Review Article

Emerging issues in multimodality treatment of gastric cancer

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Abstract: In recent years, the treatment of locally advanced resectable gastric cancer has evolved from an exclusively surgical to a multidisciplinary approach including chemotherapy and radiotherapy (RT). Worldwide several evidence-based preoperative and postoperative adjuvant strategies have been implemented in daily clinical practice. The determination of gastric cancer patients that benefit most from certain treatment modalities is a matter of debate. This review covers a comprehensive analysis of outcome and toxicity of clinical trials investigating multimodality treatment for locally advanced resectable gastric cancer to provide insight in patient groups that may benefit from certain treatments. Postoperative chemotherapy as monotherapy and doublet therapy has mainly been evaluated in Asian countries, where its efficacy has been clearly demonstrated. Whereas the added value of postoperative chemotherapy remains to be established in Western patient populations, perioperative doublet and triplet chemotherapy has been shown to improve overall survival (OS) in this part of the world. In addition, postoperative chemoradiotherapy (CRT) as an intensive locoregional treatment has been shown to reduce local recurrence rates and to improve OS. It has been suggested that postoperative CRT may particularly be of additional value in case of a microscopically incomplete R1 resection, a limited lymph node dissection (LND), and/or in case of regional lymph node metastases. Another attractive treatment strategy is preoperative CRT. Phase II trials reported good feasibility and patients' compliance, low toxicity rates, high R0 resection rates, and promising response rates. No results from randomized controlled trials applying preoperative CRT are available yet, but phase III randomized controlled trials investigating this strategy are currently accruing patients. In gastric cancer treatment, hematological and gastrointestinal toxicity are most frequently encountered in both chemotherapy and CRT either given preoperatively or postoperatively. Toxicity rates are higher with doublet and triplet chemotherapy than with monotherapy. Toxicity rates of the newer CRT regimens are lower than those of the older regimens, and lower than those of combination chemotherapy. For both chemotherapy and CRT, toxicity rates seem lower when treatment is given preoperatively, which probably explains the higher compliance with preoperative treatment. Based on multiple adjuvant preoperative and postoperative treatment regimens that have shown efficacy in patients with locally advanced resectable gastric cancer, all patients should be considered for multimodality treatment. Today, for gastric cancer patients the choice for a specific additional modality can only be based on patient and tumor characteristics regarding preoperative treatment, and surgical and pathological results regarding postoperative treatment. Taken together, preoperative chemotherapy and/or CRT are preferable to postoperative regimens. However, this has to be further confirmed in randomized controlled phase III studies.

Keywords: Chemoradiotherapy (CRT), adjuvant; chemotherapy, adjuvant; combined modality therapy; neoadjuvant therapy; stomach neoplasm

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Introduction

Gastric cancer is the fifth most common malignancy worldwide with large geographic differences in incidence (1-3). The highest incidences are encountered in Eastern Asia (3), 35.4 and 5.4 per 100,000 per year for males and females respectively (2). In descending order are the incidences per 100,000 persons per year for males and females respectively 20.3 and 0.8 in Central-Eastern Europe (2), 14.2 and 2.0 in South America (2), 5.5 and 1.1 in Northern America, and 3.3 and 0.4 in Western Africa (2,3). Overall, gastric cancer is twice as common in men compared to women (2,3). These differences in gastric cancer incidence reflect etiologic heterogeneity (3,4).

Gastric cancer is worldwide the third most common cause of cancer death and responsible for 9% of cancer-related death yearly (2). Despite large geographic differences in survival (1-3), overall, mortality rates almost resemble the incidence rates (3). Whereas, the 5-year overall survival (OS) is around 25% in Europe and the United States, this is up to 60% in Asia (2,3,5). The higher survival rates in Asia are ascribed to mass screening programs in Japan, high accuracy of staging that is accompanied by stage migration, and high quality of surgery (3,6-9).

For gastric cancer, surgery remains indispensable for curative treatment. Patients with non-metastasized gastric cancer at diagnosis are eligible for potentially curative surgery if the tumor can be resected with free margins, i.e., resectable gastric cancer. However, even after potentially curative surgery gastric cancer patients have a high risk of locoregional recurrence, peritoneal carcinomatosis and distant metastases, in both Asian and Western countries (10-14). This risk increases with advanced tumor stage and can be as high as 88% locoregional recurrence, 44% peritoneal carcinomatosis, and 49% distant metastases in autopsy series (10). Recurrence patterns are also histological type dependent (15). For example, patients with a diffuse type gastric cancer (16) have a higher risk of peritoneal carcinomatosis than patients with an intestinal type, especially when the tumor has infiltrated the serosa (15).

Different multimodality treatments added to surgery have been investigated for locally advanced resectable gastric cancer. Whereas multiple multimodality strategies have been proven beneficial, which gastric cancer patients benefit most from which treatment modality remains a matter of debate. This review covers a comprehensive analysis of outcome and toxicity of clinical trials investigating multimodality treatment for locally advanced resectable gastric cancer to provide insight in patient groups that may benefit from certain treatments.

Surgery

The obvious goal of surgery is to achieve a microscopically complete resection of the primary tumor, known as an R0 resection, and full clearance of possibly affected regional lymph nodes (17). A microscopically tumor positive luminal resection margin, known as an R1 resection, has been reported in 2-22% of patients (18-21). Irrespective of its association with advanced tumor stage and aggressive tumor biology, an R1 resection has frequently been identified as an independent poor prognostic factor (18,21-24), justifying the use of peroperative frozen sections (25). Clear guidelines regarding patient management in case of an R1 resection are lacking. When an R1 resection is assessed by frozen section examination during surgery and a tumor negative resection margin can still be obtained, extended surgery is a clear option (26). Extended surgery is, however, disputable if that entails a distal esophagectomy or pancreaticoduodenectomy both carrying substantially increased morbidity (27). When an R1 resection is assessed postoperatively, options vary from watchful waiting (28), to re-resection in patients with limited nodal disease (23) or re-resection whenever feasible (20,24). The possible benefit of performing a re-resection is mainly based on the rationale that obtaining tumor negative margins can negate the adverse prognostic impact of tumor positive margins (29).

The development of gastric cancer surgery entailed the selection of patients who could benefit from a partial, instead of a total gastrectomy. Currently it is standard of care to perform a partial gastrectomy when tumor free margins can be obtained in distally located tumors as this is proven safely with regard to tumor control, and is accompanied by beneficial effects on nutritional status, quality of life (30,31) and reduced surgical morbidity and mortality (32,33). However, the risk of an R1 resection in diffuse type gastric cancer according to the Lauren classification (16) is high and may be reason to extend the surgical resection or even to consider a total gastrectomy irrespective of the tumor location, especially in young patients (21).

