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Neoadjuvant Treatment for Gastric Cancer

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Surgery is still considered to be the mainstay for the treatment of localized gastric cancer with negative margins (R0-resection) and an adequate lymph-node-dissection (D2-lymphadenectomy). Unfortunately, most cases of gastric cancer are only diagnosed at an advanced stage due to frequent recurrences after primary resection in curative intent. In order to improve prognosis after curative resection, in the recent past, patients with locally advanced tumors were subjected to a pre-, peri-, or postoperative treatment. Interestingly, postoperative chemotherapy has significantly improved survival after gastric resection in Asia, adjuvant radiochemotherapy is favored in North America and perioperative chemotherapy is considered as a treatment of choice in Europe indicating region specific approach towards the treatment. Recently there has also been growing evidence of positive outcomes of neoadjuvant radiochemotherapy on patient survival. In the present article, we discuss the concepts of neoadjuvant treatment approach and provide recommendations to surgeons based on current evidence.

Key Words: Gastric cancer; Neoadjuvant therapy; Chemotherapy; Chemoradiotherapy; Surgery

Introduction

In comparison to most Asian countries (Korea, Japan, Taiwan), Western countries lack national screening programs, since those are not considered rational given the much lower gastric cancer incidence compared to Asia.[1] Therefore gastric cancer is usually diagnosed at an advanced stage in the West due to mostly unspecific symptoms.[2] This is why its prognosis is still bad in spite of adequate surgery with radical lymphadenectomy. While the 5-year survival of patients with early gastric cancer is about 75%,[3] it is 30% or less for patients with extensive lymph node involvement.[2] Since the early 90s of the last century neoadjuvant treatment concepts are increasingly employed in the treatment of locally advanced gastric cancer, especially in Europe. Hereby phase II studies consistently demonstrated positive effects of preoperative chemotherapy (high R0 resection-rates and good survival-rates).[4,5] Meanwhile two randomized studies were able to demonstrate the advantage of perioperative chemotherapy (pre- and postoperative) over surgery only.[6,7] Regarding the effects on the tumor tissue but due to the small number of patients not significant in terms of a survival difference, this could also be shown by another randomized trial for preoperative chemotherapy only.[8] Preoperative chemoradiotherapy (CRT), however, is not yet fully established, even though a German pilot-study was able to demonstrate a high percentage of complete responders and recent data from a Dutch trial indicate additional positive effects of radiotherapy on overall survival (OS).[9,10] While in the above-mentioned Western studies preoperative chemotherapy is an essential part of all protocols, Asian oncologists mostly rely on a postoperative oral chemotherapy regimen, for which a randomized study could show a marked survival improvement in comparison to surgery only.[11,12] In spite of numerous studies investigating adjuvant chemotherapy in gastric cancer, these good results could regrettably not be reproduced in Western series.

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The present article gives an overview of the already briefly mentioned landmark-studies investigating neoadjuvant therapy in gastric cancer and discusses them against the background of recent trends and developments.

When talking about neoadjuvant treatment of gastric cancer, one is forced to deal with the actual 7th edition of the American Joint Committee on Cancer/International Union for Cancer Control (AJCC/UICC)-classification. According to which adenocarcinomas of the esophagogastric junction (EGJ) type II and III after the Siewert-classification are prognostically no longer counted among gastric carcinomas, but rather among esophageal carcinomas. This circumstance is not taken into account by any of the studies mentioned in this article. Therefore the data have to be interpreted with caution in terms of tumor location. From the surgical point of view those tumors undoubtedly have to be treated as gastric carcinomas with a gastrectomy including transhiatal extension to the distal esophagus.

Neoadjuvant/Perioperative Chemotherapy

The advocates of neoadjuvant chemotherapy in the sense of the meaning, which means preoperative chemotherapy only, invoke certain advantages in comparison to the adjuvant, postoperative administration[13]: 1. Owing to a usually better preoperative general health condition of patients the full chemotherapy-dosage can be applied; 2. Blood-supply and architecture of lymph-vessels, which may play a role in chemotherapy-induced destruction of tumor cells, are not yet compromised by the surgical procedure; 3. A shrinkage oft the tumor may lead to higher R0 resection rates; 4. Micrometastases are being treated at the earliest time possible; 5. Reduction of contamination of the abdominal cavity with tumor cells because of a 'sterilization' of the tumor; 6. The preoperative treatment offers the possibility of an '*in vivo*' testing of the applied therapy regimen; 7. The eventual postoperative therapy can be tailored to the individual response to the preoperative treatment.

