Clinics in Surgery

Review Article
Published: 07 Dec, 2016

Treatment of Resectable Gastric Cancer: An Update on the Role of Radiation and Chemotherapy

Sarwat Ahmad and Nader Hanna*

Department of Surgery, University of Maryland School of Medicine, USA

Abstract

The operative and perioperative management of gastric cancer has been an area of controversy and ongoing study in both Eastern and Western patient populations. The extent of lymphadenectomy varies across regions. Various combinations of chemotherapy and radiation in the neoadjuvant and adjuvant setting have been studied in large randomized controlled trials. In the West, two major trials, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial and the SWOG/INT 0116 trial by Macdonald et al. have influenced perioperative therapy, but the efficacy of one versus the other has not yet been determined. Newer studies, such as the CRITICS trial, are investigating the potential benefits of neoadjuvant therapy in combination with adjuvant chemoradiation. This review describes the ongoing controversies in gastric cancer multimodal management and encompasses the evidence to date supporting current practices in the West.

Introduction

At an incidence of 950,000 new cases per year worldwide in 2012, gastric cancer is among the top five most common cancers and ranks as the 3rdand 4thleading cause of cancer death in men and women, respectively [1]. Regional variances persist, with Eastern Asia most heavily affected, partially due to differences in *H.pylori* infection, smoking, and diet [1]. While the incidence and mortality of gastric cancer has been declining overall, Western countries have seen arise in cancers of the gastric cardia, likely related to increased obesity and its comorbidities such as gastroesophageal reflux disease [2,3] as well as improved diagnostic modalities [4]. Compared to the East, gastric cancers in North America and Europe are diagnosed at more advanced stages, leading to poorer prognoses [5]. Nearly 40% of patients still present with metastases, while 50% present with locoregional disease [6]. The overall 5-year survival for patients with resectable gastric cancer ranges from 10-30% [7-9].

Curative therapy involves surgical resection with adequate lymphadenectomy; however, more than 80% of resected cases develop locoregional or systemic recurrence [10].This high rate of recurrence has invigorated researchers over the last twenty years to study various combinations of chemotherapy and radiation given before and after surgery to improve rates of recurrence and survival. Results of these trials have been variable and difficult to interpret given different study designs and patterns of disease in the East versus the West.

In Europe, for example, perioperative chemotherapy is the standard of care, based on the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in 2006 [11]. In Japan, the recommendation is to give adjuvant chemotherapy with S-1, an oral fluoropyrimidine [12,13]. In North America, adjuvant chemotherapy and radiation are the current standard of care, based on the results of the Southwest Oncology Group (SWOG) 9008/INT 0116 trial by Macdonald et al [14]. Among other limitations, study design and patient characteristics varied significantly among the three trials. The subsequent lack of consensus has led to several new studies such as the CRITICS trial that directly compare multimodal approaches.

This review will highlight management controversies and presents the major prospective phase III clinical trials that have shaped the Western approach to resectable gastric cancer, comparing and contrasting their findings with data from smaller phase II or III trials under investigation and provide clinical considerations drawn from the currently available evidence.

Extent of Lymphadenectomy

The extent of nodal dissection for gastric cancer has been controversial. In Japan, the modified D2 resection (removal of regional perigastric nodes without pancreatico-splenectomy) has acceptable morbidity and mortality [15] and is the standard approach [16]. A D1 resection entails subtotal

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Correspondence:
Sarwat Ahmad, Department of Surgery, University of Maryland School of Medicine, 22 S. Greene St, Baltimore, MD 21201, USA, Tel: 2489433437; Fax: 4107068234;
E-mail: SarwatBAhmad@gmail.com

Received Date: *14 Oct 2016*
Accepted Date: *30 Nov 2016*
Published Date: *07 Dec 2016*

Citation:
Ahmad S, Hanna N. Treatment of Resectable Gastric Cancer: An Update on the Role of Radiation and Chemotherapy. Clin Surg. 2016; 1: 1223.

Table 1: D1 vs. D2 Lymphadenectomy: 3 randomized controlled trials.

