Favours surgery plus adjuvant chemotherapy
DGTC <sup>[33]</sup> Europe	D1 surgery <i>vs</i> D2 surgery	711	0%	46%			0.34	Favours D2 resection
MRC <sup>[27]</sup> Europe	D1 surgery <i>vs</i> D2 surgery	400	0%	50%	1.10	0.87-0.39	0.43	No significant difference D1 <i>vs</i> D2
CALB8010 <sup>[15]</sup>	Surgery plus enhanced adjuvant chemoradiation <i>vs</i> Intergroup-0166 outcomes	546	Not recorded	0%	1.03	0.80-1034	0.80	No advantage to enhanced adjuvant chemoradiation
ITACA-S <sup>[40]</sup> Europe	Surgery plus adjuvant chemotherapy <i>vs</i> surgery plus enhanced chemotherapy	1106	Not recorded	75%	1.00	0.83-1.20	0.97	No advantage to enhanced adjuvant chemotherapy
ToGA <sup>[45]</sup> Asia	Inoperable patients chemotherapy <i>vs</i> chemotherapy plus trastuzumab	584	18%	N/A	0.74	0.60-0.91	0.0046	Favours chemotherapy plus trastuzumab

the outlook is grim, particularly when it has progressed to an inoperable stage, when studies of its natural history place median survival to be 5 mo with supportive care and 7-12 mo with palliative chemotherapy with or without radiotherapy<sup>[2]</sup>. Geographical variation exists with over 70% of cases occurring in developing countries, particularly eastern asia<sup>[11]</sup>. In Western advanced economies, the tumour is often at an advanced stage by time of diagnosis whereas in Japan and South Korea, screening programs have resulted in diagnosis most commonly at an early stage<sup>[3]</sup>.

In patients with advanced localized gastric cancer, surgical excision offers the only potential cure and remains the mainstay of therapy but unfortunately recurrence is relatively common, even with complete (R0) resection<sup>[4]</sup>. Globally, consensus now exists that multimodality therapies improve outcomes in patients with stage II-IV tumours where a R0 resection can be achieved<sup>[5]</sup>. This review, explores recent developments in gastric cancer treatments as well as potential enhancement of adjuvant and neoadjuvant regimes.

## CURRENT ADJUVANT TREATMENTS

Despite radical R0, resections, most patients with ad-

vanced gastric cancer develop loco-regional or distant metastatic disease<sup>[4]</sup>. This is presumably from occult metastatic disease present at the time of diagnosis. The aim of the radical surgery is to remove all site specific macroscopic and microscopic tumour, but this has no effect on occult disease. The aim of multimodality therapy is to eliminate this micro-metastatic disease. Over many decades, adjuvant therapies have been proposed to improve survival outcomes. These studies have frequently been constrained by modest sample size and inconsistent study designs and have often produced conflicting results. Nonetheless, meta-analyses of adjuvant chemotherapy trials have consistently in described small but significant improvements in survival<sup>[6,7]</sup>. At present, no regimen is universally accepted as the standard for multimodality therapy and variations in strategies exist geographically as to whether perioperative chemotherapy (neoadjuvant), postoperative (adjuvant) chemoradiation, or adjuvant chemotherapy are employed as demonstrated in the influential studies outlined in Table 1 which are further described in the relevant sections of this article

### Adjuvant chemoradiation

High loco-regional recurrence rates led to evaluation of adjuvant radiotherapy and chemoradiation. Studies