The extent of the lymph node dissection (LND) has been subject of extensive research. Traditionally, in the East more extended LND, i.e., D2 (lymph node stations 1-11 according to the Japanese classification of gastric cancer) or D3 (lymph node stations 1-14) (34), are routinely

performed and their benefit regarding OS is confirmed by randomized controlled trials (13,14). An even more extended lymphadenectomy including para-aortic lymph nodes, i.e., D4 (lymph node stations 1-16), does not seem to add to the survival benefit (13). In Western countries, a D1 LND (lymph node stations 1-6) used to be common practice and a shift towards standard performance of a D2 LND has in recent years (12,35). The benefit of a D2 LND was not adopted until the 15-year follow-up results of the randomized Dutch Gastric Cancer Trial showed that a D2 LND was associated with significantly less gastric cancer-related death and less local recurrences compared to a D1 LND (12). Short term results had not shown an OS benefit for patients who had undergone a D2 LND compared to a D1 LND (36,37). A similar observation was made in the MRC randomized trial (33). In both trials the lack of benefit on OS was explained by the higher postoperative mortality in the D2-group that was caused by the higher percentages of pancreatico-splenectomies to enable dissection of lymph node stations 10 and 11 (33,37); i.e., the higher short-term mortality offset the long-term benefit on OS. This hypothesis was confirmed by a subgroup analysis of patients who had undergone a D1 or D2 LND without pancreatico-splenectomy that showed a significantly higher 15-year OS in those who had a D2 LND (22% *vs.* 35%; HR, 1.34; 95% CI: 1.09-1.65; P=0.006) (12). Patients with advanced disease and lymph node metastases may benefit more from a D2 LND than those with limited disease (37,38), except for patients with lymph node metastases in the splenic hilus (lymph node station 10). Nodal metastases at this site indicate a very poor prognosis which will not improve after removal of the affected lymph nodes that necessitates a splenectomy (25,37). At current times, surgeons are advised to perform a D2 LND involving lymph node stations 1-9 and 11 with the removal of at least 15 nodes without routine spleen and pancreatic tail resection, sometimes also nominated as a D1+ LND (12,17). With this approach, surgical mortality and morbidity rates can be reduced, as confirmed by an Italian randomized D1-D2 trial (38). Taken together, in recent years this has led to the adoption of the standard performance of a D2 LND in Western countries.

In general, a D2 LND reduces the risk of locoregional recurrence down to 7-28% (11,13,14), but does not influence the risk of peritoneal carcinomatosis or distant metastases (11-14). Also, although gastric cancer surgery has been optimized and the 5-year OS has been improved, the prognosis still remains dismal. Hence, disappointing long-term results after optimal surgery emphasize the need to develop multimodality treatments that are more effective.

Chemotherapy

Postoperative chemotherapy

The rationale for adding postoperative chemotherapy to the treatment of locally advanced resectable gastric cancer is to improve OS by eradicating remaining micrometastases that upon outgrowth are responsible for relapse. Multiple, predominantly fluoropyrimidine-based, postoperative chemotherapy regimens have been investigated resulting in conflicting evidence of efficacy, with mainly positive results for trials conducted in Asia and negative results for trials conducted in Western countries (*Table 1*).

One of the first clinical trials that clearly showed survival benefit by adding postoperative chemotherapy was conducted in Japan (41). Patients (n=1,059) were randomized after potentially curative surgery including at least a D2 LND, for observation-only *vs.* postoperative treatment with S-1 monotherapy for 1 year. The results of the first interim analysis were disclosed because the 3-year OS in the S-1 group was significantly higher: 80.1% *vs.* 70.1% (HR, 0.68; 95% CI: 0.52-0.87; P=0.003) (41). This was later confirmed by a significantly higher 5-year OS: 71.7% *vs.* 61.1% (HR, 0.67; 95% CI: 0.54-0.83) (42). These results have led to standard postoperative treatment with S-1 after surgery for stage II and III gastric cancer patients in Japan and other East-Asian countries (45).

Another postoperative chemotherapy regimen for stage II and III gastric cancer consists of capecitabine in combination with oxaliplatin (CAPOX) that has been investigated in Korea (40,45). Data of this so-called CLASSIC trial (n=1,035) have not been finalized yet, but the results of the first interim analysis were also disclosed because the 3-year disease free survival (DFS) was significantly higher in patients randomized for 6 months capecitabine and oxaliplatin than those randomized for observation-only after surgery in combination with a D2 LND: 74% *vs.* 59% (HR, 0.56; 95% CI: 0.44-0.72; P<0.0001). A trend towards improved OS in the CAPOX-arm was also observed after 3 years (HR, 0.72; 95% CI: 0.52-1.00; P=0.0493). The data are however immature and patient follow-up is ongoing (40). The addition of postoperative CAPOX seemed to reduce locoregional recurrences and distant metastases, but not peritoneal carcinomatosis (40). The addition of postoperative S-1, on the other hand, significantly reduced locoregional

Table 1 Selection of five most recent randomized clinical trials investigating postoperative chemotherapy for locally advanced resected gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Tsuburaya *et al*. 2014 (39)	1: 12 cycles UFT 267 mg/m^2/day p.o. on days 1-28, q 4 weeks (57% of patients completed 12 cycles); 2: 16 cycles S-1 80 mg/m^2 bid. p.o. on days 1-14, q 3 weeks (60% of patients completed 16 cycles); 3: 3 cycles Pac 80 mg/m^2/day i.v. on days 1, 8 (and 15), q 3-4 weeks, followed by 9 cycles UFT 267 mg/m^2/day p.o. on days 1-28, q 4 weeks (65% of patients completed 12 cycles); 4: 3 cycles Pac 80 mg/m^2/day i.v. on days 1, 8 (and 15), q 3-4 weeks, followed by 12 cycles S-1 80 mg/m^2 bid. p.o. on days 1-14, q 3 weeks (67% of patients completed 15 cycles)						
	T4a-4b	1: 374; 2: 374; 3: 374; 4: 373	1+2+3+4, R0: NR; R1: NR	1+2+3+4, D1: 0; D2: 100	3-year 1+2: 54 *vs*. 3+4: 57; 1+3: 53 *vs*. 2+4: 58*	3-year 1+2: 56 *vs*. 3+4: 59; 1+3: 54 *vs*. 2+4: 61*	1: NR; 2: NR; 3: NR; 4: NR
Bang *et al*. 2012 (40)	A: observation, subjected to regular follow-up; B: 8 cycles Cap 1,000 mg/m^2 bid. p.o. on days 1-14, + Ox 130 mg/m^2/day i.v. on day 1, q 3 weeks (67% of patients completed 8 cycles)						
	Stage II-IIIB	A: 515; B: 520	A+B R0: 100; R1: 0	A+B D1: 0; D2: 100; D3: NR	3-year, A: 59; B: 74*	3-year, A: 78; B: 83*	A: –; B: –
Sakuramoto *et al*. 2007 and Sasako *et al*. 2011 (41,42)	A: observation, subjected to regular follow-up; B: for 1 year S-1 40 mg/m^2 bid p.o. on days 1-28, q 6 weeks (64% of patients completed 1 year of treatment)						
	Stage II-III	A: 530; B: 529	A+B R0: 100; R1: 0	A+B D1: 1; D2: 998; D3: 60	A: 53; B: 65*	A: 62; B: 76*	A: –; B: –
Kulig *et al*. 2010 (43)	A: observation, subjected to regular follow-up; B: 3 cycles Etop 120 mg/m^2/day i.v. on days 4, 5, 6, + Dox 20 mg/m^2/day i.v. on days 1, 7, + Cis 40 mg/m^2/day i.v. on days 2, 8, q 4 weeks (65% of patients completed 3 cycles)						
	T2-4/N– or T1-4/N+	A: 154; B: 155	A+B R0: 100; R1: 0	A: D1 31 [20], D2 51 [33], D3 72 [47]; B: D1 29 [21], D2 49 [35], D3 63 [44]	A: 45; B: 51	A: 40; B: 44	A: 36; B: 41
Di Costanzo *et al*. 2008 (44)	A: observation, subjected to regular follow-up; B: 4 cycles Cis 40 mg/m^2/day i.v. on days 1, 5, + Epi 30 mg/m^2/day i.v. on days 1, 5, + LV 100 mg/m^2/day i.v. on days 1-4, + 5-FU 300 mg/m^2/day i.v. on days 1-4, q 3 weeks (58% of patients completed 4 cycles)						
	Stage IB-IV (T4N2M0)	A: 128; B: 130	A+B R0: 256 [99]; R1: 2 [1]	A+B D1: 93 [36]; D2: 110 [43]; D3: 28 [11]; D4: 5 [2]	A: 42; B: 42	A: 49; B: 48	A: 58; B: 57

Treatment completion rates are calculated in reference to all the randomized patients per arm, and include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. *, significantly different; –, outcome not yet available. LND, lymph node dissection; DFS, disease free survival; OS, overall survival; UFT, Tegafur-Uracil; S1, S1-fluoropyrimidine; Pac, paclitaxel; R0, microscopically complete resection; R1, microscopically incomplete resection; NR, not reported; D1, lymph node stations 1-6; D2, lymph node stations 1-11; D3, lymph node stations 1-14; Cap, capecitabine; Ox, oxaliplatin; Etop, etoposide; Dox, doxorubicin; Cis, cisplatin; Epi, epirubicin; LV, leucovorin; 5-FU, 5-fluorouracil.

recurrences and peritoneal carcinomatosis, but not distant metastases (41). Together, these large-scale Asian trials provide sufficient evidence for the efficacy of postoperative fluoropyrimidine-based chemotherapy after potentially curative surgery in combination with a D2 LND.

