Special article

Recent advances in multimodal treatment for gastric cancer: a review

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Abstract

The prognosis after surgical treatment of gastric cancer remains poor. This review aims to clarify the indication for multimodal treatment of gastric cancer. A systematic literature research and evaluation of clinical data presented at important international cancer meetings were undertaken. Recently published results of large randomized phase III trials underscore the potential value of neoadjuvant chemotherapy or adjuvant chemoradiotherapy in gastric cancer. However, data from randomized controlled trials are still scarce, and it remains uncertain which subgroups of patients should routinely undergo multimodal treatment. In view of the side effects of pre- and foremost postoperative therapies, a more distinct definition of prognostic and predictive markers is warranted. Neoadjuvant chemotherapy is a rising option in locally advanced gastric cancer. Adjuvant chemoradiation has been shown to be beneficial in gastric cancer patients who have undergone suboptimal surgical resection. The benefits of adjuvant chemotherapy alone seem to be very small.

Key words Gastric cancer · Multimodal · Neoadjuvant · Adjuvant · Chemotherapy · Radiotherapy

Introduction

Important advances in the surgical and nonsurgical treatment of upper gastrointestinal (GI) cancer have been achieved during the last decades. However, the prognosis of gastric cancer remains poor. At least in the Western world, where esophagogastroduodenoscopy is not yet part of screening programs, upper GI tumors are commonly diagnosed in advanced stages [1]. Apart from that fact, lymphatic and hematogenous spread is often present even in early stages. Moreover, gastric cancer is only moderately sensitive to chemotherapy and radiation therapy. For this reason, the potential role of neoadjuvant and adjuvant treatment remained

uncertain. Now, with the presentation of the preliminary survival results of the MRC Adjuvant Gastric Infusional Chemotherapy “MAGIC” trial [2], there is rising evidence that patients may benefit from neoadjuvant chemotherapy. On the other hand, the publication of the Southwest Oncology Group 9008/Intergroup 0116 (SWOG9008/INT0116) trial [3] has defined adjuvant chemoradiation as a new standard of care in some countries. Hence, the interest in the role of combined-modality treatment in gastric cancer has rapidly increased among all physicians who care for gastric cancer patients. This review aims to clarify the current role of neoadjuvant and adjuvant treatment options for gastric cancer.

Surgical resection

Whenever one aims to define the role of multimodal therapy in nonmetastatic gastric cancer, one should bear in mind that surgical resection remains the mainstay of care in this disease. Unskilled surgery does reduce the chance for cure. Neither neoadjuvant nor adjuvant treatment can fully compensate for suboptimal surgical results. After years of debate on the extent of resections, recently published data help to settle the controversy. Briefly, for gastric carcinoma there is increasing confirmation of the superiority of an extended (D2) lymphadenectomy over a limited (D1) lymphadenectomy provided that splenectomy and distal pancreatectomy are omitted and that extended lymphadenectomy can be carried through with acceptable perioperative mortality and morbidity [4–9]. In adenocarcinoma of the esophagogastric junction type II and type III, extended total gastrectomy with transhiatal resection of the distal esophagus and D2 lymphadenectomy is the recommended procedure [10–13].

However, even after extended surgery carried through at experienced centers, long-term survival, at

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least in the “Western world,” does not exceed approximately 50% [4,7]. It is noteworthy that in patients with metastatic disease and patients in whom no complete resection can be achieved, long-term survival after surgery is very rare [7]. Therefore, as a general rule, patients with low probability for a complete resection (R0) should not be referred to primary surgery. Thus, for accurate treatment planning, particularly with regard to stage-dependent selection of neoadjuvant therapies, the most accurate clinical TNM stage must be worked out for patients scheduled for surgical resection.

Staging procedures prior to multimodal treatment

Endoscopic ultrasound (EUS) has proved to be superior to other methods in the prediction of pathologically confirmed T category with an accuracy of 79%–92% [14]. The clinical assessment of lymph node involvement is difficult with currently available preoperative staging techniques. Therefore, N-stage often remains uncertain after the clinical staging. As a consequence, inclusion of patients into neoadjuvant treatment studies may preferentially be based on the findings from the T category assessed by EUS. The accuracy of EUS to predict R0 resectability has been evaluated as being 85%–90% [15,16].

