Adjuvant and/or neoadjuvant therapy for gastric cancer? A perspective review

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Ther Adv Med Oncol
2015, Vol. 7(1) 39–48
DOI: 10.1177/1758834014558839

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***Abstract*:** Surgery is still the only curative therapy for locoregional gastric cancer. Hereby it is important to achieve negative margins (R0 resection) and to perform an adequate lymph-node dissection (D2 lymphadenectomy). Unfortunately most cases of gastric cancer are diagnosed in a locally advanced tumor stage. The poor prognosis of patients with these tumors is due to the frequent recurrences after primary resection in curative intent. This observation led to the development of (neo)adjuvant treatment concepts. Beginning with the end of the 1980s, more and more patients with locally advanced tumors were subjected to a preoperative, perioperative, or postoperative treatment in order to improve the prognosis after curative resection. However, in different regions of the world, different regiments are preferred. While adjuvant chemotherapy is the established treatment in Asia, adjuvant chemoradiotherapy is favored in the USA and perioperative chemotherapy is considered the treatment of choice in Europe. However, recently a certain convergence of the different philosophies is to be observed. This article covers the relevant studies dealing with neoadjuvant and adjuvant treatment concepts and gives an overview on the latest developments in this field.

Keywords: chemotherapy, chemoradiotherapy, gastric cancer, neoadjuvant therapy, surgery

Introduction

According to World Health Organization (WHO) statistics gastric cancer (GC) poses the third most common malignancy worldwide (see http://apps.who.int/ghodata/). Because there are no existing screening programs in the West, as is the case in most Asian countries, GC is usually diagnosed at an advanced stage due to mostly unspecific symptoms [Agboola, 1994]. Despite adequate surgery with radical lymphadenectomy the prognosis of GC is still poor. The 5-year survival of patients with early GC is about 75%, but at an advanced stage with extensive lymph node involvement it is less than 30%. In Europe since the early 1990s neoadjuvant therapy gained importance for the treatment of locally advanced or initially irresectable GC and phase II studies demonstrated effects on the primary tumor transforming it to a resectable growth pattern including R0 resections and compared with historical trials improved survival rates [Wilke *et al.* 1989; D'ugo *et al.* 2009].

Cunningham and colleagues and Ychou and colleagues showed the advantage of perioperative chemotherapy (CT) over surgery alone in randomized trials [Cunningham *et al.* 2006; Ychou *et al.* 2011]. Schuhmacher and colleagues were able to show higher R0 resection rates in patients receiving neoadjuvant CT, even though this effect did not translate into a prolonged overall survival (OS). Remarkable in this trial were excellent survival rates even in the pure surgery arm compared with other European trials [Schuhmacher *et al.* 2010].

A German pilot study was able to demonstrate a high percentage of complete responders from preoperative chemoradiotherapy (CRT), and recent data from a Dutch trial indicate additional positive effects of radiotherapy on OS [Stahl *et al.* 2009; Van Hagen *et al.* 2012].

While in the West perioperative CT is standard of care, Asian oncologists mostly rely on a postoperative oral CT regimen, for which a randomized study could show a marked survival improvement in comparison to surgery only [Sakuramoto *et al.* 2007; Sasako *et al.* 2010]. In spite of numerous

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studies investigating adjuvant CT in GC, these good results could regrettably not be reproduced in Western series.

Since publication of the INT0116 trial in 2001 [MacDonald *et al.* 2001] the United States are traditionally a stronghold of adjuvant CRT, despite being frequently criticized for the inadequate lymphadenectomy, when it comes to GC treatment. However, recently the results of European studies gained more and more attention in the US leading to an inclusion of perioperative CT as alternative treatment option for localized GC in the present NCCN guidelines (see http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf).

The present review gives an overview of the already briefly mentioned landmark studies investigating neoadjuvant and adjuvant therapies in GC and tries to sum up the issues that are presently subject to ongoing discussions.

Neoadjuvant/perioperative chemotherapy

Neoadjuvant or perioperative CT is an accepted and national guideline recommended therapeutic approach of GC treatment in most European countries. This goes back to the results of the British MAGIC and the French FNLCC/FFCD trials, both of which included a rather large number of patients and were thus adequately powered. Both trials directly compared surgery with or without neoadjuvant or perioperative CT and showed a significant benefit for the multimodal approach.