Based on the results of three European randomized phase III trials investigating the effect of perioperative chemotherapy in the treatment of gastric cancer it has advanced to the standard treatment in Europe. In the so called 'MAGIC-trial'[6] patients with resectable gastric cancer and adeoncarcinomas of the EGJ were randomized to surgery flanked by perioperative chemotherapy (n=250) or surgery only (n=253). Chemotherapy consisted of three preoperative and three postoperative cycles of i.v. epirubicin, cisplatin and continuous 5-fluorouracil (5-FU). Postoperative complications and 30-day-mortality in both treatment arms did not differ significantly (46% vs. 45% and 5.6% vs. 5.9%). For patients in the chemotherapy 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 chemotherapy was significantly increased compared to patients treated by surgery only (P=0.009 and P < 0.001). The 5-year survival rate was 36% for patients receiving perioperative chemotherapy and 23% for patients treated by surgery only.

On the 2007 American Society of Clinical Oncology (ASCO) congress the results of the French FNLCC ACCORD 07 FFCD 9703 trial were presented and were finally published in 2011 as full manuscript.[7] Patients with resectable gastric cancer or esophageal adenocarcinoma were enrolled. The chemotherapeutic regimen consisted of 2~3 cycles of i.v. 5-FU and cisplatin. A postoperative chemotherapy was recommended in case of a response to the preoperative treatment or stable disease with positive lymph nodes. 113 patients received preoperative chemotherapy and 111 patients underwent primary surgery. The R0 resection rate among the patients receiving chemotherapy was significantly higher compared to the primary surgery arm (84% vs. 73%; P=0.04). OS and disease-free survival (DFS) were significantly prolonged after chemotherapy (P=0.02 and P=0.003, respectively). The 5-year survival rates largely match those reported for the MAGIC-trial (see above) with 38% in the chemotherapy and 24% in the surgery only arm. Critics of both studies invoke the long recruiting period (8 years in both studies), the poor preoperative staging workup, the improper histopathological workup, the poor surgical quality and the high drop out rate in the postoperative chemotherapy arm. However, since it can assumed that all those points were evenly distributed among both treatment arms, the results of these two studies are generally accepted in the Western hemisphere, which presently makes perioperative chemotherapy the standard treatment in Europe.

In 1999 the EORTC 40954-trial[8] was issued with the goal to achieve a higher surgical quality and higher grade of standardization in comparison to the trials mentioned before. In this trial preoperative chemotherapy only with cisplatin, 5-FU and folinic acid (PLF-protocol) was employed in a phase III setting. Only patients with locally advanced, resectable gastric cancer or adenocarcinoma of the EGJ (adenocarcinoma of the esophagogastric junction [AEG] II and III) were included. All patients were subjected to an elaborate staging workup with esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), computed tomography (CT) and a standardized staging-laparoscopy.[14] Resection was performed obeying

strict surgical quality standards, including a D2-lymphadenectomy. Regrettably the trial had to be closed early due to poor accrual after inclusion of 144 patients (n=72 per treatment arm). This decline of the numbers was a result of the meanwhile published data from the MAGIC trial favoring the neoadjuvant treatment arm. The analysis of the patients included up to then showed a higher R0 resection rate among the patients treated with neoadjuvant chemotherapy compared to those undergoing primary surgery (81.9% vs. 66.7%; P=0.036). Additionally the percentage of nodal-positive patients was significantly lower after chemotherapy compared to surgery only (38.6% vs. 19.1%; P=0.018). A downstaging and a tendency towards a prolonged OS and DFS for the neoadjuvant treatment arm could be observed (P=0.113 and P=0.065) but did not reach significance level. Postoperative complications and deaths were also more common among patients treated with neoadjuvant chemotherapy (27.1% vs. 16.2%; P=0.09 and 4.3% vs. 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 chemotherapy arm (median survival 64.6 mo vs. 52.5 mo; P=0.466) (in order to reach a power of 80% 282 deaths would have been necessary). However, the achieved OS in both arms can be considered excellent and might not least be attributed to the high rate of D2-lymphadenectomies, the exclusion of patients with occult peritoneal seeding and the fact that 75% of patients were enrolled by only two centers with a long standing experience in upper-gastrointestinal (GI) surgery. The missing significance regarding patient-survival in spite of higher R0 resection rates may most probably be attributed to the low patient number and the high surgical quality.

Two recent meta-analyses dealing with this subject showed hazard-ratios of 0.68 (95%CI 0.48~0.97; P=0.03)[15] and 0.82 (CI 0.73~0.91; P=0.0002)[16] for 5-year survival in favor of neoadjuvant chemotherapy. Ronellenfitsch et al.[16] additionally performed a subgroup analysis in which this survival advantage could just be observed of tumors located at the EGJ and not for gastric cancer in the proper sense (P=0.007 and P=0.31). The authors admit, however, that the analysis was underpowered to reach significance level.