The most recently published Asian trial investigating postoperative chemotherapy for gastric cancer, Stomach cancer Adjuvant Multi-Institutional group Trial (SAMIT, n=1,495), compared four treatment groups in a two-by-two factorial design (39). The four treatments consisted of UFT-monotherapy, S-1 monotherapy, paclitaxel followed by UFT, and paclitaxel followed by S-1. Sequential chemotherapy treatment did not improve DFS nor OS compared to monotherapy. S-1 seemed superior to UFT (3-year DFS UFT: 53.0%; 95% CI: 49.2-56.6; S-1: 58.2%; 95% CI: 54.4-61.8; HR, 0.81; 95% CI: 0.70-0.93; P=0.0048; P non-inferiority =0.151).

Multiple randomized controlled trials investigating postoperative chemotherapy for resected gastric cancer have been conducted in the West (43,44,46-49). And yet, none of these has provided similar positive results as the Asian trials. The lack of effectiveness was initially ascribed to the use of old regimens (46,47) but newer regimens did not prove to be effective either (44,48,49). Multiple factors have been suggested to play a role in the different outcomes after chemotherapy for Asian and Western populations, among others patient- and tumor characteristics including ethnic variability in genes regarding the drug metabolizing enzymes (40,42,50,51), the poor compliance of patients to the full chemotherapy regimen (44), the use of different surgical techniques (45) or the small sample sizes. Several meta-analyses have been performed to investigate a possible positive effect of postoperative chemotherapy, but also showed conflicting results (52-56). The (subgroup) meta-analysis that included only Western trials showed a non-significant small benefit of postoperative chemotherapy for resectable gastric cancer (53,55,57). Hence, postoperative chemotherapy is not routinely advised for gastric cancer patients in the West (35).

Preoperative and perioperative chemotherapy

The main rationale for administration of preoperative chemotherapy is to improve OS by eradicating micrometastases as early as possible and to improve surgical results by downsizing and/or downstaging of the tumor (*Table 2*). The first randomized controlled trials that observed a beneficial effect of adding perioperative chemotherapy for resectable gastric cancer was the British Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC, n=503) trial (60). Patients were randomly assigned to surgery-only or preoperative chemotherapy followed by surgery and postoperative chemotherapy, consisting of epirubicine, cisplatin and fluorouracil. The results showed significantly improved R0 resection rates, 5-year relapse-free survival (HR, 0.66; 95% CI: 0.53-0.81; P<0.001) and an absolute 5-year OS benefit of 13% for the perioperative chemotherapy-arm (36% *vs.* 23%; HR, 0.75; 95% CI: 0.60-0.93; P=0.009). The benefits of perioperative chemotherapy were not at the cost of higher surgical morbidity and mortality (60). The French FNCLCC-FFCD trial (n=224) was the second randomized controlled trial in which the role of perioperative chemotherapy in gastric cancer was investigated, although in the majority of patients the tumor was located in the lower esophagus or at the gastro-esophageal junction (58). In this trial chemotherapy consisted of 2-3 preoperative and 3-4 postoperative cycles of fluorouracil and cisplatin, to a total of 6 cycles. Again, perioperative chemotherapy significantly improved R0 resection rates (84% *vs.* 73%; P=0.04), 5-year DFS and 5-year OS, without increasing surgical morbidity and mortality (58). After perioperative chemotherapy both local (60) or locoregional recurrences (58) and distant metastases were decreased (58,60). Consequently, in Europe perioperative chemotherapy became the new standard of care in patients with resectable gastric cancer (35).

More recently, multiple phase II and III studies investigating preoperative chemotherapy have also been initiated in Asia (45,62-64). In Asia, this approach was firstly investigated in patients who are at high risk for peritoneal carcinomatosis and distant metastases, i.e., locally advanced marginally resectable Bormann type 3 and 4 (65), para-aortic/bulky nodal disease (66), and/or serosa positive/T4a (67) gastric cancer. Phase III trials are initiated following promising results of phase II trials. For example, the JCOG 0501 trial randomizes patients with resectable Bormann type 3 or 4 gastric cancer for surgery followed by postoperative S-1 for 1 year, *vs.* perioperative chemotherapy consisting of 2 preoperative cycles S-1 and cisplatin followed by surgery and postoperative S-1 for 1 year (ClinicalTrials.gov number NCT00252161). The results of these trials will contribute to define the role of preoperative chemotherapy in Asia.

In the MAGIC and FNCLCC-FFCD trials a significant proportion of the patients could not start and/or complete postoperative chemotherapy as planned (58,60).

Table 2 Randomized clinical trials investigating preoperative or perioperative chemotherapy for locally advanced initially resectable gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Ychou *et al*. 2011† (58)	A: surgery only; B: preoperatively 2-3 cycles 5-FU 800 mg/m^2/day i.v. on days 1-5, + Cis 100 mg/m^2/day i.v. on day 1, q 4 weeks (87% of patients completed 2-3 cycles), and postoperatively 3-4 cycles 5-FU/Cis as described before (36% of patients completed 3-4 cycles) to a total of 6 cycles (NR what % completed 6 cycles)						
	Resectable adenocarcinoma	A: 111; B: 113	A: R0 81 [73]; B: R0 95 [84]	A: D0-2 NR; B: D0-2 NR	A: 19; B: 34*	A: 24; B: 38*	A: NR; B: NR
Schuhmacher *et al*. 2010† (59)	A: surgery only; B: preoperative 2 cycles Cis 50 mg/m^2/day i.v. on days 1, 15, 29, + LV 500 mg/m^2/day i.v. on days 1, 8, 15, 22, 29, 36, + 5-FU 2,000 mg/m^2/day i.v. on days 1, 8, 15, 22, 29, 36 (63% of patients completed 2 cycles)						
	Resectable adenocarcinoma stage III-IV (M0)	A: 72; B: 72	A: R0 48 [67]; B: R0 59 [82]	A: D1 5 [7], D2 63 [88]; B: D1 2 [3], 67 [93]	A: NR; B: NR	2-year, A: 70; B: 73	A: 53; B: 65
Cunningham *et al*. 2006† (60)	A: surgery only; B: preoperatively 3 cycles Epi 50 mg/m^2/day i.v. on day 1, + Cis 60 mg/m^2/day i.v. on day 1, + 5-FU 200 mg/m^2/day i.v. on days 1-21, q 3 weeks (86% of patients completed 3 cycles), and postoperatively 3 cycles Epi/Cis/5-FU as described before (42% of patients completed 3 cycles) to a total of 6 cycles (41% completed 6 cycles)						
	Resectable adenocarcinoma stage II-IV (M0)	A: 253; B: 250	A: R0 166 [66]; B: R0 169 [68]	A: D1 50 [20], D2 96 [38]; B: D1 39 [16], D2 93 [37]	A: NR; B: NR	A: 23; B: 36*	A: NR; B: NR
Hartgrink *et al*. 2004‡ (61)	A: surgery only; B: preoperatively 4 cycles 5-FU 1,500 mg/m^2/day i.v. on day 2, + LV 30-60 mg/m^2/6h i.v. on days 3, 4, + Dox 30 mg/m^2/day i.v. on day 15, + MTX 1,500 mg/m^2/day i.v. on day 2, q 4 weeks (52% of patients completed 4 cycles)						
	Resectable adenocarcinoma >T1 (M0)	A: 30; B: 29	A: R0 19 [63]; B: R0 18 [62]	A: D0-2 NR; B: D0-2 NR	A: NR; B: NR	A: 34; B: 21	A: 30; B: 18

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. *, significantly different; †, included also patients with adenocarcinoma of the lower third of the oesophagus or gastro-esophageal junction; ‡, trial was prematurely closed. LND, lymph node dissection; DFS, disease free survival; OS, overall survival; 5-FU, 5-fluorouracil; Cis, cisplatin; NR, not reported; R0, microscopically complete resection; D0, no removal of lymph node stations; D1, lymph node stations 1-6; D2, lymph node stations 1-11; LV, leucovorin; Epi, epirubicin; Dox, doxorubicin; MTX, methotrexate.