		N	Morbidity rate, p-value		Mortality rate, p-value		5-year survival	
Degiuli et al. [18]	D1	76	10.5%	NS	1.3%	NS	Not evaluated	
	D2	86	16.3%		0%			
Cuschieri et al. [17]	D1	200	28.0%	<0.001	6.5%	0.04	35%	0.72
	D2	200	46.0%		13.0%		33%	
Hartgrink et al. [19]	D1	380	25.0%	<0.001	4.0%	0.004	30%	0.35
	D2	331	43.0%		10.0%		35%	

or total gastrectomy plus greater and lesser omentum (stations 1-6). A D2 lymphadenectomy involves removal of omental bursa along with the front leaf of the transverse mesocolon with clearance of the nodes along the left gastric artery (station 7), common hepatic artery (stations 8), celiac artery (station 9), and splenic artery (stations 10 and 11). Western countries have begun to limit D2 resections since several randomized controlled trials (RCT) showed no survival benefit of D2 over D1 lymphadenectomy, morbidity and mortality of which are summarized in Table 1 [17-19]. In the Dutch cancer group study of 711 patients from 1989 to 1993, patients in the D2 group had a higher rate of complications, postoperative deaths, and longer hospital stays versus the D1 group, with little difference in the risk of recurrence at five years: 43% for D1 and 37% for D2 [20]. A 15-year follow-up study of the Dutch D1D2 trial showed that again there was no difference in overall survival (21% for D1 and 29% for D2, p=0.34); however, locoregional recurrence and gastric cancer-related death rate were significantly higher in the D1 group (48% vs. 37%, p=0.001), and postoperative deaths were higher after D2 (10% vs. 4%, p=0.004). When hospital deaths were excluded, the survival rates improved to 32% for D1 and 39% for D2. The authors concluded that with the availability of a safer, spleen-preserving D2 lymphadenectomy in high volume centers, this approach should be employed when possible to reduce locoregional recurrence in patients with resectable gastric cancer [21]. Nevertheless, practice patterns continue to vary across regions, but most expert surgical oncologist performs D2 lymphadenectomy without distal pancreatectomy and splenectomy with acceptable morbidity and mortality. As such, the extent of lymphadenectomy varies significantly among the major gastric cancer trials discussed in this review, making it difficult to draw valid conclusions regarding therapeutic efficacy.

Perioperative Chemotherapy

The MAGIC trial was the first RCT to show a conclusive survival benefit from the use of perioperative chemotherapy for resectable gastric and gastroesophageal junction (GEJ) cancer over surgery alone [Table 2]. The MAGIC trial randomized 503 patients with locally advanced resectable gastric (74%) and GEJ (11%) cancer for surgery alone (n=253) or perioperative chemotherapy (n=250) with three pre-operative and three post-operative cycles of ECF (epirubicin, cisplatin, and infused 5-fluorouracil (5-FU)). Perioperative chemotherapy significantly improved resectability, progression-free and overall survival (PFS and OS, respectively), demonstrating a 5-year survival of 36% for perioperative chemotherapy compared to 23% for surgery-alone (HR 0.75, 95% CI, 0.60-0.93; P=0.009) [11].

As such, perioperative chemotherapy has become the standard of care in the UK and much of Europe. But while the MAGIC regimen improved tumor stage, node negativity, and subsequent curative resection, the efficacy of pre-operative versus post-operative chemotherapy could not be determined. Only 55% of patients randomized to chemotherapy actually received chemotherapy after surgery, and only 42% of them completed all six cycles post-operatively [11]. The most common reason for not enrolling into postoperative chemotherapy was disease progression or early death. Critics of the MAGIC trial also point out that outcomes for these patients were not stratified by disease stage or histopathology, thus making it difficult to decide which patients would benefit from chemotherapy before surgery. The authors argue that accurate pre-operative diagnosis of locally advanced disease is difficult in itself, especially since endoscopic ultrasound was not widely available when the MAGIC trial was conducted [22].

Alternative regimens with more intensified chemotherapy have been investigated since MAGIC. The German AIO phase II/III FLOT4 study randomized patients to six cycles of perioperative ECF or four cycles of pre-operative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) followed by four cycles of FLOT postoperatively. Preliminary results show that FLOT led to better pathological complete response (pCR) than ECF (12.8% vs. 5.1%) [23]. These results encourage further study of FLOT to characterize toxicity and long-term survival benefits.