showed no survival benefit from adjuvant radiotherapy alone, but suggested improved loco-regional control<sup>[8,9]</sup>. Adjuvant chemoradiation was however adopted as the standard for adjuvant therapy following resection with curative intent in North America following publication of the Intergroup-0116 study<sup>[10]</sup>. In this study, 556 patients with localized gastric or oesophagogastric cancer (stage I B-IV) undergoing resection with curative intent, were randomized into 2 groups: surgery plus postoperative chemoradiation or surgery alone. Adjuvant therapy consisted of five days of bolus 5-fluorouracil (FU) and leucovorin (LV), followed by 5 wk of concurrent radiation (4500 cGy) followed by two 5 d cycles of 5-FU and LV 2 mo apart. With a 5 year median follow-up, the chemoradiation plus surgery group had significantly prolonged overall [median 36 mo *vs* 27 mo, hazard ratio (HR), 1.35, 95%CI: 1.09-1.66,  $P = 0.005$ ] and relapse-free survival (median 30 mo *vs* 19 mo, HR = 1.52, 95%CI: 1.23-1.86,  $P < 0.001$ ). There was, however, a low compliance rate within the chemoradiation arm with planned therapy completed in 64% of patients, with adverse events responsible for treatment withdrawal in 17% and patient decision in another 8%. There was also criticism of the quality of surgery and extent of lymphadenectomy which was performed as 54% of all patients had a D0 resection and only 10% had a D2 resection. Many centres argued this to be oncologically inadequate and that the study merely illustrated that local control could be achieved after suboptimal surgery, accounting for the survival improvement in the trimodality study arm<sup>[11,12]</sup>. However, analysis after 10 year median follow-up, confirmed increased survival in the chemoradiation plus surgery group for both overall (HR = 1.32, 95%CI: 1.10-1.60,  $P = 0.0046$ ), and disease-free survival (HR = 1.51, 95%CI: 1.25-1.83,  $P < 0.001$ )<sup>[13]</sup>.

The ARTIST trial<sup>[14]</sup> was a South Korean prospectively randomized phase III study where 458 patients were randomized to adjuvant chemotherapy (cisplatin and capecitabine) (XP) or to adjuvant chemoradiation (cisplatin, capecitabine and chemoradiation) (XP/XRT/XP) following D2 gastrectomy. There was no difference in 3 year survival between the two groups (78% *vs* 74%,  $P = 0.0862$ ) though a benefit was seen in patients with tumour positive nodes (77% *vs* 72%,  $P = 0.03$ ). Although this study differed from the Intergroup-0116 by having a control arm which underwent chemotherapy rather than observation it did not demonstrate any benefit from the addition of radiotherapy for patients undergoing D2 gastrectomy. The large proportion of patients (60%) with early stage (stage I B and II) may have influenced the outcome. Nonetheless the results supported the belief that radiation merely gave a loco-regional effect to compensate for suboptimal surgery.

Alternate strategies of combination chemotherapy, such as adding epirubicin, cisplatin and 5FU pre and post surgery with adjuvant chemoradiation remain under evaluation (CALGB 80101 and CRITICS trials)<sup>[15,16]</sup> but to date such studies have failed to show a benefit.

### Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is standard of care across Europe and the United Kingdom for patients with resectable gastric cancer. This regime was given impetus by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial<sup>[17]</sup> in the United Kingdom. In the MAGIC study, 503 patients with resectable adenocarcinoma of stomach, oesophagogastric junction, or lower oesophagus were randomized to a neoadjuvant chemotherapy arm consisting of three cycles of epirubicin, cisplatin, and 5-FU given both pre and post operatively, or to a surgery alone arm. In the neoadjuvant chemotherapy group, there was a significantly improved overall (HR = 0.7, 95%CI: 0.60-0.93,  $P = 0.009$ ) and progression-free survival (HR = 0.66, 95%CI: 0.53-0.81,  $P < 0.001$ ) with similar surgical morbidity and mortality in both arms. As with the Intergroup 116 study, the postoperative component of therapy remained problematic as demonstrated by only 65% of patients starting the adjuvant component of treatment and only 50% of these being able to complete this treatment. The study was criticized for the variable preoperative staging methods used in the assessment, the addition of lower oesophageal cancer patients, some missing data collection, the D2 lymphadenectomy rate of 38% and the very high R2 resection rates in both arms, but overall, this paper provided a paradigm shift in standard of care in treatment of advanced gastric cancer in the West.

This neoadjuvant strategy was reinforced by the French FNCLCC multicenter phase III study<sup>[18]</sup> where 224 patients with adenocarcinoma of the stomach, oesophagogastric junction, and lower oesophagus undergoing surgery with curative intent, were randomized into arms of either surgery alone or neoadjuvant chemotherapy and surgery, following a similar regime to MAGIC. Analysis showed the neoadjuvant chemotherapy group had improved overall (HR = 0.69, 95%CI: 0.50-0.95,  $P = 0.02$ ) and disease-free survival (HR = 0.65, 95%CI: 0.48-0.89,  $P = 0.003$ ).