Therefore, the beneficial effect observed in these trials is often attributed to the preoperative chemotherapy only. Subsequently, studies that investigate the benefit of purely preoperative chemotherapy were again initiated. An example is the EORTC 40954 trial (n=144), that randomized patients for surgery-only or preoperative chemotherapy followed by surgery. This trial was closed prematurely due to a low accrual rate, and failed to demonstrate an OS benefit despite the significant higher R0 resection rate in the preoperative chemotherapy group (59). Today, it remains difficult to acknowledge the beneficial effect of preoperative and postoperative chemotherapy separately.

Toxicity of and treatment compliance with chemotherapy

The most common adverse events of preoperative and/or postoperative chemotherapy in gastric cancer patients were hematological and gastrointestinal (40,41,58,60). Less severe toxicity, grade 1 and 2, was very common in this patient population (40,41,58,60). Especially with combination chemotherapy, grade 1 and 2 side effects can be present in up to 99% of patients (40,58,60). The common occurrence

Table 3 Grade 3-4 hematological and gastrointestinal toxicity of preoperative and postoperative chemotherapy reported in selected clinical trials

Toxicity grade 3-4	Bang *et al.*[1] (40)	Sakuramoto *et al.*[2] (41)	Ychou *et al.*[3] (58)	Cunningham *et al.*[4] (60)
Granulocytopenia/ neutropenia (%)	22	NR	20; NR	22; 27
Leukopenia (%)	0	1	6; NR	11; 11
Thrombocytopenia (%)	8	0.2	6; NR	0.4; 3
Nausea (%)	8	4	9[§]; NR	6; 12
Vomiting (%)	7	1	9[§]; NR	5; 10
Anorexia/decreased appetite (%)	5	6	NR	NR
Diarrhea (%)	2	3	2; NR	3; 4

[1], percentages relative to 496 patients who received at least 1 cycle of CAPOX; [2], percentages relative to 517 patients who received S-1; [3], percentages relative to 109 patients who started preoperative chemotherapy. Percentages of toxicity during postoperative chemotherapy not reported; [4], percentages relative to 237 patients who started preoperative chemotherapy and 137 patients who started postoperative chemotherapy. [§], percentage reported for nausea and vomiting combined. NR, not reported.

of adverse events is reflected in the high percentages of chemotherapy dose modifications up to 42-90% (40,41).

More severe toxicity, grade 3 and 4, was present in up to 27% of patients per scored item (*Table 3*). In comparison to the patients who were treated with surgery-only, several severe grade 3-4 adverse events were more common in the patients treated with chemotherapy (40,41). Unfortunately not all before mentioned trials reported adverse events for the surgery-only group, hampering comparison (58,60). Interestingly, no significant differences in preoperatively and postoperatively occurring adverse events was found in the MAGIC trial (60), which could be explained by the selection of patients that started postoperative chemotherapy. Severe side effects depend on the chemotherapy regimen and were reported more frequently for combination chemotherapy compared to for example S-1 monotherapy with the exception of anorexia (40,41,58,60). This finding was also observed in the SAMIT trial with the exception of anorexia, nausea and vomiting (39). The reported percentages of deceased patients related to the treatment with chemotherapy were between 0-3% (39-41,43,44,58,60).

In the MAGIC trial 5% of patients stopped preoperative chemotherapy due to toxicity. Reasons for discontinuation of postoperative chemotherapy were not reported (60). In the FNCLCC-FFCD trial toxicity was the main reason to discontinue preoperative chemotherapy in 8% of patients, reasons for discontinuation of postoperative chemotherapy were again not reported (58). Discontinuation of postoperative S-1 due to adverse events or complications occurred in 14% (41) and discontinuation of CAPOX because of adverse events occurred in 10% of patients (40). However, this might be an underestimation due to the selection of patients for these trials who had to be well recovered after surgery.

In the five most recent randomized controlled trials that investigated postoperative chemotherapy (*Table 1*), compliance with the entire treatment regimen was 58-67% (39-41,43,44). In these trials, no information on the number of patients who were not eligible for postoperative treatment (and thus not for the trial), was provided. This limits the opportunity to discuss feasibility and treatment compliance with postoperative chemotherapy in a clinical setting. In the MAGIC and the FNCLCC-FFCD trial, compliance with chemotherapy was higher when administered before surgery than after surgery. While more than 95% and 85% (or 90% of those started) of patients could start and complete preoperative chemotherapy respectively, only around 50% and 40% (or 75% of those started) could start and complete postoperative chemotherapy respectively (58,60).

Chemoradiotherapy (CRT)

Postoperative CRT

The high rate of locoregional recurrences after potentially curative surgery for advanced gastric cancer makes CRT an attractive postoperative treatment modality (*Table 4*).

Table 4 All randomized clinical trials investigating postoperative chemoradiotherapy for locally advanced resectable gastric cancer