The MAGIC trial also led to the implementation of MAGIC B, or the UK NCRI ST03 trial, which opened accrual in 2007 to investigate the effect of bevacizumab, the monoclonal antibody to vascular endothelial growth factor (VEGF), in advanced gastric cancer. Bevacizumab combined with chemotherapy has shown efficacy in the treatment of various solid tumors [24-26]. VEGF is expressed in gastric cancer [27] and is a negative prognostic factor [28]. In a multicenter phase II trial of 47 patients with unresectable gastric cancer, bevacizumab was shown to be safe and effective at improving time to progression and overall survival when combined with chemotherapy (irinotecan and cisplatin) [29]. The ST03 trial randomized patients to perioperative chemotherapy with ECX (epirubicin, cisplatin, and capecitabine) +/- bevacizumab in HER2-negative patients in addition to two other treatment arms testing the feasibility of lapatinib in HER2-positive patients. Capecitabine given orally is more convenient than the 5FU infusion and thus avoids need for central lines and infusion pumps and their associated infectious complications. Unfortunately, ST03 did not demonstrate an improvement in overall survival (OS), progression-free survival (PFS), or disease-free survival (DFS) for resectable gastric cancer. Moreover, patients treated with bevacizumab had an increased risk of postoperative anastomotic leaks [30], likely due to impaired wound healing from inhibited angiogenesis. Despite these negative results, targeted therapy is still an area of interest in developing chemotherapeutic regimens, and other agents are being explored [31].

Neoadjuvant Chemotherapy

The effect of neoadjuvant chemotherapy on resectability was also

Table 2: Summary of three major phase III trials.

	MAGIC	US INT 0116	CRITICS
Years	1994-2002	1991-1998	2007-2015
Region	UK	USA	Europe
Total (n)	503: Control: surgery only, n=253 Experimental: perioperative chemotherapy, n=250	556: Control: surgery only, n=275 Experimental: adjuvant chemoradiation, n=281	788: (All received Neoadjuvant chemo) Control: adjuvant chemotherapy only, 393 Experimental: adjuvant chemoradiation, n=395
Stage of adenocarcinoma	II-IV	IB-IV	IB-IV a
Neoadjuvant therapy	In experimental arm only: ECF x 3 cycles(epirubicin, cisplatin, infusional 5-FU)	Not applicable	ECC x 3 cycles (epirubicin, cisplatin, capecitabine)
Surgery	R0 resection—69.3% Esophago-gastrectomy: 23% D1: 19% D2: 40% Non-curative/Unknown: 40%	R0 resection: 100% D0 – 54% D1—36% D2—10%	Information not yet available.
Adjuvant therapy	ECF x 3 cycles	Bolus 5-FU, leucovorin, radiation with 45 Gy	3x ECC, radiation with 45 Gy
Completion of adjuvant therapy	42%	64%	Control arm: 46% Experimental arm: 55%
5-year overall survival	25% for surgery only 42% for perioperative chemotherapy	23% for surgery only 36% for adjuvant chemoradiation	41.3% for adjuvant chemotherapy 40.9% for adjuvant chemoradiation

demonstrated in a French multicenter phase III trial of 224 patients with stage II or greater gastric or GEJ cancer (FNLCC/FFCD trial). Compared to surgery alone, perioperative therapy with infusional 5-FU and cisplatin resulted in a higher likelihood of obtaining an R0 resection (73 vs. 84%). Similar to MAGIC, only half of the patients randomized to receive chemotherapy actually received their post-operative treatment. Thus, authors limited their conclusions to preoperative 5-FU and cisplatin, which improved DFS and OS [32]. In the EORTC 4095 phase III trial, those who received preoperative chemotherapy (cisplatin, leucovorin, infusional 5-FU) had more postoperative complications and no survival advantage over surgery alone, although the study was underpowered due to poor accrual [33]. A meta-analysis of 14 trials and 2271 patients who received neoadjuvant chemotherapy versus surgery alone for locally advanced gastric cancer concluded that neoadjuvant chemotherapy improves OS, PFS, R0 resectability rate, and does not worsen perioperative complications or mortality [34]. Another benefit of neoadjuvant therapy is the ability to assess tumor biology and response to therapy in the time before surgery, which may spare gastrectomy for a patient with particularly aggressive disease [35].