### Adjuvant chemotherapy

In "Western" centres, it has been traditionally felt that adjuvant chemotherapy did not confer any survival benefit in the setting of operable gastric cancer<sup>[19]</sup>. Two randomized Western studies showed only a small benefit<sup>[20,21]</sup> and however a meta analysis of 17 randomised studies containing 3838 patients using adjuvant 5-FU based chemotherapy compared to surgery alone showed a 6% absolute improvement in survival (53% *vs* 49.6%,  $P < 0.001$ )<sup>[7]</sup>.

In Asia, multiple studies have been conducted with oral fluoropyrimidine-based regimens, resulting in this being adopted as the adjuvant therapy standard of care. The two most influential studies have been the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC)<sup>[22]</sup> and the CLASSIC trial<sup>[23]</sup>. The Japanese ACTS-GC study, randomised 1059 patients with stage II-III gastric cancer undergoing D2 gastrectomy, to surgery alone or to surgery plus 12 mo treatment with adjuvant oral S-1

(fluoropyrimidine). S1 contains a 5-FU prodrug, tegafur, and gimeracil, which inhibits dihydropyrimidine dehydrogenase, as well as oteracil which inhibits phosphorylation of 5-FU in the gut. Following interim analysis, the study was terminated early. With a median follow-up of 3 years, there was a 10% improvement in overall survival in the S1 group (80.1% *vs* 70.1%, HR = 0.68, 95%CI: 0.52-0.87, *P* = 0.003) and relapse-free survival (HR = 0.62, 95%CI: 0.50-0.77, *P* < 0.001) compared to the surgery alone group. Follow-up at 5 years confirmed this improved overall survival of 72.6% *vs* 61.4% (HR = 0.67; 95%CI: 0.54-0.83) and relapse free survival (HR = 0.65, 95%CI: 0.54-0.79)<sup>[24]</sup>.

The CLASSIC study assessed combination adjuvant therapy using capecitabine and oxaliplatin in stage II–III B gastric cancer. An Asian multicentre randomized trial, 1035 patients were randomized to two arms following D2 gastrectomy: either eight cycles of adjuvant chemotherapy or to observation. This study was also terminated after interim analysis showed a significantly improved 3yr disease-free survival in the chemotherapy arm when compared to surgery alone (74% *vs* 60%, HR = 0.56, 95%CI: 0.44-0.72, *P* < 0.0001). For overall survival, there was also a non significant trend to improved survival for patients receiving adjuvant therapies (HR = 0.74, 95%CI: 0.53-1.00, *P* = 0.0775) though this data was not mature.

### **Rationale for geographical variation in multimodality therapies**

This data indicates that benefit may be obtained by adjuvant targeting of micro-metastatic disease even after optimal surgery, but it is rarely practiced outside of Eastern Asia due to a perceived lack of benefit in Western patients. Similarly neoadjuvant therapy is rarely used in Asia. This geographical discrepancy regarding the types of multimodality therapy may be explained by differing regional attitudes to surgical technique. The extent of lymphadenectomy in curative surgical resection has been debated for many years. In Asia, extended (D2) lymph node dissection is the established standard of care. Western surgeons however, have traditionally been less convinced of the benefit of D2 resection over a more limited (D0 or D1) lymphadenectomy.

Two European randomized trials, the Dutch Gastric Cancer Trial (DGCT)<sup>[25]</sup> and the United Kingdom Medical Research Council (MRC) trial<sup>[26]</sup>, compared the outcomes of D2 and D1 surgery without any adjuvant treatment. These trials, showed no improvement in the 5 year survival of patients undergoing a D2 resection compared to D1, but D2 resection had a significantly increased postoperative morbidity and mortality when compared to D1 resection. These higher morbidity rates arose from the splenectomy and/or pancreatectomy, which was included as part of the D2 surgery mandated in these trials. However, the necessity of including a distal pancreatectomy and/or splenectomy has been questioned. The lymph nodes removed in this resection are stations 10 and 11. However the yield of involved nodes for station