Different theoretical advantages of neoadjuvant therapy over adjuvant therapy are discussed for potentially resectable GC [Ott *et al.* 2011]. One proposed advantage is the usually better general health condition of patients in the neoadjuvant setting. Another advantage is that downstaging of the tumor may lead to higher R0 resection rates. Several other benefits, such as effects on occult metastasis or single tumor cell dissemination (micrometastasis) at the earliest point in time, are discussed.

The MAGIC trial is, presently, the most recognized landmark study for perioperative CT. Between 1994 and 2002 45 centers in the UK, Europe and Asia recruited patients with resectable GC and adenocarcinomas of the esophagogastric junction (EGJ). Patients were randomized to surgery with perioperative CT (n = 250) or surgery only (n = 253). CT consisted of three preoperative and three postoperative cycles of i.v. epirubicin, cisplatin and continuous 5-fluorouracil (5-FU). The fear that preoperative CT jeopardizes the perioperative outcome was not justified. Although remarkable and higher than common numbers presented by Asian authors, there was at least no significant difference in postoperative complications and 30-day mortality in both treatment arms (46% *versus* 45% and 5.6% *versus* 5.9%, respectively). For patients in the CT arm, a downstaging effect could be observed regarding the ypT and N-categories. OS as well as progression-free survival (PFS) of patients receiving perioperative CT was significantly increased compared with patients treated by surgery only (p = 0.009 and $p < 0.001$). The 5-year survival rate was 36% for patients receiving perioperative CT and 23% for patients treated by surgery only [Cunningham *et al.* 2006].

Critics of the perioperative treatment pointed out that many patients in the MAGIC trial did not receive the full number of postoperative CT cycles because of poor performance status, complications or compliance issues in the postoperative period. In fact, only about half (49.5%) of the patients that underwent preoperative treatment in the study also received the full courses of the planned postoperative CT.

Because the importance of the adjuvant component of the MAGIC regimen was still not certain, this issue was addressed by a retrospective study from the UK on a series of 66 patients undergoing perioperative CT according to the MAGIC protocol. The results of this study showed a considerable prognostic benefit in terms of disease-free survival (DFS) for patients receiving neoadjuvant as well as adjuvant treatment compared with patients who did not undergo postoperative CT, while OS was not significantly different between the two groups. So administration of the adjuvant part of the regimen seemed to postpone tumor recurrence rather than preventing it [Mirza *et al.* 2013].

The results of the French FNLCC ACCORD 07 FFCD 9703 trial confirmed data in favor of the establishment of perioperative CT for patients with resectable GC and esophageal adenocarcinoma. The chemotherapeutic regimen consisted of 2 or 3 cycles of i.v. 5-FU and cisplatin. A postoperative CT was recommended in case of a response to the preoperative treatment or stable

disease with positive lymph nodes. 224 were randomized to receive preoperative CT or primary surgery. The R0 resection rate among the patients receiving CT was significantly higher compared with the primary surgery arm (84% *versus* 73%; $p = 0.04$). OS and DFS were significantly prolonged after CT ($p = 0.02$ and $p = 0.003$, respectively). The 5-year survival rates largely matched those reported for the MAGIC trial (see above) with 38% in the CT and 24% in the surgery only arm [Ychou *et al.* 2011].

The European Organization for Research and Treatment of Cancer (EORTC) 40954 phase III trial investigated the same patient population as the MAGIC and the FNLCC ACCORD 07 FFCD 9703 trial, while adenocarcinomas of the distal esophagus (AEG I according to the Siewert's classification) were excluded. Unfortunately the trial had to be closed early due to poor accrual after inclusion of 144 patients ($n = 72$ per treatment arm), while 360 patients were initially planned. The goal of the study was to achieve a surgical quality and higher grade of standardization. In contrast to the aforementioned studies, this trial solely relied on preoperative CT with cisplatin, 5-FU and folinic acid (PLF protocol). Resection was performed obeying strict surgical quality standards, including a D2 lymphadenectomy. The analysis of the patients included up to then showed a higher R0 resection rate among the patients treated with neoadjuvant CT compared to those undergoing primary surgery (81.9% *versus* 66.7%; $p = 0.036$). A significant survival benefit could not been shown but a downstaging and a tendency towards a prolonged OS and DFS for the neoadjuvant treatment arm was observed ($p = 0.113$ and $p = 0.065$). Postoperative complications and deaths were also more common among patients treated with neoadjuvant CT (27.1% *versus* 16.2%; $p = 0.09$ and 4.3% *versus* 1.5%), but did not differ significantly. With only 67 deaths occurring during the follow-up period no survival benefit could be shown for the CT arm (median survival 64.6 months *versus* 52.5 months; $p = 0.466$; in order to reach a power of 80%, 282 deaths would have been necessary). The fact that patient survival missed significance level in spite of higher R0 resection rates was attributed to the low patient number and the high surgical quality by the authors [Schuhmacher *et al.* 2010].