Neoadjuvant Chemoradiation

Recent randomized trials from Europe have compared neoadjuvant chemotherapy versus chemoradiation in esophageal and GEJ adenocarcinoma and noted improved histologic complete response, R0 resection rate, and lower frequency of lymph node metastases, but no significant effect on survival [36,37]. It is uncertain, however, whether these results can be applied to non-cardia gastric cancers. At this time, no large phase III trials have examined chemoradiotherapy in the neoadjuvant setting for non-cardia gastric cancers. The few small studies that have combined neoadjuvant chemoradiation with chemotherapy for locally advanced gastric cancer have been promising, however. The Radiation Therapy Oncology Group (RTOG) 9904 trial demonstrated improved R0 resection rate (70% vs. 30%) and pathological response rate of 26% for neoadjuvant chemoradiation with infusional 5-FU and paclitaxel [38,39]. Similarly, docetaxel-based chemoradiotherapy demonstrated a 24% pathological complete response and was not associated with postoperative complications [40]. As centers around the world continue to build experience with multimodal cancer therapy, neoadjuvant chemoradiation will likely gain popularity and has been identified as a focus of study in upcoming European and Asian clinical trials.

Adjuvant Chemotherapy

The decision to give perioperative chemotherapy largely depends on referral of the patient to an oncologist prior to surgery. Therefore, accrual for patients in FNLCC/FFCD and other trials of neoadjuvant chemotherapy has been low. In contrast, several studies have examined the efficacy of adjuvant chemotherapy versus surgery, but they are generally small, heterogeneous, and underpowered. Thus, a meta-analysis was conducted by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group which studied 17 trials (3838 patients, median follow-up >7 years) and identified a 6% improvement in overall 5- and 10-year survival and 18% reduction in the risk of relapse, second primary, or death in patients who received adjuvant fluorouracil regimens versus surgery alone [41].

Another large phase III trial to show a survival benefit of chemotherapy with S1 (an oral fluoropyrimidine) over surgery alone was the Adjuvant Chemotherapy Trial for S-1 for Gastric Cancer (ACTS-GC) in Japan, in which S1 was given for a year postoperatively. Overall survival and RFS was significantly higher in the S-1 group (72.2% vs. 59.6%) at 3- and 5-year follow-up. Therapeutic efficacy of S-1 has not yet been definitively shown in non-Asian countries [42], as pharmacokinetics of this drug may differ between Eastern and Western populations [43]. However, a recent phase III RCT of S1 and cisplatin vs. infusional 5-FU and cisplatin showed non-inferiority and a better safety profile for the S1pluscisplatin group [42], encouraging further studies of S1 in non-Asian countries.

All patients in ACTS-GC underwent D2 dissection; in contrast, 40% patients in the MAGIC trial underwent D2 dissection. The CLASSIC trial (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) studied the effect of adjuvant chemotherapy with capecitabine and oxaliplatin x 8 cycles after D2 lymphadenectomy. This trial also showed a higher 3-year DFS for chemotherapy (83%) vs. surgery alone (78%) [44,45]. Both the ACTS-GC and CLASSIC trials studied Asian populations who underwent D2 lymphadenectomies and had higher overall survival rates than Western trials of adjuvant

Table 3: Select ongoing clinical trials.

Trial	Identifier	Phase	Country	Experimental Regimen
Neoadjuvant Chemotherapy				
Japan Clinical Oncology Group 0501	NCT00252161	III	Japan	Neoadjuvant cisplatin +S1 vs. surgery alone
PRODIGY	NCT01515748	III	Korea	Neoadjuvant docetaxel, oxaliplatin, S1,followed by standard S1 adjuvant therapy
AIO FLOT4	NCT01216644	II/III	Germany	Standard 6 cycles of perioperative ECF or to 4 cycles of 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) preoperatively and 4 cycles of FLOT postoperatively
Perioperative Chemotherapy				
NEO-FLOT	NCT01160419	II	Germany	Perioperative 5-FU, leukovorin, oxaliplatin, docetaxel
Trial of Adjuvant XELOX Chemotherapy and Concurrent Capecitabine and Radiotherapy for Resected Gastric Carcinoma	NCT01711242	II	China	Adjuvant chemo alone (4 days of XELOX vs. chemoradiation 45 Gy in 1.8-Gy fractions with concurrent capecitabine, 825 mg/m2 twice daily on days of radiation), then 2 further cycles of XELOX after D2 lymphadenectomy
CAPITAL	NCT01795027	III	China	Adjuvant oxaliplatin + S1 vs. S1 alone
Neoadjuvant chemoradiation				
TOPGEAR, Gastro-Intestinal Trials Group (AGITG)	NCT01924819	II/III	Australia, Canada, Europe	Neoadjuvant. Control = 3 pre, 3 post of ECX/ECF. Experimental arm receive 2 cycles of preoperative ECX/ECF followed by chemoradiation with fluoropyrimidine, then 3 cycles of postop ECX/ECF. , D1 LAD
Targeted therapy				
RAMSES trial	NCT02661971	II/III	Germany	Perioperative FLOT vs. Ramucirumab plus FLOT
TOXAG	NCT01748773	II	Turkey	Adjuvant trastuzumab, oxaliplatin, and capecitabine (TOX), then chemoradiation with capecitabine, then mono therapy with trastuzumab
HerFLOT	NCT01472029	II	Germany	Perioperative FLOT plus trastuzumab