Trial	Inclusion	N	Radicality of resection (%)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Lee *et al*. 2012 (68)	A: 6 cycles Cap 1,000 mg/m^2 bid. p.o. on days 1-14, + Cis 60 mg/m^2/day i.v. on day 1, q 3 weeks (75% of patients completed 6 cycles); B: 2 cycles Cap/Cis as described above, followed by RT 45 Gy + Cap 825 mg/m^2 bid p.o. for 5 weeks, followed by 2 cycles Cap/Cis as described above (chemotherapy completion rate: 82%, RT completion rate: 87%, overall completion rate: 82%)						
	Stage II-IV (M0)	A: 228; B: 230	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 458 [100]	3-year A: 74.2; B: 78.2	3-year, A: –; B: –	A: –; B: –
Yu *et al*. 2012‡ (69)	A: 5 cycles 5-FU 425 mg/m^2/day i.v. on days 1-5 + LV 25 mg/m^2/day i.v. on days 1-5, q 4 weeks (100% of patients completed 5 cycles) B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU 400 mg/m^2/day i.v./LV 25 mg/m^2/day i.v. on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 88%, RT completion rate: 88%, overall completion rate: 88%)						
	T3-4 and/or N+	A: 34; B: 34	A + B R0: 100; R1: 0	A + B D1: 21 [31]; D2: 47 [69]	3-year A: 29.4; B: 55.8*	3-year A: 44.1; B: 67.7*	A: –; B: –
Zhu *et al*. 2012¶ (70)	A: 5 cycles 5-FU 400 mg/m^2/day i.v. on days 1-5 + LV 20 mg/m^2/day i.v. on days 1-5, q 4 weeks (94% of patients completed 5 cycles); B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU/LV as described above on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 95%, RT completion rate: 96%, overall completion rate: 91%)						
	T3-4 and/or N+	A: 175; B: 205	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 380 [100]	A: 35.8; B: 45.2*	A: 41.8; B: 48.4	A: 38; B: 54
Kim *et al*. 2012‡ (71)	A: 5 cycles 5-FU 425 mg/m^2/day i.v. on days 1-5 + LV 20 mg/m^2/day i.v. on days 1-5, q 4 weeks (93% of patients completed 5 cycles); B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU 400 mg/m^2/day i.v./LV 20 mg/m^2/day i.v. on RT-days 1-4 and 29-31, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 91%, RT completion rate: 89%, overall completion rate: 87%)						
	Stage III-IV (M0)	A: 44; B: 46	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 90 [100]	A: 50; B: 61	A: 55; B: 65	A: NR; B: NR
Kwon *et al*. 2010‡ (72)	A: 6 cycles 5-FU 1,000 mg/m^2/day i.v. on days 1-5, + Cis 60 mg/m^2/day i.v. on day 1, q 3 weeks (73% of patients completed 6 cycles, including patients with delays and dose reductions); B: 1 cycle 5-FU/Cis as described above, followed by RT 45 Gy + Cap 825 mg/m^2 bid. p.o. on RT-days, followed by 3 cycles 5-FU/Cis as described above (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 74%)						
	Stage IIIA-IV (M0)	A: 30; B: 31	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 61 [100]	A: 59.1; B: 76.7	A: 70.0; B: 70.1	A: –; B: –
Kim *et al*. 2005& (73)	A: Observation, subjected to regular follow-up; B: 1 cycle 5-FU 400 mg/m^2/day i.v. on days 1-5 + LV 20 mg/m^2/day i.v. on days 1-5, followed by RT 45 Gy + 5-FU/LV as described before on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described before on days 1-5, q 4 weeks (chemotherapy completion rate: 78%, RT completion rate: 86%, overall completion rate: 75%)						
	Stage IB-IV (M0)	A: 446; B: 544	A + B R0: 100; R1: 0	A + B D1: 0 [0], D2: 990 [100]	A: 47.9; B: 54.5*	A: 51.0; B: 57.1*	A: 62.6; B: 95.3*
Macdonald *et al*. 2001 and Smalley *et al*. 2012 (74,75)	A: observation, subjected to regular follow-up; B: 1 cycle 5-FU 425 mg/m^2/day i.v. on days 1-5 + LV 20 mg/m^2/day i.v. on days 1-5, followed by RT 45 Gy + 5-FU 400 mg/m^2/day i.v./LV 20 mg/m^2/day i.v. on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU 425 mg/m^2/day i.v. on days 1-5 + LV 20 mg/m^2/day i.v. on days 1-5, q 4 weeks (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 64%)						
	Stage IB-IV (M0)	A: 275; B: 281	A + B R0: 100; R1: 0	A + B D0: NR [54]; D1: 199 [36]; D2: 54 [10]	3-year A: 31; B: 48*	A: 25, B: 42*	A: 27; B: 36*

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. –, outcome not yet available; *, significantly different; ‡, trial was prematurely closed; ¶, per protocol analysis available only; &, not a randomized clinical trial. LND, lymph node dissection, DFS, disease free survival, OS, overall survival; Cap, capecitabine; Cis, cisplatin; RT, radiotherapy; R0, microscopically complete resection; R1, microscopically incomplete resection; D0, no removal of lymph node stations; D1, lymph node stations 1-6; D2, lymph node stations 1-11; 5-FU, 5-fluorouracil; LV, leucovorin; NR, not reported.

The first randomized study that observed an OS benefit for gastric cancer patients by adding another treatment modality was the US intergroup-0116 trial (n=556) (74). This trial randomly assigned patients who had undergone an R0 resection to observation-only or postoperative CRT. Postoperative CRT, consisting of 45 Gy irradiation with concurrent fluorouracil/leucovorin on radiotherapy (RT) days 1-4 and 31-33, and preceded by 1 cycle and followed by 2 cycles of fluorouracil/leucovorin during 5 days, improved the median OS by 9 months (36 *vs*. 27 months; HR, 1.35; 95% CI: 1.09-1.66; P=0.005) and the median relapse-free survival by 11 months (30 *vs*. 19 months; HR, 1.52; 95% CI: 1.23-1.86; P<0.001) (74). In the updated analysis of this trial at a median follow-up time of 10 years for living patients, the benefit of postoperative CRT persisted equally strongly (HR for OS 1.32; 95% CI: 1.10-1.60; P=0.0046; HR for RFS 1.51; 95% CI: 1.25-1.83; P<0.001) (75). The lower rate of locoregional recurrence in the postoperative CRT group compared to the observation-only group (24% *vs*. 47%) confirms that the survival benefit of CRT is mainly caused by increased locoregional control. These results have led to the standard use of postoperative CRT in the United States (76,77). In Europe and Asia the administration of postoperative CRT is limited to specific indications (35,45).

Several data indicate that postoperative CRT is especially effective in gastric cancer patients with lymph node positive disease. The ARTIST trial (n=458), in which patients were randomized to postoperative CRT including 4 cycles chemotherapy *vs*. chemotherapy-only after an R0 resection with a D2 LND, showed no significant difference in DFS between study arms. However, for patients with pathological tumor positive lymph nodes, DFS at 3 years was significantly better in the CRT-arm (77.5%) than in the chemotherapy-arm (72.3%) (68). In addition, a survival benefit for node positive gastric cancer patients treated with RT was reported by a meta-analysis performed by Ohri *et al*. (HR, 0.73; 95% CI: 0.62-0.86; P<0.001) (78). Furthermore, in the prospective trials with beneficial outcomes, the majority of patients had node positive disease (69-71,73,74), and subgroup analysis suggests a stronger benefit when more lymph nodes are affected (75).

As the majority of patients in the INT-0116 trial had undergone a D0 LND (54%) (74), it has been argued that postoperative CRT compensated for suboptimal surgery although subset analysis did not show a lack of benefit for patients with a D2 LND (75). Thereafter, several studies have investigated the efficacy of postoperative CRT after a D2 LND but thus far no conclusive evidence has been provided (68-73,78,79). The largest of these studies, an Korean observational study (n=990) with a similar CRT regimen as in the INT-0116 trial, showed a significant relapse free and OS benefit for patients treated with postoperative CRT after D2 gastric cancer surgery compared to patients who were treated with D2 surgery alone (73). In a Chinese trial (n=380) by Zhu *et al*. in which patients were randomized to postoperative CRT *vs*. chemotherapy after an R0 gastric cancer resection with a D2 LND, the 5-year local recurrence rate was significantly decreased in the CRT-arm (70), which was also observed in similarly designed other studies (69,71). In a second Chinese trial (n=68) that was prematurely closed, also a significantly increased OS for patients treated with postoperative CRT was observed (69). The abovementioned meta-analysis showed a significantly improved DFS after D2 surgery followed by CRT, but not an improved OS (78). The detection of an OS benefit was hampered by the small sample size. Also, all studies used for the analysis tested CRT against chemotherapy. Moreover, the heterogeneity of the included trials regarding RT treatment regimens was large (78). Taken together, postoperative CRT reduces locoregional recurrences (69,73,74,78,79) that results in a survival benefit (69,73,74,78), also after adequate D2 gastric cancer surgery (69,73).