Ronellenfitsch and colleagues performed an interesting meta-analysis showing an absolute improvement in survival of 9% at 5 years for patients undergoing perioperative CT. This effect could be observed starting 18 months after surgery and was observable for 10 years. The odds of a R0 resection in patients treated with perioperative CT were 1.4 times higher than in untreated patients. In addition no increase in postoperative morbidity and mortality as well as duration of hospitalization could be recognized. Also an interaction between age and treatment effect was considered. In contrast to a recent German series mentioned below, no survival benefit from perioperative CT could be shown for elderly patients. Another remarkable point of a subgroup analysis was that there seemed to be a higher survival benefit for patients with tumors of the EGJ as compared to other sites [Ronellenfitsch *et al.* 2013]. An observation we could basically confirm on our own patient population [Reim *et al.* 2012].

Even though the median age of patients at diagnosis of gastroesophageal adenocarcinomas is 70 years, the benefit of neoadjuvant CT in elderly patients remains elusive since randomized trials are lacking for this subgroup because these patients were excluded because of age in most of the aforementioned trials. This is a shortcoming that needs to be overcome, since patient age can be expected to increase in the future. This current issue is addressed by a recent German retrospective oligo-institutional analysis including 460 patients. Here comparable outcomes of patients aged 70 years and older compared with their younger counterparts could be shown in terms of survival in spite of a slight increase in adverse events and the necessity for dose reduction during the course of treatment [Spoerl *et al.* unpublished data].

There is also evidence in the literature that patients with signet ring cell adenocarcinoma do not benefit from perioperative CT. Messager and colleagues investigated this issue in a multicenter comparative study including 3010 patients from 19 French centers including 1050 patients (34.9%) with signet cell histology [Messager *et al.* 2011]. In our own patient cohort including 200 patients with diffuse type histology having undergone neoadjuvant CT, only 14.5% showed a good histopathologic response (TRG1 according to Becker and colleagues) [Becker *et al.* 2003]. In comparison 27.7% of patients with an intestinal-type growth pattern ($n = 331$) showed a TRG1 in the histopathologic workup [Oesterlin *et al.* unpublished data].

Based on the results of the REAL-2 trial in metastasized GC, in which the statistic noninferiority of oxaliplatin in comparison to cisplatin and of capecitabine in comparison with 5-FU could be demonstrated, those drugs are regarded as alternatives for perioperative CT [Cunningham *et al.* 2008; Ychou *et al.* 2011].

An ongoing British trial is presently investigating the safety and efficacy of adding the monoclonal VEGF antibody, bevacizumab, to ECX CT administered perioperatively in patients with resectable gastric and EGJ adenocarcinomas [Smyth *et al.* 2012]. This concept is based on the demonstrated beneficial effect of bevacizumab in the treatment of colorectal cancer and promising results in advanced GC (AVAGAST trial) [Ohtsu *et al.* 2011].

Even though Asia is the traditional stronghold of adjuvant CT, neoadjuvant concepts recently gained interest for certain indications which are difficult to cure.

Currently the value of neoadjuvant CT in locally advanced, marginally resectable GC with poor prognosis, such as tumors with paraaortal and/or bulky N2 and N3 nodal disease (JCOG 0001, JCOG 0405), large type 3 (⩾8 cm) or 4 (linitis plastic) tumors (JOCG 0210, JCOG 0501, JCOG 1002) and T2-3 N+ or T4 tumors (PRODIGY trial) is investigated in the East.

The findings of the ToGA study, which demonstrated the beneficial effects of trastuzumab for HER2-positive advanced gastric and gastroesophageal junction cancers in combination with a platinum-based CT [Bang *et al.* 2010], gave rise to studies investigating the HER2-positivity in advanced GC with bulky N2 or N3 nodal disease (JCOG2005-A) with eventual implications for a future use of this substance in a neoadjuvant setting.