11 is only 10% and for station 10 is less than 1% in distal tumours though it can increase to up to 25% for tumours in the upper third or on greater curve of stomach<sup>[27]</sup>. Asian studies have suggested potential survival advantages with pancreatic preservation<sup>[28]</sup>. As a result, pancreas preserving lymphadenectomy of stations 11p and 11d is now recommended in a D2 gastrectomy<sup>[29]</sup>. Splenectomy is now avoided for distal and body tumours, though the situation remains somewhat less clear for upper third and greater curve tumours where the results of the JCOG0110 of splenectomy *v* non splenectomy in proximal tumours is keenly anticipated with its 5 years survival analysis due in 2014<sup>[30]</sup>. Studies in Western centres have demonstrated that pancreas and spleen preserving D2 surgery can be performed with acceptable morbidity and mortality<sup>[31]</sup>. In addition, the 15-year follow-up of the DGCT trial demonstrated that patients undergoing D2 surgery had a lower rate of disease related death to those undergoing D1 surgery<sup>[32]</sup>. This indicates that D2 surgery excluding routine pancreatectomy and splenectomy may be performed with acceptable outcomes in Western patients

In two of the most influential Western trials, the Intergroup-011<sup>[10]</sup> and MAGIC<sup>[17]</sup> trials, D2 lymphadenectomy was performed in 10% and 38% of patients, respectively. As previously noted, it can be argued that the surgical treatment in these studies was suboptimal compared to Asian studies, perhaps explaining why additional local control measures such as radiotherapy (in Intergroup-0116) and neoadjuvant chemotherapy (in MAGIC) may have improved survival outcomes. This argument is supported by a European retrospective study which showed a survival benefit in patients undergoing D1 resection with adjuvant chemoradiation when compared to surgery alone, which was not seen in those patients who underwent D2 resection and adjuvant chemoradiation<sup>[33]</sup>. In addition, the survival outcomes of stage-matched patients in Western trials where D2 surgery was not performed, remains inferior to those in South Korean and Japanese trials, even where radiotherapy or neoadjuvant chemotherapy was given<sup>[10,17,22,23]</sup>. Stage migration associated with the more extensive lymphadenectomy may account for some of this discrepancy, however in retrospective studies on western cohorts where D2 gastrectomy alone was performed, stage by stage survival outcomes were similar to those in South Korea and Japan<sup>[34,35]</sup>. This suggests that the Western neoadjuvant and radiation regimes may merely provide a degree of compensation for more limited surgical treatments.

Heterogeneity of the patients included in studies may also account for some of the differences seen between the European and Asian studies. The Asian studies have generally only included patients with gastric cancer, however Western studies, most notably the MAGIC study<sup>[17]</sup>, included patients with lower oesophageal adenocarcinoma. This increased heterogeneity was intended to improve recruitment given the decreasing incidence of gastric adenocarcinoma but increasing incidence of

lower oesophageal adenocarcinoma seen in the West. In comparison, the incidence of lower oesophageal adenocarcinoma in Asia is low<sup>[36]</sup>. There are, significant clinicopathological differences between oesophageal cancer, with its lack of serosa and abundant lymphatic drainage in comparison to gastric adenocarcinoma, as oesophageal cancer is more likely to invade surrounding tissue and regional lymph nodes early, resulting in patients presenting at a more advanced pathological stage, with poorer survival. Multimodality therapy has been extensively investigated for other oesophageal tumours in the past with positive outcome<sup>[37]</sup>. Understanding these clinicopathological differences between oesophageal and gastric adenocarcinomas, it can be foreseen that the inclusion of lower oesophageal tumours in these studies is somewhat problematic.

## FUTURE STRATEGIES FOR IMPROVED MANAGEMENT

Developments of multimodality therapies have improved results, but overall outcomes for gastric cancer remain poor and there is a need to improve treatment strategies. With the debate over surgery now more or less resolved in favour of radical lymphadenectomy, future studies need to concentrate on the neoadjuvant and adjuvant regimes using either conventional or more novel therapeutic agents.