As yet, postoperative CRT in gastric cancer treatment has been investigated almost invariably in patients who had undergone an R0 resection (68-74). However, as postoperative CRT increases locoregional control after surgery, patients with an R1 resection may benefit from such intensified local treatment as well. In a retrospective analysis (n=83) from Dikken *et al*. postoperative CRT after an R1 resection decreased the local recurrence rate (6% *vs*. 29% in the surgery-only R1 group, HR, 5.36; P=0.02) and improved the 2-year OS rate (66% *vs*. 29% in the surgery-only R1 group, HR, 2.91; P=0.002) (79). Another retrospective study (n=110) found that in patients treated with postoperative CRT after an R0 or R1 resection, an R1 resection was not associated with a higher tumor recurrence rate, nor did it lead to poorer OS (80). This finding suggests that the poor prognosis associated with an R1 resection may be offset by the use of postoperative CRT. This hypothesis was further investigated in a national Dutch cohort study (n=409). OS after an R1 resection was better in patients who were treated with postoperative CRT compared to patients who did not receive postoperative CRT (81). These results lend support to the use of postoperative CRT in patients who have undergone an R1 gastric cancer resection.

Preoperative CRT

CRT can be administered preoperatively in patients with advanced disease in order to improve R0 resection rates by downstaging and to enhance locoregional tumor control (*Table 5*). Major concerns of applying this strategy for gastric cancer were delay of or withdrawal from surgery due to toxicity of the CRT, and an increase in surgical morbidity and mortality. To our knowledge no randomized controlled trial applying this strategy in gastric cancer has been completed nor published. In contrast, in patients with esophageal and gastro-esophageal junction cancer, there is convincing evidence from randomized controlled trials that preoperative CRT leads to improved OS (88,94). The phase III German trial (n=62) by Stahl *et al*. that was prematurely closed, randomized patients with an adenocarcinoma located at the gastro-esophageal junction for induction chemotherapy followed by preoperative CRT and surgery *vs*. preoperative chemotherapy followed by surgery (88). CRT consisted of 2 cycles' induction chemotherapy of fluorouracil, leucovorin and cisplatin, followed by 30 Gy irradiation in 3 weeks with concurrent cisplatin and etoposide. Chemotherapy consisted of 2.5 cycles of fluorouracil, leucovorin and cisplatin. Analysis showed a trend towards higher pathological complete response (pCR) and improved OS in the CRT-arm. The currently accruing TOP GEAR trial initiated by the Australasian Gastro-Intestinal Trials Group (ClinicalTrials.gov number NCT01924819) randomizes patients with resectable gastric or gastro-esophageal junction cancer for perioperative chemotherapy and surgery *vs*. induction chemotherapy, followed by preoperative CRT, surgery and postoperative chemotherapy. This trial has not completed accrual yet, and results have to be awaited.

For gastric cancer specifically, several phase I and II studies have investigated the feasibility and efficacy of preoperative CRT since 2002 (*Table 5*) (82-87,89-93). In all of these studies preoperative CRT has been documented as a feasible treatment strategy, because toxicity of CRT was not the predominant reason of withdrawal from surgery. Indeed, 73-100% of patients could complete the preoperative CRT as planned, and 76-100% could proceed to surgery. Furthermore, surgical mortality rates (0-8%) were well within the range of reported percentages in trials investigating surgery-only (37,95). Encouraging R0 resection rates of 67-92% and pCR rates of 5-29% have been reported (82-93). Locoregional control was reported in approximately 70-80% at 5-year (96,97). Distant metastases have been frequently reported as most common site of relapse (85,87,89,97). This is also true for peritoneal carcinomatosis (82,91,96) while this was significantly decreased after preoperative CRT for esophageal cancer (98).

The high pCR rates raise the question whether preoperative CRT could also induce resectability in patients with locally advanced, but initially irresectable gastric cancer. In the phase I/II study by Trip *et al*., a subset of patients initially had irresectable disease without signs of peritoneal carcinomatosis confirmed by laparoscopy and without signs of distant metastases on diagnostic imaging (82). Eight out of 12 patients (67%) with initially irresectable gastric cancer underwent R0 surgery after preoperative CRT. In this study, preoperative CRT consisted of RT to a total dose of 45 Gy with concurrent weekly paclitaxel and carboplatin.

Toxicity of and treatment compliance with CRT

In general CRT for gastric cancer is an intense but feasible regimen. Several different CRT regimens were used in clinical trials, of which toxicity rates vary (*Table 6*). In several studies a treatment regimen according to the INT-0116 trial was administered postoperatively. Patients suffered most from hematological (7-54%) and gastrointestinal (1-33%) toxicity grade 3 or higher (69,70,73,74). Based on developments in chemotherapeutic agents, and concurrent CRT regimens in other types of cancer, Jansen *et al*. performed a series of phase I/II studies to optimize concurrent postoperative CRT for gastric cancer with the aim to define a less toxic regimen. The RT dose was set at 45 Gy, and the concurrent chemotherapy consisted of capecitabine with or without cisplatin (99-101). Acute toxicity was low with 7% grade 3-4 hematological, 5% grade 3-4 nausea, and 2% grade 3-4 vomiting. Similar toxicity rates were observed in other phase III trials that administered postoperative RT in combination with concurrent capecitabine only (68,72).

Although preoperative CRT is not yet investigated in randomized controlled phase III trials, the reported toxicity rates in phase II trials were in line with toxicity rates of postoperative CRT, and for specific regimens even lower. Nonetheless, it remains difficult to conclude that either preoperative or postoperative CRT is less toxic, because the toxicity profiles of preoperative and postoperative CRT have not yet been compared in a randomized controlled phase III trial and because of the use of different CRT regimens. Notable, however, are the low toxicity rates

Table 5 All pilot and phases 1-3 clinical trials investigating preoperative chemoradiotherapy for locally advanced gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	Surgical mortality (n, %)	pCR (n, %)
Trip *et al*. 2014[†] (82)	RT 45 Gy + Pac 50 mg/m^2/day i.v. on RT-days 1, 8, 15, 22, 29 + Car AUC 2 i.v. on RT-days 1, 8, 15, 22, 29 (chemotherapy completion rate: 92%, RT completion rate: 96%, overall completion rate: 92%), followed by surgery (88% of patients proceeded to surgery)					
	Resectable and irresectable T3-4/N0-2	25	R0: 18 [72]; R1: 3 [12]; R2: 1 [4]	D1: 13 [52]; D2: 9 [36]	1 [4]	4 [16]
Matsuda *et al*. 2014 (83)	RT 40 Gy + S-1 80-120 mg p.o. on RT-days 1-15 + Cis 15-25 mg/m^2/day i.v. on RT-days 1, 15, followed by S-1 80-120 mg p.o. on days 1-28 + Cis 15-25 mg/m^2/day i.v. on days 1, 15, 29 (chemotherapy completion rate: 89%, RT completion rate: 89%, overall completion rate: 89%), followed by surgery (89% of patients proceeded to surgery)					
	Resectable T3-4/N+	9	R0: 8 [89]; R1: 0 [0]	D1: 0 [0]; D2: 8 [89]	0 [0]	2 [22]
Michel *et al*. 2014[†#] (84)	4 cycles of LV 400 mg/m^2/day i.v. on day 1 + Iri 180 mg/m^2/day i.v. on day 1 + 5-FU 400 mg/m^2/day i.v. on day 1 + 5-FU 2,400 mg/m^2/46h i.v. on days 1, 2, q 2 weeks, followed by RT 50 Gy + 5-FU 200 mg/m^2/day i.v. on RT-days 1-33 (chemotherapy completion rate: 93%, RT completion rate: 86%, overall completion rate: 74%), followed by surgery (83% of patients proceeded to surgery)					
	Resectable	42	R0: 28 [67]; R1: 1 [2]; UK: 2 [5]	D1: NR; D2: NR	6 [14]	3 [7]
Pera *et al*. 2012[†] (85)	RT 45 Gy + Ox 85 mg/m^2/day i.v. on RT-days 1, 29 + Cis 55 mg/m^2/day i.v. on RT-days 1, 29 + 5-FU 750 mg/m^2/day i.v. on RT-days 1-4 and 29-32 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 90%), followed by surgery (76% of patients proceeded to surgery)					
	Resectable T2-4/N0N+	41	R0: 29 [71]; R1: 1 [2]; R2: 1 [2]	D1: NR; D2: NR	3 [7]	G + GEJ: 3 [7]
Lee *et al*. 2012[†] (86)	RT 41.4 Gy + S-1 60-80 mg/m^2/day bid p.o. on RT-days 1-29 + Ox 40 mg/m^2/day i.v. on RT-days 1, 8, 15, 22 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 92%), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T2/N+ or T3-4/any N	12	R0: 11 [92]; R1: 0; R2: 1 [8]	D1: NR; D2: NR	0 [0]	1 [8]
Inoue *et al*. 2012 (87)	RT 50 Gy + S-1 65 mg/m^2/day p.o. on RT-days 1-14, 22-35 (chemotherapy completion rate: 83%, RT completion rate: 100%, overall completion rate: 83%), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T3/N2 or T4/N1	12	R0: 11 [92]; R1: 0; R2: 1 [8]	D1: 2 [17]; D2: 10 [83]	0 [0]	1 [8]
Stahl *et al*. 2009[†‡] (88)	2 cycles of 5-FU 2,000 mg/m^2/day i.v. on days 1, 8, 15, 22, 29, 36 + LV 500 mg/m^2/day i.v. on days 1, 8, 15, 22, 29, 36 + Cis 50 mg/m^2/day i.v. on days 1, 15, 29, q 6 weeks, followed by RT 30 Gy + Cis 50 mg/m^2/day i.v. on RT-days 1, 8, + Etop 80 mg/m^2/day i.v. on RT-days 3-5, (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 73%), followed by surgery (79% of patients proceeded to surgery)					
	Resectable T3-4/Nx	62	R0: 43 [69] R1+R2: 2 [3]	D1: NR D2: NR	5 [8]	7 [11]