Neoadjuvant/perioperative chemoradiotherapy

Based on the results of the German POET trial [Stahl *et al.* 2009], most European guidelines consider neoadjuvant or perioperative CRT an alternative to CT in adenocarcinomas of the EGJ [Moehler *et al.* 2011; Van Cutsem *et al.* 2011; Lutz *et al.* 2012; Rivera *et al.* 2012].

This trial compared neoadjuvant CT with neoadjuvant CRT in patients with adenocarcinomas of the EGJ. Patients with locally advanced AEG I–III were randomly allocated to two courses of PLF (cisplatin, 5-FU, FA) followed by 3 weeks of combined CRT (30 Gy, 2 Gy per fraction, five fractions per week, cisplatin/etoposide) followed by surgery or 2.5 courses of PLF only followed by surgery. The trial was closed early due to low accrual showing no significant survival benefit for CRT with a median survival of 33.1 months for the CRT arm and 21.1 months for the CT arm. In the CRT group mortality was higher compared with the CT group (10.2% *versus* 3.8%); this difference, however, again was not significant ($p = 0.26$).

Meanwhile a study from the Netherlands (CROSS trial) investigated the role of neoadjuvant CRT in the treatment of esophageal cancer and cancer of the EGJ in a multicenter, randomized, controlled, phase III setting [Van Hagen *et al.* 2012]. Patients with resectable tumors (T1N1 or T2-3N0-1, M0) were randomly assigned to CRT (carboplatin, paclitaxel, 41.4 Gy in 23 fractions, 5 days per week) followed by surgery or surgery only. A total of 75% of the 366 patients had adenocarcinoma. The R0 resection rate in the CRT group was significantly higher compared with the surgery only group (92% *versus* 69%, $p < 0.001$). In the former 29% of patients showed a pathological complete response. Hereby response rates were better in patients with squamous cell carcinoma (SCC). A pathologic complete response was observed in 23% of patients with adenocarcinoma and 49% of patients with SCC. Median OS was also significantly better after CRT + surgery compared with surgery only (49.9 *versus* 24.0 months; $p = 0.003$; hazard ratio [HR] 0.675; 95% confidence interval [CI] 0.495–0.871), while postoperative complications and in-hospital mortality (4% in both) were comparable in both arms. Even though the benefit of neoadjuvant CRT on survival was consistent across the analyzed subgroups, it was most pronounced in the subgroup of patients with SCC.

Based on the results of this trial, preoperative chemoradiation is now referred to as the preferred approach for localized adenocarcinoma of the EGJ in the US, whereas CT is regarded as an alternative, but less preferred option (see http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf).

The ongoing TOPGEAR trial addresses the question, whether neoadjuvant CRT is superior to CT in a phase II/III setting [Leong *et al.* 2012]. It is

an international, intergroup trial led by the Australasian Gastro-Intestinal Trials Group (AGITG), in collaboration with the Trans-Tasman Radiation Oncology Group (TROG), the EORTC and the NCIC Trials Group. Patients with resectable adenocarcinoma of the stomach or EGJ are randomized to either receive three cycles of ECF alone (as per MAGIC regimen) or CRT (two cycles of ECF followed by 45 Gy or radiation with concurrent 5-FU). Following surgery both groups receive three further cycles of ECF. Part I of the trial (phase II component) will recruit 120 patients with the aim of demonstrating efficacy and safety of preoperative CRT as well as feasibility of the trial. The following second part (phase III component) will recruit a further 632 patients providing a total number of 752 patients. Primary endpoints are pathological complete response rates (part I) and OS (part II). The trial is presently recruiting; results are eagerly awaited.