Intensification of adjuvant regimes has been proposed, but to date there is little evidence to support this approach. The AMC 0201 study<sup>[38]</sup> increased oral S1 treatment duration to 12 mo whilst also adding cisplatin to the combination of mitomycin-C and 3 mo of oral S1. This study showed no benefit with the more intense regime, in either recurrence-free (HR = 1.07, 95%CI: 0.85-1.35,  $P = 0.59$ ) or overall survival (HR = 1.10, 95%CI: 0.84-1.44,  $P = 0.48$ ). The Cancer and Leukemia Group B 80101 study trial<sup>[15]</sup> intensified the Intergroup-0116 chemoradiation regime, by adding epirubicin and cisplatin to the 5-FU and LV. In the enrolled 546 patients, who underwent D0 or D1 lymphadenectomy, the more intensive regime did not show an improved overall (HR = 1.03, 95%CI: 0.80-1.34,  $P = 0.80$ ) or disease-free survival (HR = 1.00, 95%CI: 0.79-1.27,  $P = 0.99$ ) when compared to the Intergroup-0166 regime. The ITACA-S trial, included 1106 patients undergoing curative resection with radical lymphadenectomy (D1 25%, D2/3 75%), with 1 group receiving enhanced chemotherapy (four cycles of 5-FU, LV and irinotecan, followed by three cycles of docetaxel and cisplatin) and a control group who received nine cycles of 5-FU and LV. There was no difference in disease-free (HR = 0.98, 95%CI: 0.83-1.16,  $P = 0.83$ ) or overall survival (HR = 1.0, 95%CI: 0.83-1.20) between the group<sup>[39]</sup>. These trials suggest that intensification of adjuvant chemotherapy or chemoradiation regimes is not effective.

The role of different styles of combination therapies is currently under assessment to attempt to understand

the role of neoadjuvant regimes when a D2 lymphadenectomy has been performed. Studies are also exploring the role of radiotherapy in neoadjuvant regimes. Phase III trials currently underway include: (1) PRODIGY (preoperative docetaxel, oxaliplatin, and S-1 followed by postoperative S-1 *vs* postoperative S-1, for patients with D2 resection; NCT01515748): This study aims to assess neoadjuvant chemotherapy in combination with D2 resection; (2) TOPGEAR: This is an international randomized phase III trial of preoperative chemoradiation *vs* preoperative chemotherapy for resectable gastric cancer (ACTRN12609000035224); and (3) CRITICS (NCT00407186): This assesses the addition of adjuvant radiotherapy to a neoadjuvant chemotherapy protocol.

Timing and routes of administration of therapies also offers an area of potential exploration. The AMC 0101 study<sup>[40]</sup> evaluated intra-operative intraperitoneal cisplatin chemotherapy as well as early commencement of systemic chemotherapy on day 1 postoperatively, when compared to a control arm of mitomycin-C and 3 mo of oral fluoropyrimidine. All 521 patients had a D2 resection for a serosa-involving gastric cancer (T4). The intraperitoneal and early chemotherapy group had improved recurrence-free (HR = 0.70, 95%CI: 0.54-0.90,  $P = 0.006$ ) and overall survival (HR = 0.71, 95%CI: 0.53-0.95,  $P = 0.02$ ) compared to the control arm. Long term follow-up out to a median of 6.6 years has confirmed this benefit<sup>[41]</sup>. This suggests that intraperitoneal and early post operative commencement of chemotherapy may increase the effectiveness of our current adjuvant regimes particularly in the more advanced T stage tumours.

## BIOLOGICAL TARGETING

Traditionally, personalization and discussion of multimodality therapy has been based purely on the physical staging of the patients' cancer, combined with the patients general condition and co morbidities. In the past 10 years however, there has been an increased understanding of the complexity and variation of tumours seen at the molecular level, and intracellular pathways are now being assessed as potential targets to allow selective modulation as part of a cancer control strategy. Angiogenesis pathways have been identified in several cancer types, and in gastric cancer, increased expression of vascular endothelial growth factor-A (VEGF-A) is associated with tumour aggression and poor prognosis. The AVAGAST trial<sup>[42]</sup>, assessed a humanized monoclonal antibody against VEGF-A, bevacizumab, combined with standard chemotherapy in patients with locally advanced and metastatic gastric cancer. Both median progression-free survival (6.7 mo *vs* 5.3 mo, HR = 0.80, 95%CI: 0.68-0.93,  $P = 0.0037$ ) and overall response rate (46.0% *vs* 37.4%,  $P = 0.0315$ ) were significantly improved in the bevacizumab group but overall survival was not improved.