Incipient peritoneal carcinomatosis cannot be detected by noninvasive techniques. Hence, although under debate for primary surgery [17], laparoscopy should be performed in any patient who is to undergo neoadjuvant treatment within clinical studies in order to achieve the most accurate information on the pretreatment tumor stage [18]. In addition, with the availability of staging laparoscopy, cytological examination of abdominal lavage fluid can be carried through. Positive findings are associated with poor prognosis [19–21].

Consequently, before a decision on multimodal treatment is to be taken, staging procedures may comprise endoscopic ultrasound to define T category, computed tomography to exclude distant metastases, and laparoscopy to exclude peritoneal carcinomatosis. The value of fluorodeoxyglucose (FDG) positron emission tomography (PET) is limited in gastric cancer as its sensitivity is as low as 41%–63% in nonintestinal type histology according to the Lauren classification [22,23].

Rationale for neoadjuvant and adjuvant therapy

Multimodal approaches are based either on radiotherapy, which basically may increase the local tumor control, and/or chemotherapy in order to improve the systemic disease control. Both may be applied pre- or postoperatively, which is usually called neoadjuvant

and adjuvant, respectively. Before going into a more detailed discussion of the pivotal clinical study results, three more general aspects merit some attention.

Feasibility

After a radical tumor resection in the upper gastrointestinal tract, the potential effectiveness of adjuvant treatment is often hampered by poor tolerance. This is mainly due to the postoperatively impaired physical condition of the patients. Body-weight loss during the first 6 months after gastrectomy approximates 10% in relation to the preoperative body weight [24]. As a consequence, patients may encounter an increased rate and intensity of side effects. Neoadjuvant treatment strategies, on the other hand, have proved to be feasible and well tolerated by patients in different phase II and phase III trials. Results of the recently presented MAGIC trial have shown that 88% of patients completed three cycles of preoperative chemotherapy, whereas only 55% of patients started with postoperative chemotherapy and only 40% were able to receive all six planned perioperative cycles of chemotherapy [2].

Local and systemic effects

Neoadjuvant treatment may, theoretically, be superior to postoperative therapy for two further reasons. First, neoadjuvant treatment potentially leads to “down-sizing” of the tumor and therefore may improve the complete resectability rate, which is the cornerstone of cure in oncological surgery. Second, neoadjuvant induction chemotherapy is the earliest way of tackling the systemic spread of cancer cells, which in many cases is the cause of the poor long-term prognosis [25]. Studies evaluating the pattern of recurrence after curative gastrectomy revealed that in only 30%–38% of patients a sole locoregional failure was found, whereas the remainder of the patients encountered distant or combined local and distant failure [4,26].

Follow-up during neoadjuvant therapy

Owing to progress in investigational techniques, the accuracy of clinical staging has certainly improved. On the other hand, monitoring during neoadjuvant treatment and accurate response evaluation are still entirely unsatisfactory. With the exception of bulky lymph node involvement [27], clinical response evaluation criteria frequently used for metastatic disease have not been validated for localized tumors limited to the gastric wall [28]. Endoscopic ultrasound, although accurate in assessing T category in patients who have not been pretreated, cannot be relied on in patients who have

Table 1. Neoadjuvant chemotherapy for gastric cancer: results of phase II and small phase III studies

Study (First author; ref. #)	Regimen	No. patients	Resectable (R0) no. (%)	Median survival	2-year survival
Wilke 1989 [31]	EAP	34	10 (29%)	18mo	26%
Ajani 1991 [32]	EFP	25	18 (72%)	15mo	44%
Alexander 1993 [33]	FU-FA-INFalfa2a	22	18 (82%)	18mo	52%
Kelsen 1996 [29]	pre-op. FAMTX post-op. ip. CDDP/FU; iv. FU	56	34 (61%)	15mo	40%
Crookes 1997 [34]	CDDP-FU post-op. ip. CTx	59	40 (68%)	>4yr	64%
Siewert 1997 [35]	CDDP-FU-FA	41	30 (73%)	NS	56%
Schuhmacher 2001 [36]	EAP	42	31 (74%)	19mo	40%
Ott 2003 [37]	PLF	42	32 (76%)	25mo	NS
Hartgrink 2004 [38]	FAMTX	27	18 (67%)	18mo	44%