Adjuvant chemotherapy

A big Japanese trial (ACTS-GC) comparing patients with stage II/III GC (Japanese classification) undergoing adjuvant oral CT based on the oral fluoropyrimidins S-1 with primary surgery only, showed excellent results in the CT group [Sakuramoto *et al.* 2007]. In this study 529 patients received postoperative oral CT with S-1 for 1 year after resection, while 530 patients underwent surgery alone. In both groups, a D2 lymphadenectomy was performed. Survival rate after 3 and 5 years was 80.1% *versus* 70.1% ($p = 0.003$) and 71.7% *versus* 61.1% [Sasako *et al.* 2010]. The excellent survival rate in both groups and the high surgical quality (100% D2 lymphadenectomies) are remarkable. It is not clear, though, whether these excellent results are also achievable in a White population. In a phase III study (FLAGS trial) a comparable combination of cisplatin/S-1 and cisplatin/5-FU (i.v.) was administered to patients with irresectable GC, showing a significantly better tolerance of the first combination [Ajani *et al.* 2010]. Tegafur, present in S-1, is a precursor of 5-FU, which is transformed in the body by cytochrome P450 to 5-FU. The hypothesis that the different metabolism of tegafur in European and Asian patients is due to polymorphisms of CYP2A6-Gene is still to be demonstrated [Ajani *et al.* 2005].

In the CLASSIC trial [Bang *et al.* 2012], adjuvant capecitabine and oxaliplatin were compared with surgery alone in patients with stage II–IIIB (UICC 2003) GC after curative gastrectomy with D2 lymphadenectomy in a phase III randomized controlled trial. A total of 1035 patients from 37 Asian centers were randomized. The 3-year DFS was 74% in the CT group and 59% in the surgery only group ($p < 0.0001$), while 3-year OS was 83% *versus* 78% ($p = 0.0493$). Therefore, capecitabine plus oxaliplatin can be considered as an alternative to S-1 in the adjuvant setting.

A patient-based meta-analysis, including 3838 patients from 17 different trials undergoing adjuvant CT, showed a slight but statistically significant benefit for surgical treatment followed by adjuvant 5-FU-based CT *versus* surgery alone [Paoletti *et al.* 2010]. Adjuvant CT reduced the risk of death by 18%. Furthermore, the overall 5-year survival rate was increased by 6%.

Adjuvant chemoradiotherapy

In 2001 MacDonald and colleagues published the results of the Intergroup (INT) trial 0116 [MacDonald *et al.* 2001]. In this study 556 patients with GC who underwent a potentially curative resection were randomized in a follow-up group or a CRT group. In the CRT group a 5-day cycle of 5-FU/LV i.v. was administrated, followed by 45 Gy in 1.8 Gy/day fractions after a month (with 5-FU/LV i.v. on days 1, 4, and the last 3 days of the radiotherapy administration), followed by a new administration of two more 5-day cycle of 5-FU/LV i.v. every month. The recurrence-free survival rates after 3 years and the OS were significant longer (48% *versus* 31% and 50% *versus* 41%) in the CRT group. The median survival as well was longer in the adjuvant therapy group (36 months *versus* 27 months). There were 20% of the enrolled patients who presented with a cardia adenocarcinoma, meaning that also benefit from adjuvant CRT.

The follow-up study published in 2012, confirmed the efficacy of the described protocol. The HR for OS after CRT compared with surgery alone was 1.32 ($p = 0.004$) and 1.51 for recurrence-free survival ($p < 0.001$). Furthermore an analysis of the subsets showed efficacy in all subsets except for patients with diffuse histology, which only showed a minimal nonsignificant treatment effect [Smalley *et al.* 2012].

Based on these results, adjuvant CRT is currently the standard treatment after curative

gastrectomy in the USA (see http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf). Remarkably, the optimal regimen, however, remains to be defined. A follow-up study INT-0116 sponsored by the National Cancer Institute compared the standard regimen with the administration of continuous radiotherapy and infusion of 5-FU 200mg/m². Results are still pending.

The results of a phase II study of the Radiation Therapy Oncology Group (RTOG) showed that there is no advantage in concomitant administration of paclitaxel and cisplatin with radiation in an adjuvant setting over the administration of radiation with fluoropyrimidine [Schwartz *et al.* 2009].

Despite the different philosophies for the multimodal treatment of GC between the USA and Europe a recent convergence is to be registered. In the latest issue of the NCCN guidelines (see http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf), perioperative CT is recommended as an alternative to postoperative chemoradiation based on the convincing results of European trials [Cunningham *et al.* 2006; Ychou *et al.* 2011].