In the setting of operable cancer, it is hoped that targeting this pathway in addition to standard neoadjuvant regimes may facilitate a greater R0 resection rate and lead

to a longer duration of disease free and overall survival. The MRC-ST03 trial<sup>[43]</sup> is currently recruiting to assess the effect of adding bevacizumab to neoadjuvant therapy [perioperative epirubicin, cisplatin and capecitabine, with or without bevacizumab] and aims to randomise 950 patients.

The epidermal growth factor receptor family has been proposed as a key driver of tumour genesis with the human epidermal growth factor receptor (*HER-2*) being the subject of intense investigation. The trastuzumab for gastric cancer (ToGA) trial<sup>[44]</sup> of 584 patients with locally advanced or metastatic gastric cancer and an over expression of *HER-2* by immunohistochemistry or fluorescence *in situ* hybridization testing, found that combination therapy with cisplatin, 5FU and trastuzumab (a monoclonal antibody against *HER-2*) gave a significantly improved progression free and median overall survival (11.1 mo *vs* 13.8 mo,  $P = 0.0046$ , HR = 0.74, 95%CI: 0.60-0.91) over chemotherapy alone. However in the small subgroups of patients with locally advanced disease (20 patients) or who had undergone previous gastrectomy (133 patients), no survival benefit was seen between the two regimes.

The utility of the ToGA study finding remains under investigation remembering that a minority of gastric cancer patients exhibit *HER-2* overexpression (range: 6%-33%). Similarly the majority of studies looking at *HER-2* therapies have focused on patients with unresectable or metastatic disease. Newer *HER* family targeting agents such as pertuzumab, afatinib and lapatinib are being developed as primary treatment agents or in the case of resistance to trastuzumab. Additionally interest is now being shown in the use of these agents in the adjuvant or neoadjuvant settings for *HER-2* positive tumours<sup>[45]</sup>.

However, there remains controversy as to whether *HER-2* overexpression or amplification is an indicator of poor prognosis. It may be argued that in the ToGA trial, the overall survival of 11.1 mo in the chemotherapy alone cohort was greater than expected, indicating that that *HER 2* overexpression in itself conferred a better prognosis. Several studies have associated *HER-2* amplification with a poorer prognosis, but this has not been consistent and associated with the non standardized methods used to determine *HER-2* positivity, it can be argued that the prognostic impact in resectable gastric cancer is weak<sup>[45]</sup>. A systematic review by Jorgensen found that in 32 of 40 papers covering 12749 patients, *HER-2* amplification was associated with poorer survival outcomes and worse clinicopathological features<sup>[46]</sup>. It is also interesting that apart from a single study of fewer than 100 patients<sup>[47]</sup> none have found a survival benefit associated with *HER-2* overexpression although it must be remembered that publication bias in itself may slant the results of systematic reviews, as studies not demonstrating any association are less likely to be published<sup>[45]</sup>.

Overall the data on *HER-2* is not as consistent as that which is seen in breast cancer, but nonetheless there appears to be a trend towards over-expression as being

a negative prognostic factor. It has therefore been proposed that *HER-2* overexpression is a molecular abnormality linked to the development of gastric cancer<sup>[46]</sup>.

Other potential therapeutic targets are also being assessed. These include *c-met* and *FGFR2* which have been identified as potential cellular oncogenic drivers. As with the *HER-2*, these agents will be tested initially in the metastatic or inoperable setting and if value is demonstrated, then their use in the adjuvant or neoadjuvant setting should be assessed<sup>[12]</sup>.

Allied with the selectivity of these targeted agents and traditional chemotherapy, must come assessment of response in real time. The use of imaging modalities such as positron emission tomography or CT response may be used to assess early response and failure of response may permit change to other modalities or salvage therapy or surgery<sup>[48]</sup>.

## CONCLUSION

There is now general consensus that multi modality therapy encompassing both radical surgery and adjuvant or neoadjuvant regimes to target occult micrometastatic disease, offers the best possibility of cure in gastric cancer. There remains however significant regional variation as to the preferred regime. There is general agreement now that radical gastrectomy and lymphadenectomy is the surgical procedure of choice, but the optimal additional treatment is unclear. Traditional radiological and clinicopathological staging methods are now being supplemented by molecular markers. The selectivity seen by these markers holds the promise of a personalized approach to gastric cancer therapy in the future.

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