CDDP, cisplatin; CTx, chemotherapy; EAP, etoposide-adriamycin-cisplatin; EFP, etoposide-fluorouracil-cisplatin; FAMTX, fluorouracil-doxorubicin-methotrexate; FA, folinic acid; FU, 5-fluorouracil; ip, intraperitoneal; iv, intravenous; NS, not specified; PLF = cisplatin-leucovorin-fluorouracil

received neoadjuvant chemotherapy [29]. The use of PET in order to assess metabolic response during neoadjuvant chemotherapy for gastric cancer is a very interesting approach but certainly still in a preliminary phase and should be reproduced by larger sample sizes and other investigators [30]. In short, there is as yet no reliable morphological or functional surrogate parameter for response and for the true value of neoadjuvant chemotherapy in gastric cancer. Therefore, the endpoint of neoadjuvant treatment must remain the rate of R0 resections and, more importantly, overall survival.

Results of neoadjuvant chemotherapy

Phase II studies have demonstrated that neoadjuvant chemotherapy can be given with acceptable toxicity and without excessive postoperative morbidity and mortality (Table 1). However, some adverse effects associated with neoadjuvant treatment, such as chemotherapy-induced anemia necessitating preoperative allogenic red cell transfusion, should be carefully investigated for their prognostic impact [39]. What we know from phase II trials is that patients who respond to neoadjuvant chemotherapy have a markedly improved prognosis compared with nonresponders [36,37,40].

However, until recently, no data from adequately powered randomized studies were available. At the 2003 meeting of the American Society of Clinical Oncology, the first results and preliminary survival analysis from the UK Medical Research Council "MAGIC" trial were presented [2]. In this multi-institutional trial, 503 patients with stage II and III gastric cancer were randomized to receive surgery alone or three cycles of preoperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) followed by surgery followed by three postoperative ECF-cycles. A higher proportion of

smaller tumors and of pT1 and pT2 category tumors was found after induction chemotherapy resulting in a higher proportion of potentially curative resections (79% versus 69%, $P = 0.018$, χ^2 test). Unfortunately, pathologically assessed data on the R classification are unavailable at present. Consequently we do not know, how many resections deemed "curative" by the surgeon later revealed residual microscopic disease (R1). After a median follow-up of 2.0 years, progression-free survival was reported as being significantly prolonged in patients randomized to the perioperative chemotherapy arm (log rank P -value = 0.002; hazard ratio = 0.7; 95% CI 0.56–0.88). For overall survival, the hazard ratio was 0.8 in favor of chemotherapy, but this difference had not reached significance ($P = 0.063$) at the time of the first evaluation. With a longer follow-up, the survival advantage may become clearer and statistically significant. The 2-year survival rate was 48% for perioperative chemotherapy versus 40% for surgery alone. However, one can criticize the inclusion of 11% patients with cancer of the distal esophagus in this study. This may trouble the interpretation of the results to a certain extent. More importantly, the assessment of the clinical stage lacks routinely performed endoscopic ultrasound and diagnostic laparoscopy. Furthermore, it seems that the surgical quality control was weak. The type of resection was left at the discretion of the participating surgeon, and there was no recommendation given regarding D1 or D2 lymph node dissection.

In summary, the MAGIC trial is the first large randomized trial that strongly supports the efficacy of perioperative chemotherapy in gastric cancer. On the other hand, the trial leaves us with some questions. Therefore, the updated results including the primary endpoint, which is 5-year overall survival, and the results of confirmatory studies should be waited for before one draws definitive conclusions regarding the impact

of neoadjuvant chemotherapy on the outcome after resection of gastric cancer.