Table 5 *(continued)*

Table 5 *(continued)*

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	Surgical mortality (n, %)	pCR (n, %)
Wydmański *et al*. 2007 (89)	RT 45 Gy + 5-FU 325 mg/m^2/day i.v. on RT-days 1-3/5, 29-31/33 +/- LV 20 mg/m^2/day i.v. on RT-days 1-3/5, 29-31/33 (chemotherapy completion rate: 95%, RT completion rate: 100%, overall completion rate: 95%), followed by surgery (93% of patients proceeded to surgery)					
	Resectable	40	R0: 30 [75]; R1: 2 [5]; R2: 0 [0]	D1: NR; D2: NR	0 [0]	7 [18]
Ajani *et al*. 2005† (90)	2 cycles of 5-FU 750 mg/m^2/day i.v. on days 1-5 + Cis 15 mg/m^2/day i.v. on days 1-5 + Pac 200 mg/m^2/day i.v. on day 1, q 4 weeks, followed by RT 45 Gy + 5-FU 300 mg/m^2/day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 + Pac 45 mg/m^2/day i.v. on RT-days 1, 8, 15, 22, 29 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: NR), followed by surgery (98% of patients proceeded to surgery)					
	Resectable T1/N1 or T2-3/any N	41	R0: 32 [78]; unknown: 1 [2]	D1: NR; D2: NR	0 [0]	8 [20]
Ajani *et al*. 2004† (91)	2 cycles of 5-FU 200 mg/m^2/day i.v. on days 1-21 + LV 20 mg/m^2/day i.v. on days 1, 8, 15 + Cis 20 mg/m^2/day i.v. on days 1-5, q 4 weeks, followed by RT 45 Gy + 5-FU 300 mg/m^2/day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: NR), followed by surgery (82% of patients proceeded to surgery)					
	Resectable T1/N1 or T2-3/any N	34	R0: 23 [68]; R1: NR; R2: NR	D1: NR; D2: NR	1 [3]	10 [29]
Roth *et al*. 2003 (92)	1 cycle 5-FU 800 mg/m^2/day i.v. on days 1-4 + LV 60 mg/m^2 bid. i.v. on days 1-4 and 60 mg/m^2/day i.v. on days 22-25 + Cis 100 mg/m^2/day i.v. on day 1, followed by RT 31.2-45.6 Gy + 5-FU/LV/Cis as described before on RT-days 1-4 (chemotherapy completion rate: 95%, RT completion rate: NR, overall completion rate: NR), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T1-2/N+ or T3-4/any N	19	R0: NR; R1: NR; R2: NR	D1: 0 [0]; D2: 19 [100]	0 [0]	1 [5]
Lowy *et al*. 2001 (93)	RT 45 Gy + 5-FU 300 mg/m^2/day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 (chemotherapy completion rate: NR, RT completion rate: 92%, overall completion rate: 92%), followed by surgery (76% of patients proceeded to surgery), followed by intraoperative RT 10 Gy for all patients who underwent resection					
	Resectable T1/N+ or T2-4/any N	25	R0: 18 [72]; R1: 1 [4]; R2: 0 [0]	D1: NR; D2: NR	1 [4]	2 [8]

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. †, included also patients with adenocarcinoma of the lower third of the esophagus or gastro-esophageal junction; ‡, trial was prematurely closed; $^{\#}$, in this trial was postoperative CRT also investigated. LND, lymph node dissection; pCR, pathologic complete response; RT, radiotherapy; Pac, paclitaxel; Car, carboplatin; R0, microscopically complete resection; R1, microscopically incomplete resection; R2, macroscopically incomplete resection; D1, lymph node stations 1-6; D2, lymph node stations 1-11; S-1, S1-fluoropyrimidine; Cis, cisplatin; LV, leucovorin; Iri, irinotecan; 5-FU, 5-fluorouracil; NR, not reported; Ox, oxaliplatin; Etop, etoposide; G, gastric cancer; GEJ, gastro-esophageal junction cancer.

Table 6 Grade 3-4 hematological and gastrointestinal toxicity of preoperative and postoperative chemoradiotherapy reported in selected clinical trials

Toxicity grade 3-4	Lee *et al.*[1] (68)	Macdonald *et al.*[2] (74)	Trip *et al.*[3] (82)	Matsuda *et al.*[4] (83)
Granulocytopenia/neutropenia (%)	48	54[+]	4	11
Leukopenia (%)	0	54[+]	12	11
Thrombocytopenia (%)	1	54[+]	0	11
Nausea (%)	12	33[§]	4	11
Vomiting (%)	3	33[§]	0	0
Anorexia/decreased appetite (%)	0	33[§]	4	0
Diarrhea (%)	1	33[§]	0	11

[1], percentages relative to 227 patients who started postoperative treatment; [2], percentages relative to 273 patients who started postoperative CRT; [3], percentages relative to 25 patients who started preoperative chemoradiotherapy; [4], percentages relative to 9 patients who started preoperative chemoradiotherapy. [+], percentage reported for hematologic side effects combined; [§], percentage reported for gastrointestinal side effects combined.

reported for the CRT regimen with concurrent carboplatin and paclitaxel (*Tables 5*,*6*) (82), as was also observed in the CROSS trial that administered a similar regimen preoperatively for patients with resectable esophageal cancer (94). The reported percentages of deceased patients related to the treatment with postoperative or preoperative CRT including any additional chemotherapy were between 0-1% (68-74,82,83).

Compliance rates to postoperative CRT including any induction chemotherapy were reported between 64% and 91% (68-74). This seems higher with the newer optimized CRT regimens that use concurrent oral fluoropyrimidines. For example the RT completion rate in the ARTIST trial was 87%, even after 2 courses of induction chemotherapy (68), and up to 89-97% in the phase I/II studies of Jansen *et al.* (99-101). Compliance rates to preoperative CRT including any induction chemotherapy were reported from 74% up to 95% as investigated in phase I and II studies (82-87,89,93). With the older CRT regimens including any induction chemotherapy, toxicity was the reason to discontinue treatment in 10-19% of patients (69,72-74), while this was around 5% with the newer CRT regimens (68,82,83,100).