chemotherapy. It is important to note, however, that results in the East cannot be readily applied to the West due to inherent differences in patient disease, surgical experience and technique. Nevertheless, the results of these studies demonstrate that post-operative chemotherapy prolongs survival in resectable gastric cancer in studies that did not administer pre-operative chemotherapy or radiation.

Adjuvant Chemoradiation

To further reduce the risk of recurrence, radiation has been studied as an adjuvant therapy in the treatment of gastric cancer. The SWOG/INT 0116 phase III trial randomized 553 patients after resection to either adjuvant chemoradiation or observation [Table 2]. External beam radiation was administered to the tumor bed, regional nodes, and two centimeters beyond the proximal and distal resection margins. The chemoradiation arm demonstrated significant improvement in 3-year relapse-free survival, overall survival, and local recurrence rates (19 vs. 29%) [11]. These advantages persisted at more than 10 years follow-up [46].

Due to treatment toxicity, only 64% completed the adjuvant treatment. However, given the significant survival advantage, adjuvant chemoradiation became the standard of care for resectable gastric cancer in the United States. To reduce toxicity, bolus 5-FU has been replaced by either oral capecitabine or continuous infusion 5-FU [47]. Other attempts at reducing toxicity include using the alternative regimen of ECF plus radiation, as done in the CALGB 80101 trial in the US. Results have shown lower toxicity rates but no change in overall survival [48].

The question remains as to whether adjuvant radiation benefits D2 and D1lymphadenectomy equally. In INT 0116, less than 10% of patients (n=54) underwent a D2 lymphadenectomy and 54% received a D0 lymphadenectomy. Therefore, criticism arose as to whether the survival advantage of adjuvant chemoradiation could be substituted by a more extensive lymphatic dissection. A subgroup analysis in the 10-year updated results showed no difference in survival between D1 vs. D2 lymphadenectomy, but the subgroups were insufficiently powered. Nevertheless, the authors obtained a Maruyama index of unresected disease (MI) on each patient and showed that MI was an independent prognosticator of RFS, OS, and response to chemoradiotherapy. The MI predicts the positivity of remaining lymph nodes and can indicatethe adequacy of a nodal dissection [49,50]. A retrospective study by Dikken et al. [51] controlled for MI and found no advantage for adjuvant chemoradiation after D2 dissection. Therefore, though data remains conflicted, inadequacy of lymph node dissection may be considered an indication for adjuvant chemoradiation.

Adjuvant Chemotherapy vs. Chemoradiation

The value of radiation in the post-operative setting was challenged by the ARTIST trial (Adjuvant Chemoradiotherapy Trial in Stomach Tumors) from Korea. 458 patients with R0 resections and D2 lymphadenectomies were randomized to either adjuvant chemotherapy with capecitabine and cisplatin (XP) vs. XP plus radiation. There was no difference in 3-year DFS. However, subset analysis of those with node-positive disease showed significantly better DFS with chemoradiotherapy vs. chemotherapy alone [52]. This led to the design of the ARTIST-II trial, which will compare adjuvant chemotherapy versus chemoradiation in D2 resected node-*positive* patients. The results of ARTIST-II may not be fully applicable to Western populations where D2 lymphadenectomy is not the standard of care, but will address an important question regarding patient selection for adjuvant radiation.