To a certain extent, the results of the MAGIC trial seem to replicate the data obtained in the previously published study of the Medical Research Council Oesophageal Cancer Working Party [41]. Both trials demonstrated an absolute 2-year survival difference in the range of 8% to 9%. The Medical Research Council (MRC) trial compared surgical resection with or without neoadjuvant chemotherapy in esophageal cancer and revealed a significantly higher number of R0 resections after preoperative treatment, which translated into a statistically significant difference in the median survival (16.8 versus 13.3 months; $P = 0.004$). It is fair to say that the results from an esophageal cancer trial should not be applied to the problem of gastric cancer without important restrictions. On the other hand, 10% of the patients included in the MRC trial had a cancer at the cardia and not an esophageal carcinoma. Moreover, the risk reduction by neoadjuvant chemotherapy was particularly high in the group of patients with lower-third esophageal cancers and with cardia cancers. With regard to survival, only in the subgroup of patients with adenocarcinoma was a statistically significant difference demonstrated. Therefore, although not designed for definitive conclusions concerning adenocarcinomas at the gastroesophageal junction, the results from the MRC trial suggest a clinically meaningful benefit from neoadjuvant chemotherapy for adenocarcinomas at or adjacent to the esophagogastric junction.

Results of adjuvant chemotherapy

There is wide use of adjuvant chemotherapy after gastric cancer resection in many countries. However, data are not convincing and do not support the general use of this modality in unselected patient populations who underwent curative resection for gastric cancer. One should bear in mind that very few single trials have shown a survival advantage for adjuvant treated patients. In non-Asian countries, only two trials, both limited by the small number of included patients, have

shown a significant improvement in survival by adjuvant chemotherapy [42,43]. Meanwhile, several meta-analyses on the effect of adjuvant chemotherapy in gastric cancer have been published [44–47]. As indicated by the odds ratios and the confidence intervals, three of the meta-analyses have demonstrated a very small and statistically borderline significant effect in favor of adjuvant chemotherapy (Table 2). In the most recently published and also largest meta-analysis from the Scandinavian group, this advantage was restricted to the studies carried through in Asia. The cause of this difference is not apparent. Several other restrictions should also be considered. First, many of the trials have a relatively high baseline mortality rate. Therefore, the odds ratio may overestimate the relative risk reduction substantially. Second, the limitations of literature-based meta-analyses in general have to be taken into account. Third, the quality of the literature addressing chemotherapy for gastric cancer is frequently poor with few properly designed randomized trials. In a number of randomized multicenter adjuvant studies the inclusion rates have been remarkably low, which reduces the scientific value of the studies.

The authors of all meta-analyses therefore concluded that there is not sufficient evidence to recommend adjuvant chemotherapy as a routine treatment.

Of note, in one subgroup analysis a trend toward a larger magnitude of the effect of adjuvant chemotherapy was shown when analysis was restricted to trials in which at least two-thirds of patients had node-positive disease [44]. This finding is interesting, because it is consistent with adjuvant treatments in breast and colon cancer and with effects seen in other studies. For instance, in a randomized Italian multicenter trial a subgroup of patients with a nodal involvement of more than 6 lymph nodes had a clinically meaningful benefit from adjuvant chemotherapy after gastrectomy and D2 lymphadenectomy (5-year survival 42% versus 22%) [48]. Furthermore, both European studies being in favor of adjuvant chemotherapy included node-positive [43] or stage III and therefore mainly node-positive [42] gastric tumors. However, as this finding is based on a subgroup analysis and on two relatively small studies,

Table 2. Meta-analyses on randomized adjuvant chemotherapy studies in gastric cancer

Meta-analysis (First author; ref. #)	No. studies	No. patients	Odds ratio (CI)
Hermans 1993 [46]	11	2096	0.88 (0.78–1.08)
Earle 1999 [45]	13	1990	0.80 (0.66–0.97)
Mari 2000 [47]	21	3658	0.82 (0.75–0.89)
Janunger 2002 [44]	21	3962	0.84 (0.74–0.96)

CI, confidence interval

respectively, it can only serve to generate hypotheses and should be studied in a large prospective randomized trial. Nevertheless, it suggests that patients at higher risk for recurrence may be the ones who benefit most from adjuvant chemotherapy. Future trials might increase their efficiency by focussing on this group of patients. The right selection could be based on modern prognostic nomograms like the New York Memorial Sloan Kettering Cancer Center Score [49] or on the ratio of the number of invaded in relation to the number of removed lymph nodes, which proved to be of prognostic significance in a multicenter trial carried out in Germany [7].