Based on promising results in an observational study [Kim *et al.* 2005], the Korean ARTIST trial was devised. Patients either received adjuvant CT with capecitabine plus cisplatin only or an additional adjuvant course of CRT with capecitabine embedded within two cycles of adjuvant CT with capecitabine plus cisplatin each [Lee *et al.* 2012]. The overall DFS could not be prolonged by the addition of CRT, however, the subgroup of patients with pathologic lymph-node metastases at the time of surgery seemed to benefit from CRT which translated into a superior DFS compared with those just receiving adjuvant CT. Presently, the authors are trying to reconfirm this observation in a subsequent phase III trial (ARTIST-II).

The ongoing CRITICS trial from the Netherlands explores a similar question, investigating whether a combination of preoperative CT and postoperative CRT will improve the clinical outcome of patients with GC [Dikken *et al.* 2011]. Patients are to receive three cycles of epirubicin, cisplatin and capecitabine (ECC) followed by surgery and another three cycles of ECC or concurrent CRT (45 Gy, cisplatin, capecitabine). Results are still pending.

Conclusions

Interestingly, different approaches in multimodal GC therapy can be observed in Asia, Europe and the US: Asian countries primarily rely on surgery followed by adjuvant CT, perioperative CT has become the standard of care in Europe whilst actually being challenged by neoadjuvant CRT, while in the US postoperative CRT and just recently also perioperative CT is considered the standard of care for patients with locally advanced GC. The reasons for those differences are multifactorial.

Traditionally, primary surgery with D2 lymphadenectomy is considered as one of the most important criteria for surgical quality when talking about curative gastrectomy for locally advanced GC. However the adherence to D2 dissection is varied in different parts of the world. Historically, D2 resection has been developed by Japanese surgeons, who nowadays consider any dissection less than D2 as inappropriate in advanced GC. Nonetheless adjuvant treatment concepts were introduced in Eastern Asia, which proved to be effective and demonstrated improved oncologic outcomes. The positive effect of the combination of surgery and CT seems to be proven for stage II and stage III GC (CLASSIC-trial) [Sakuramoto *et al.* 2007].

In Europe, preoperative CT has been developed in order to downstage primarily irresectable tumors. Promising results led to the introduction of neoadjuvant CT in locally advanced situations. Since the landmark trial by Cunningham and colleagues, perioperative CT is considered the standard of care in Europe. However, this trial was criticized by many opinion leaders all over the world because of the rather poor surgical quality with inadequate lymphadenectomy. Furthermore many participating centers did not have adequate case numbers which led to a high morbidity and mortality rate [Cunningham *et al.* 2006; Ronellenfitsch *et al.* 2013]. Although underpowered and inconclusive, in the final result the EORTC 40954 trial [Schuhmacher *et al.* 2010] revealed no significant differences in survival when D2 dissection was performed.

Conclusively, perioperative CT may be an appropriate tool to catch up inadequate lymph-node dissection. This is also supported by the results from the INT-0116 trial, in which patients received even less aggressive lymph-node

Table 1. Completed randomized controlled trials of multimodal gastric cancer treatment.

Trial	Regimen	Treatment arms	Tu-loc.	R0 res. rate, *p*	OS, *p*	PFS/DFS, *p*
Neoadjuvant CT						
MAGIC	CT perioperative	res. *versus* mult.	GC + EGJ	0.018*	0.009	<0.001
FFCD 9703	CT perioperative	res. *versus* mult.	GC + EGJ	0.04	0.021	0.003
EORTC 40954	CT preoperative	res. *versus* mult.	GC + EGJ	0.036	0.466 n.s.	0.2 n.s.
Neoadjuvant CRT						
POET	C(R)T preoperative	mult. (CRT) *versus* mult. (CT)	EGJ (AEG I/II/III)	n.s.	0.07& n.s.	0.06& n.s.
CROSS	CRT preoperative	res. *versus* mult.	Esoph.# + EGJ	<0.001	0.003	<0.001
Adjuvant CT						
ACTS-GC	CT postoperative	res. *versus* mult.	Not specified	only R0 included	0.002§	<0.001§
CLASSIC	CT postoperative	res. *versus* mult.	GC + EGJ	only R0 included	0.049&	<0.0001&
Adjuvant CRT						
INT 0116	CRT postoperative	res. *versus* mult.	GC + EGJ	only R0 included	0.005	<0.001
ARTIST	CRT postoperative	res. *versus* mult.	GC	only R0 included	Not analyzed	0.0824& n.s.