Besides acute toxicity of CRT for gastric cancer, late toxicity is important as well, however, few studies reported on this. With CRT for gastric cancer, a large area of the upper abdomen is irradiated, whether this is administered preoperatively or postoperatively (102). As a result, surrounding tissues of the liver, kidneys and spleen, are irradiated as well. The most important late toxicity is radiation-induced nephrotoxicity. This is radiation dose- and volume-dependent, progressive in time, and associated with renovascular hypertension (103-105). The radiation dose to both kidneys (106) should be kept as low as possible to better preserve its function which can be accomplished by the use of highly conformal RT techniques such as Intensity Modulated Radiation Therapy (IMRT) (107) and Image Guided Radiation Therapy (IGRT). A relatively low-dose of concurrent cisplatin (20 mg/m^2 i.v. weekly), a well-known nephrotoxic drug, can be administered safely with regard to nephrotoxicity (104,107). However, the consequences of the combination of concurrent cisplatin in a CRT regimen with administrating high-dose cisplatin for example as part of preoperative chemotherapy, are not yet established (107,108).

In contrast to the high amount of consideration that is placed on the kidneys, the spleen is not accounted for when administering CRT for gastric cancer, despite the fact that it is encompassed in the high dose region. However, nowadays the extremely important and unique immunological and hematological functions of the spleen are acknowledged (109-112). Following surgical splenectomy or in case of functional hyposplenia, patients are at an increased risk for fatal thromboembolic events and overwhelming postsplenectomy infections (OPSI) by encapsulated bacteria (109,110). For this matter, guidelines regarding preventive measures, including immunization against encapsulated bacteria such as *Streptococcus pneumoniae* and prophylactic and on-demand antibiotics have been implemented. Although radiation of the spleen has been associated with hyposplenia, it is largely unknown whether and to what extent the functions of the spleen are affected by radiation,

and to what extent we can draw a parallel from radiating the spleen to surgical splenectomy (109), or hyposplenia (111). Guidelines regarding the management of patients that have received irradiation to the spleen have not yet been established.

Discussion

Based on the accumulating evidence of the past decade that multimodality treatment improves OS in locally advanced resectable gastric cancer, all patients should be discussed by multidisciplinary teams and considered for multimodality treatment. The variety on multimodality regimens creates opportunities to improve the treatment of gastric cancer patients by considering subgroups that benefit most from certain treatments.

Both chemotherapy and CRT added to the surgical resection of gastric cancer have shown to improve OS in randomized controlled trials (40,41,60,74). Only a few trials have compared chemotherapy and CRT directly, which were all conducted in Asia (68-72). The outcomes of the completed trials did not show an OS benefit for either one of the treatments, but a trend favoring CRT could often be observed. The meta-analysis by Ohri *et al*. including these trials, detected a significant beneficial effect of postoperative CRT over chemotherapy (78). Currently, two large-scale phase III randomized controlled trials investigate the possible superiority of CRT to chemotherapy, i.e., the Dutch CRITICS trial initiated by the Dutch Colorectal Cancer Group (ClinicalTrials.gov number NCT00407186) that randomizes patients for perioperative chemotherapy *vs*. preoperative chemotherapy followed by surgery and postoperative CRT, and the Australian TOP GEAR trial that randomizes patients for perioperative chemotherapy *vs*. preoperative CRT followed by surgery and postoperative chemotherapy.

One subgroup of gastric cancer patients is formed by patients who have undergone an R1 resection. As an R1 resection is associated with a dismal prognosis, many physicians question whether these patients should continue with a potentially curative treatment regimen. These patients were invariably excluded from randomized controlled trials, and to perform a trial exclusively with these patients is not feasible and may be unethical. Therefore, evidence for optimal treatment is and will be limited to retrospective analyses and/or subgroup analyses of large randomized trials in which no deviations from the randomized treatment arm are made after an R1 resection. Several retrospective analyses from our group have shown a clear benefit from postoperative CRT for gastric cancer patients who had undergone an R1 resection (79-81). In these articles, only a few patients received preoperative chemotherapy, and therefore questions remain on the efficacy of postoperative CRT after an R1 resection when preoperative chemotherapy has been administered. Subgroup analyses of the CRITICS trial might inform us on the efficacy of postoperative CRT under these circumstances (113).

Preferably, an R1 resection and its associated dismal prognosis should be prevented. Preoperative CRT is a promising approach to obtain an R0 resection (82,88,94). This treatment might also have the potential to induce resectability in initially irresectable gastric cancer (82). Pathologic complete response rates after preoperative CRT are independently prognostic for OS in several studies, as well as pCR rates after preoperative chemotherapy (90,114,115). Pathologic CR rates tend to be higher after preoperative CRT compared to chemotherapy alone though (60,88). Rightfully, preoperative CRT is nowadays not anymore confined to the higher located gastro-intestinal tumors such as esophageal and gastro-esophageal junction tumors, but also applied in more proximally located gastric tumors, for example within the TOP GEAR trial.

The majority of gastric cancer patients in the Western part of the world present themselves with lymph node metastases at diagnosis, forming a large subgroup of patients with node positive disease. Consequently, these patients also form the majority in clinical trials investigating the addition of chemotherapy (40,41,58,60) as well as CRT (68,74). In subgroup analyses, postoperative CRT is more beneficial when node positive disease is present than when no lymph node metastases are present (75,78). Moreover, in the subset of node positive patients in the ARTIST trial, postoperative CRT was more beneficial than chemotherapy-only (68). However, this does not mean that node negative patients do not benefit from CRT or from chemotherapy. Hopefully the ARTIST-II trial (ClinicalTrials.gov number NCT01761461) that includes only node positive patients, will further clarify the role of postoperative CRT and chemotherapy in this group of patients.

Other subgroups of patients can be based on the extent of the surgical LND. A lot of debate focusses on the efficacy of additional treatment modalities when optimal surgery, i.e., at least a D1+ LND, has been performed, because in the past the majority of patients in all large-scale clinical trials conducted in the West

underwent suboptimal surgery, and outcomes between clinical trials conducted in the West or East that differ in surgical quality, are conflicting. Conceptually, the combination of multimodality treatment and a D2 LND could be overtreatment if these two modalities would both prevent the same relapses, i.e., locoregional recurrences or secondary distant metastases resulting from residual affected lymph nodes. Based on positive outcomes of multimodality treatment, both chemotherapy and CRT, after a D2 LND from all (subsets of) Eastern and Western clinical trials (40,41,60,68,73,74), we can only assume that multimodality treatment is beneficial irrespective to the extent of the LND. Future trials will give further insight in this issue as recently a D2 LND has become the standard of care in Western countries and is applied in currently ongoing trials (113), and as Asian trials are initiated that routinely apply D2 LND.

A major problem concerning the addition of extra treatment modalities to surgery in the treatment of gastric cancer is the accompanied toxicity, when this leads to non-compliance with treatment and especially to the delay of or withdrawal from potentially curative surgery. The reported outcomes of clinical trials thus far refute these concerns. The reported toxicity rates of preoperative chemotherapy and CRT are in general lower than those of postoperative treatment. Furthermore, toxicity rates of the newer optimized CRT regimens are lower than of chemotherapy, either preoperatively or postoperatively. In addition, compliance with preoperative chemotherapy and CRT regimens is higher than with postoperative treatment. Importantly, this higher compliance offers the chance to administer more intensified, combination chemotherapy or CRT. Moreover, preoperative regimens improve pathology-related surgical results without increasing surgical morbidity and mortality. Taken together, preoperative chemotherapy and/or CRT are preferable to postoperative regimens. However this has to be further confirmed in phase III studies.

To conclude, future randomized controlled trials for locally advanced resectable gastric cancer should include preoperative multimodality treatment.

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