Results of adjuvant chemoradiation

After the publication of the SWOG9008/INT0116 study, adjuvant chemoradiation after curative gastric resection became a standard of care in some countries. Adjuvant therapy consisted of five cycles of 5-fluorouracil given intravenously as a bolus plus leucovorin plus 45 Gy of external beam radiation at 1.8 Gy per day, given 5 days per week together with the dose-reduced second and third cycles of chemotherapy [3]. At first glance, the statistically significant survival advantage in the adjuvant treatment arm would justify the general use of this adjuvant treatment (Table 3). However, one has to keep in mind that the results were obtained from surgically undertreated patients. Although the study protocol recommended D2 lymphadenectomy based on the resection of the second-tier lymph nodes according to the AJCC TNM classification, which at that time was very similar to the Japanese stage classification, and included appropriate instructions, 54% of the study patients underwent a "less than D1" lymphadenectomy. As reported in a second publication by the same group of authors, surgical undertreatment clearly undermined survival [50]. Therefore, one might presume that adjuvant chemoradiation did no more than compensate to a certain extent for the

sequels of inadequate surgery. While on the one side the absolute number of local relapses (51 patients after surgery alone versus 23 patients after surgery plus chemoradiation) and regional relapses (127 versus 78 patients) was higher in the surgery alone group, on the other side no difference was observed in the number of distant relapses (32 versus 40 patients). The improvement in survival after chemoradiation observed in this study therefore arises solely from a better locoregional tumor control. Compared to other series, the magnitude of locoregional relapses seems to be particularly high in this trial. As it has become clear now that extended lymphadenectomy leads to better tumor control and survival [51], one might assume that after D2 lymphadenectomy, adjuvant chemoradiation would add little or nothing to the patients' prognosis. Therefore, the efficacy of adjuvant chemoradiation should absolutely be reproduced in a quality-controlled multicenter study which includes patients after D2 lymphadenectomy and which has a control arm without postoperative adjuvant treatment.

Another matter of concern is the limited tolerability of adjuvant chemoradiation. The SWOG9008/INT0116 study included only patients deemed fit for adjuvant therapy. There is no information at this point on how many patients could not be enrolled due to prolonged postoperative recovery and due to typical postsurgical complications. However, of the 281 patients assigned to the chemoradiotherapy group, only 181 (64%) completed treatment as planned. This drop-out rate exceeds by far the numbers usually seen during adjuvant chemotherapy protocols in many malignancies. The most commonly severe toxicity was reported to be hematologic (54% of patients) and gastrointestinal (33%) side effects. It was frequently brought up that the relatively large radiation fields being applied in the SWOG9008/INT0116 study may account for the mediocre tolerance of the treatment. However, even with modern strategies of adjuvant chemoradiation, toxicity remains considerable. Weight loss is a considerable concern in this group of patients [52]. Recently presented data suggest that late

Table 3. Results of the randomized phase III "SWOG 9008/INT 0116" trial assessing the role of adjuvant chemoradiation after curative gastric cancer resection compared to surgery alone [3]

	Adjuvant (<i>n</i> = 281)	Surgery alone (<i>n</i> = 275)	<i>P</i> value
Median duration of survival	36 months	27 months	0.005
Three-year survival rate	50%	41%	
Hazard ratio for death	1.0	1.35 (95% CI 1.09–1.66)	0.005
Median relapse-free survival	30 months	19 months	0.001
Three-year relapse-free survival	48%	31%	
Hazard ratio for relapse	1.0	1.52 (95% CI 1.23–1.86)	0.001

SWOG9008/INT0116, Southwest Oncology Group 9008/Intergroup 0116; CI, confidence interval

renal toxicity after postoperative chemoradiotherapy in gastric cancer also merits thorough attention [53].