Neoadjuvant Chemotherapy Plus Adjuvant Chemoradiation

It is not possible to directly compare results from the MAGIC

and Macdonald (INT 0116) trials as they differ in their study design and eligibility criteria. Therefore, to determine whether adjuvant radiation offers benefit to patients who have undergone perioperative chemotherapy and adequate surgery (D1+), the European CRITICS trial was undertaken in 2007 [53]. The main features of the CRITICS trial compared to MAGIC and INT 0116 are summarized in Table 2. This large, multinational phase III trial randomized 788 patients' status post neoadjuvant chemotherapy and adequate surgical resection to receive either adjuvant chemotherapy or adjuvant chemoradiation. Preliminary results presented at the World Congress on Gastrointestinal Cancer (WCGC) in 2016 showed no survival benefit for chemoradiation vs. chemotherapy; both groups had a 5-year survival of 40% [54]. This again calls into question the benefit of adjuvant radiation and emphasizes that perhaps only a limited number of patients are good candidates for adjuvant therapy and this population remains to be defined. Secondary endpoints such as toxicity and quality of life and subgroup analysis are pending as well. The study does, however, suggest that intensifying neoadjuvant therapies may be a better approach toward improving survival. Indeed, future directions for the CRITICS investigators may include a new study that will compare outcomes between three different neoadjuvant treatments: 1) four courses of chemotherapy; 2) two courses of chemotherapy combined with chemoradiation; versus 3) chemoradiation only.

Ongoing Trials and Future Directions

Table 3 highlights some of the ongoing clinical trials that are currently studying new multimodal combinations for resectable gastric cancer. Assessing the role of perioperative chemoradiation combined with standard regimens of chemotherapy was the focus of ARTIST-II and CRITICS, final results of which are pending. Other trials are studying intensification and diversification of chemotherapeutic regimens. Because participants in previous trials had relatively low completion rates of post-operative treatment, a goal of these newer trials is to reduce toxicity and maximize efficacy of neoadjuvant therapies. Intensification is this setting is better tolerated than when given post-operatively. In the East, Korean and Japanese groups are conducting phase III trials that add docetaxel, oxaliplatin, and/or cisplatin to standard S-1 therapy [55,56].The phase III CAPITAL study (NCT01795027) in China is studying oxaliplatin + S1 in the adjuvant setting, while another Chinese study (NCT01711242) is studying adjuvant XELOX (capecitabine, oxaliplatin) with and without chemoradiation. The German NEO-FLOT trial prolonged preoperative chemotherapy with docetaxel, 5-FU, leucovorin, and oxaliplatin. Phase II results showed an R0 resection rate of 86%, pCR of 20%, and <10% residual tumor [57]. Intensification of perioperative chemotherapy is represented by the FLOT-4 trial, which has randomized 714 patients with resectable gastric cancer to either the standard six cycles of perioperative ECF/ECX or 4+4 cycles of perioperative FLOT. Phase II results from this head-to-head trial have shown more pathological remissions with FLOT than with ECF/ECX [23].

Alternative options such as targeted therapy have been explored. Bevacizumab has not yet shown a survival benefit for resectable gastric cancer, but current and ongoing trials are investigating ramucirumab (NCT02443883), which targets VEGF receptor-2 and has shown improved OS in advanced gastric cancer [31]. The Her FLOT trial (NCT01472029) will combine FLOT with trastuzumab to assess for superior response in HER2-positive adenocarcinoma of the stomach or GEJ. Within the next several years, the results of these trials will be eagerly anticipated and applied toward improving outcomes.

Summary and Recommendations

Surgery with adequate lymph node dissection (at least D1, preferably D2 with preservation of distal pancreas and spleen) remains the only curative option for locoregional gastric adenocarcinoma. In both Western and Eastern populations, adjuvant chemotherapy plays a role in reducing recurrence and improving overall survival after surgery; however, standard pharmaceutical regimens vary globally. The MAGIC and INT 0116 trials have influenced subsequent trials significantly, resulting in systematic combinations of neoadjuvant and adjuvant approaches in both the East and the West. For example, pre-operative chemotherapy added to the standard adjuvant chemotherapy is now under investigation in Japan using S-1.The benefit of adjuvant chemoradiation demonstrated by INT 0116 continues to garner controversy. The recent report from the CRITICS trial that adjuvant chemoradiation did not significantly improve survival in those who had received preoperative chemotherapy and adequate resection will challenge the North American approach defined by INT 0116 even further. Final results and subgroup analyses are anticipated and will be critical for this discussion. The study is not likely to change practice in Europe, where radiation is not yet a first-line treatment for resectable gastric cancer.

Patients with resected N1 disease should be considered for adjuvant chemoradiation as opposed to chemotherapy alone. This recommendation is supported by subset analysis of the ARTIST trial and also the INT 0116 trial, which showed that adequacy of lymph node dissection, correlated with response to chemoradiation. For patients with T2N0 gastric cancer, current data supports either observation after surgery or adjuvant therapy.