EORTC 40954 and POET closed early due to low accrual.
*As determined by the surgeon.
#Also included 23% of esophageal SCC in each arm.
§Interim analysis 1 year after enrollment of last patient.
&3-year survival data.
Tu-loc., tumor localization; res., resection; OS, overall survival; PFS/DFS, progression-free survival/disease-free survival; mult., multimodal therapy; res., resection; CT, chemotherapy; CRT, chemoradiotherapy; n.s., nonsignificant; GC, gastric cancer; EGJ, esophagogastric junction.

dissection before undergoing adjuvant radiation therapy [MacDonald *et al.* 2001].

Another difference between the East and the West most probably does have an epidemiological background, which seems to be reflected by the tumor localization. While the incidence of adenocarcinoma of the lower esophagus and the gastric cardia (AEG I–III) is increasing in most Western populations [Blot *et al.* 1991; Powell and McConkey, 1992; Botterweck *et al.* 2000], in Asian countries where gastric carcinoma in the proper sense is more common, junctional adenocarcinomas are still rare [Okabayashi *et al.* 2000; Chung *et al.* 2009]. There is evidence from a meta-analysis and a retrospective analysis of a large single-center cohort, that predominantly patients with cancer of the EGJ seem to benefit from neoadjuvant CT [Ronellenfitsch, 2010; Reim *et al.* 2012]. Also both landmark trials showing a positive effect of neoadjuvant CRT just included adenocarcinomas of the EGJ [Stahl *et al.* 2009; Van Hagen *et al.* 2012].

However, a multimodal approach seems to consistently result in a survival benefit when used in operable GC. Table 1 gives an overview of the most important completed trials of multimodal GC treatment (Table 1). The actual dilemma we are facing is that the positive effects of adjuvant CT have been shown for GC in the proper sense in an Asian population, while the positive effects of perioperative CT (with an emphasis on the neoadjuvant part) have been shown in a European population of GC patients with a high percentage of tumors located at the EGJ and a less radical lymphadenectomy [Cunningham *et al.* 2006]. For esophageal and junctional adenocarcinomas on the other hand, the positive effects of neoadjuvant CRT have been shown, that might even outperform those of neoadjuvant CT [Stahl *et al.* 2009; Van Hagen *et al.* 2012]. The task for the near future will be to determine whether the preoperative or the postoperative part of the perioperative CT is responsible for the positive survival effects. This issue still remains unclear since only 54.8% of patients assigned to perioperative CT in the MAGIC trial actually received postoperative CT due to various reasons [Cunningham *et al.* 2006]. This is currently investigated in the Polish STOPEROCHEM trial [ClinicalTrials.gov identifier: NCT01787539]. First results are not to be expected before 2022.

Future studies should consider the patients individual response to neoadjuvant CT when deciding upon the administration of an additional adjuvant treatment. Patients benefiting from neoadjuvant

treatment have to be determined exactly in terms of tumor location and maybe also Laurén histotype [Messager *et al.* 2011; Reim *et al.* 2012]. It was demonstrated by a French group that neoadjuvant CT appears to be ineffective in patients with signet ring cell histology. This retrospective analysis gave rise to a prospective randomized controlled trial which is about to elucidate the role of chemotherapeutic treatment for this special entity [Piessen *et al.* 2013]. The increasing variability of new compounds and regimens is probably going to further improve outcomes after multimodal treatment. A very promising regimen was published by Homann and colleagues demonstrating pathological complete remission rates of up to 30%. The ongoing phase II/III trial is expected to close by 2015 [Homann *et al.* 2012]. The ST03 trial is going to reveal whether the incorporation of bevacizumab into the standard regimen will have an impact on oncologic outcomes [Smyth *et al.* 2012]. Further compounds such as panitumomab, catumaxomab, lapatinib and other biologicals will reveal their role in perioperative multimodal treatments in the near future. The promising technology of intraperitoneal CT and (HIPEC) hyperthermic intraperitoneal chemoperfusion in a curative setting may demonstrate promising results as well [Sun *et al.* 2012].

Another field of interest besides personalized therapy should be the research on response prediction, as histopathologic response is a major parameter for prognosis.

Although multimodal treatment concepts may improve oncologic outcomes the surgical issues should also be addressed in ongoing trials, especially in the Western world where D2 dissection is still not commonly accepted. Surgical training of trialists should be enforced in future studies.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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