In summary, the controversial role of adjuvant chemoradiation in gastric cancer is still being discussed. Based on the findings of the SWOG9008/Intergroup0116 trial, postoperative chemoradiation should only be recommended when the surgical objective of an extended (D2) lymphadenectomy is missed. The situation of microscopically incomplete resection (R1) has not been sufficiently studied to draw definitive conclusions.

Nonmetastatic gastric cancer: suggestion for a multimodal treatment approach

As data from the literature supporting multimodal strategies are not persuasive at this stage, clinically staged standard risk gastric cancer should be resected (D2 lymphadenectomy) and, in the absence of risk factors apparent from the pathological report, patients should not routinely undergo adjuvant treatment. This procedure should also be the control arm of new clinical trials evaluating the role of specific pre- or postoperative interventions. But in the case of a positive survival endpoint reported by the “MAGIC” investigators, neoadjuvant chemotherapy should be considered in all stage II and stage III tumors.

In cancers with a limited probability of a complete (R0) resection, i.e., endoscopically staged uT3 and uT4 tumors, it can already be recommended at present that neoadjuvant chemotherapy be administered. The sensitivity to chemotherapy can best be judged from the histomorphological grading of regression obtained after preoperative treatment, when the patient underwent resection [54].

At our clinic, the recommendation for or against postoperative, adjuvant treatment is based on the response to neoadjuvant treatment, on the presence of pathological risk factors, i.e., the extent of lymph node involvement, and on the completeness of the surgical resection including a D2 lymphadenectomy, being judged appropriate when at least 25 lymph nodes are removed (Fig. 1).

Perspectives

One major goal of future clinical research will be to get a clearer definition of prognostic and predictive markers. This should help to customize adjuvant and neoadjuvant treatment strategies for the individual patient.

One approach is based on biochemical technologies. Detection of tumor targets or molecules associated with the mechanisms of action of anticancer drugs may pre-

Fig. 1. Individualized recommendation for adjuvant treatment strategies in gastric cancer patients who underwent neoadjuvant chemotherapy or those who underwent primary resection. CTX, Chemotherapy; LN-ratio, ratio between invaded and removed lymph nodes; RCTX, radiochemotherapy

dict the likelihood of treatment response. Expression of 5-fluorouracil-related genes or enzymes such as the tumor thymidilate synthase, thymidine phosphorylase, and dipyrimidine dehydrogenase, and of cisplatin-related genes such as *ERCC1* or *GADD45a* may help to predict response to chemotherapy containing 5-fluorouracil and cisplatin [55–58]. However, it must be emphasized that these findings have not yet been validated in large-scale studies and therefore cannot serve as a basis for clinical decision making at this stage.

An alternative approach is the early assessment of metabolic changes in the tumor by means of molecular imaging techniques such as PET. One such model is the quantification of changes in the 5-FDG uptake into tumor tissue. Two studies have demonstrated that PET imaging may differentiate responding and nonresponding tumors early in the course of neoadjuvant systemic chemotherapy [30,59].

With the expansion of our chemotherapeutic armamentarium by compounds such as oxaliplatin, irinotecan, and docetaxel, all of which have shown promising activity in the treatment of gastric cancer, there is certainly a need for new, more active, or better tolerated induction chemotherapy protocols to be tested in phase II and phase III studies. Probably, the introduction of new biologically targeted compounds will further improve the efficacy of adjuvant and neoadjuvant treatment.

Presumably, the future will bring tailored treatment strategies based on the reliable specification of constitutional and tumor-related characteristics. As indicated by preliminary data [60], genomic profiling may be a key technology in this context. It is hoped that a better understanding of the individual tumor biology will make treatments more effective and will reduce over- and undertreatment of patients with gastric cancer.

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