As multiple studies have shown improved outcomes after neoadjuvant chemotherapy with or without adjuvant treatment, it is our recommendation that all patients with stage II or higher gastric cancer should be evaluated by a multidisciplinary panel of oncologists and radiation oncologists prior to surgery. Pathological response to neoadjuvant therapy correlates with baseline T and N stage [40] and selects patients who will benefit from further intensive therapy. Indeed, if clinical features are suggestive of a high likelihood of metastasis (e.g. bulky tumor, visible nodes, linitis plastica, positive peritoneal cytology), one should certainly consider neoadjuvant chemotherapy. Based on the preliminary results of the CRITICS trial and the observation that MAGIC and other perioperative chemotherapy trials only enrolled about half of their patients into postoperative chemotherapy, the emphasis on developing and refining neoadjuvant therapies is evident in current and future trials.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65: 87-108.
2. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol. 2007; **5**: 17-26.
3. Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, et al. Recent patterns in gastric cancer: a global overview. Int J Cancer. 2009; 125: 666-673.
4. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol. 2000; 29: 645-564.

5. Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK SEER Cancer Statistics Review 1973-1994, National Cancer Institute, NIH Publication No. 97-2789. Bethesda: Department of Health and Human Services; 1997.

6. National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER 18: 2005-2011). Stat fact sheets: stomach cancer.

7. Green D, Ponce de Leon S, Leon-Rodriguez E, Sosa-Sanchez R. Adenocarcinoma of the stomach: univariate and multivariate analysis of factors associated with survival. Am J Oncol. 2002; 25: 84-89.

8. Msika S, Benhamiche A, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection of gastric cancer. A population-based study. Eur J Cancer. 2000; 36: 390-396.

9. Harrison L, Karpeh M, Brennan M. Extended lymphadenectomy is associated with a survival benefit for node-negative gastric cancer. J Gastrointest Surg. 1998; 2: 126-131.

10. Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. Br J Surg. 2000; 87: 236-242.

11. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006; 355: 11-20.

12. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007; 357: 1810-1820.

13. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3) Gastric Cancer. 2011; 14: 113-123.

14. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001; 345: 725-730.

15. Griffith JP, Sue-Ling HM, Martin I, Dixon MF, McMahon MJ, Axon AT, et al. Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut. 1995; 36: 684-690.

16. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric cancer. 2011; 14: 113-123.

17. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: Long-term results of the MRC randomized surgical trial. Surgical Co-operative Group Br J Cancer. 1999; 79: 1522-1530.

18. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. Journal of Clinical Oncology. 1998; 16: 1490-1493.

19. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Kranenbarg EK, Songun I, et al. Extended lymph node dissection for gastric cancer: Who may benefit? Final results of the randomized Dutch gastric cancer group trial J Clin Oncol. 2004; 22: 2069-2077.

20. Bonenkamp JJ, Hermans J, Sasako M, Welvaart K, Songun I, Meyer S,et al. Extended lymph-node dissection for gastric cancer. N Engl J Med. 1999; 340: 908-914.

21. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. The lancet oncology. 2010; 11: 439-449.

22. Chua YJ, Cunningham D. The UK NCRI MAGIC trial of perioperative chemotherapy in resectable gastric cancer: implications for clinical practice. Annals of surgical oncology. 2007; 14: 2687-2690.

23. Pauligk C, Tannapfel A, Meiler J, Luley KB, Kopp HG, Homann N, et al. Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO. InASCO Annual Meeting Proceedings 2015; 33: 4016.

24. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004; 350: 2335 -2342.

25. Sandler AB, Gray R, Brahmer A, Dowlati A, Schiller JH, Perry MC, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial - E4599. J Clin Oncol. 2005; **23**: 2s.

26. Miller KD, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, et al. E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first line therapy for locally recurrent or metastatic breast cancer. Breast Can Treat Res. 2005; 94: S6.

27. Karayiannakis A, Syrigos KN, Polychronidis A, Zbar A, Kouraklis G, Simopoulos C, et al. Circulating VEGF levels in the serum of gastric cancer patients. Ann Surg. 2002; 236: 37-42.

28. Maeda K, Chung YS, Ogawa S, Takatsuka S, Kang SM, Ogawa M, et al. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. Cancer. 1996; 77: 858-863.

29. Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. Journal of Clinical Oncology. 2006; 24: 5201-5206.

30. Cunningham D, Smyth E, Stenning S, Stevenson L, Robb C, Allum W, et al. 2201 Peri-operative chemotherapy±bevacizumab for resectable gastro-oesophageal adenocarcinoma: Results from the UK Medical Research Council randomised ST03 trial (ISRCTN 46020948). European Journal of Cancer. 2015; 51: S400.

31. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014; 383: 31-39.

32. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, et al. Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. InASCO Annual Meeting Proceedings 2007; 25: 4510.

33. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. Journal of Clinical Oncology. 2010; 28: 5210-5218.

34. Li W, Qin J, Sun YH, Liu TS. Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis. World J Gastroenterol. 2010; 16: 5621-5628.

35. Lowy AM, Mansfield PF, Leach SD, Pazdur R, Dumas P, Ajani JA. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Annals of surgery. 1999; 229: 303.

36. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. Journal of Clinical Oncology. 2009; 27: 851-856.

37. Klevebro F, von Döbeln GA, Wang N, Johnsen G, Jacobsen AB, Friesland S, et al. A randomised clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Annals of Oncology. 2016; 27: 660-667.

38. Ajani JA, Mansfield P, Janjan N, Morris J, Pisters PW, Lynch PM, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol. 2004; 22: 2774-2780.

39. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol. 2006; 24: 3953-3958.

40. Rostom Y, Zaghloul H, Khedr G, El-Shazly W, Abd-Allah D. Docetaxel-based preoperative chemoradiation in localized gastric cancer: impact of pathological complete response on patient outcome. Journal of gastrointestinal cancer. 2013; 44: 162-169.

41. Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. Jama. 2010; 303: 1729-1737.

42. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010; 28: 1547-1553.

43. Ajani JA, Faust J, Ikeda K,Yao JC, Anbe H, Carr KL,et al. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. J Clin Oncol. 2005; 23: 6957-6965.

44. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. The Lancet. 2012; 379: 315-321.

45. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. The Lancet Oncology. 2014; 15: 1389-1396.

46. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. Journal of Clinical Oncology. 2012; 30: 2327-2333.

47. Ashraf N, Hoffe S, Kim R. Adjuvant treatment for gastric cancer: chemotherapy versus radiation. The Oncologist. 2013; 18: 1013-1021.

48. Fuchs CS, Tepper JE, Niedzwiecki D, Hollis D, Mamon HJ, Swanson R, et al. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101. InASCO Annual Meeting Proceedings 2011; 29: 4003.

49. Hundahl SA, Peeters KC, Kranenbarg EK, Hartgrink H, Van De Velde CJ. Improved regional control and survival with "low Maruyama Index" surgery in gastric cancer: autopsy findings from the Dutch D1-D2 Trial. Gastric Cancer. 2007; 10: 84-86.

50. Peeters KC, Hundahl SA, Kranenbarg EK, Hartgrink H, Van De Velde CJ. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. World journal of surgery. 2005; 29: 1576-1584.

51. Dikken JL, Jansen EP, Cats A, Bakker B, Hartgrink HH, Kranenbarg EM, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. Journal of Clinical Oncology. 2010; 28: 2430-2436.

52. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. Journal of clinical oncology. 2012; 30: 268-273.

53. Dikken JL, van Sandick JW, Swellengrebel HM, Lind PA, Putter H, Jansen EP, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer. 2011; 11: 1.

54. Verheij M, Jansen E, Cats A, van Grieken N, Aaronson NK, Boot H, et al. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study. Abstract only. 2016.

55. Kang YK, Yook JH, Ryu MH, Lee JS, Park Y, Chung IJ, et al. A randomized phase III study of neoadjuvant chemotherapy with docetaxel (D), oxaliplatin (O), and S-1 (S)(DOS) followed by surgery and adjuvant S-1 vs. surgery and adjuvant S-1 for resectable advanced gastric cancer (PRODIGY). Abstract only, ASCO Annual Meeting Proceedings 2015; 33: TPS4136.

56. Japan Clinical Oncology Group. Randomized phase III trial of surgery plus neoadjuvant TS-1 and cisplatin compared with surgery alone for type 4 and large type 3 gastric cancer: Japan Clinical Oncology Group Study (JCOG 0501). Clinical Trials. gov NCT00252161.

57. Schulz C, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U, et al. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. International journal of cancer. 2015; 137: 678-685.