All in all the efficacy and superiority of perioperative chemotherapy in combination with surgery in comparison to surgery only could be shown in two European randomized phase III trials, while a third trial at least tendentially supports the findings of the first-mentioned trials. In all three randomized trials no significant increase in postoperative complications and mortality, as well as duration of hospitalization could be observed.

Based on the results of the REAL-2-trial in metastasized gastric cancer, in which the statistic non-inferiority of oxaliplatin in comparison to cisplatin and of capecitabine in comparison to 5-FU could be demonstrated, those drugs are regarded as alternatives for perioperative chemotherapy.[7,17]

Neoadjuvant Chemoradiotherapy

After several meta-analyses had proven preoperative CRT to increase survival in esophageal adenocarcinomas,[18-20] in 2009 Stahl et al.[9] reported the results of a prospective randomized phase III trial testing neoadjuvant chemotherapy against neoadjuvant CRT in patients with adenocarcinomas of the EGJ-often also referred to as the POET trial. Hereby patients with locally advanced (uT3-4NxM0) AEG I~III were randomly allocated to 2 courses of PLF (cisplatin, 5-FU, folinic acid) followed by 3 weeks of combined CRT (30 Gy, 2 Gy per fraction, 5 fractions per week, cisplatin/etoposide) followed by surgery or 2.5 courses of PLF only followed by surgery. Regrettably the trial did not meet its accrual goals and was closed

Table 1. Randomized trials investigating the effect of neoadjuvant therapy in locally advanced esophagogastric cancer with curative intention

Parameter	MAGIC[6]	FFCD 9703[7]	EORTC 40954[8]	CROSS[10]
Regimen	CT perioperative	CT perioperative	CT preoperative	CRT preoperative
Tumor location	GC+EGJ	GC+EGJ	GC+EGJ	Esophagus†+EGJ
R0-resection rate, P (res. vs. mult.)	0.018*	0.04	0.036	<0.001
Received full preoperative treatment	86%	87%	65.2%	91%
Received full treatment pre- and postoperative	42%	50%	-	-
OS, P (res. vs. mult.)	0.009	0.021	0.466 n.s.	0.003
PFS/DFS, P (res. vs. mult.)	<0.001	0.003	0.2 n.s.	<0.001

CT = chemotherapy; CRT = chemoradiotherapy; GC = gastric cancer; EGJ = esophagogastric junction; res. = surgery only; mult. = multimodal therapy; OS = overall survival; PFS = progression free survival; DFS = disease-free survival. *As determined by the surgeon, †also included 23% of esophageal squamous cell carcinoma in each arm.

early with a total of 116 patients for analysis. Median survival for the CRT arm was 33.1 months and 21.1 months for the CT arm, which however missed significance level (P=0.07). Hospital mortality in the CRT group was higher compared to the CT group (10.2% vs. 3.8%); this difference, however, again was not significant (P=0.26).

A recent study from the Netherlands, the so-called 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.[10] 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 366 patients were analyzed, 75% of which had adenocarcinoma. The R0 resection rate in the CRT group was significantly higher compared to the surgery only group (92% vs. 69%, P<0.001) with a pathological complete response in 29% in the former. Hereby a pathologic complete response was observed in 23% of patients with adenocarcinoma and 49% of patients with squamous cell carcinoma. Median OS was also significantly better after CRT+surgery compared to surgery only (49.9 vs. 24.0 mo; P=0.003; HR 0.675; 95% CI, 0.495~0.871), while postoperative complications and in-hospital mortality (4% in both) were similar in both arms. Even though the benefit of neoadjuvant CRT on survival was consistent across all subgroups analyzed, it was most pronounced in the subgroup of patients with squamous-cell carcinoma.

Table 1 gives an overview on the relevant randomized trials investigating neoadjuvant therapy in locally advanced gastric cancer.

Conclusions

Interestingly different approaches in multimodal gastric cancer therapy can be observed in Asia and Europe: while Asian countries rely on surgery followed by adjuvant chemotherapy perioperative chemotherapy has become the standard of care in the Europe, now actually being challenged by neoadjuvant CRT. What is the reason for those differences? One has already been mentioned in the introduction: owing to national screening programs gastric cancer tends to be diagnosed earlier in Asian countries compared to countries in the western hemisphere so that there is no need for down-staging in most cases—the initial idea that led to the development of neoadjuvant protocols. Critics of the multimodal approach in gastric cancer argue that neoadjuvant or perioperative chemotherapy just makes up for inadequate sugery. In Asian countries the issue of lymphadenectomy has traditionally been taken more attention than it has in the West, which is always a point of criticism when it comes to Western trial investigating multimodal treatment of gastric cancer.[6,21] The results of the EORTC 40954-trial[8] also indicate that the effect of multimodal treatment protocols are more pronounced in patients with inadequate lymphadenectomy. Anyhow, at least in the adjuvant setting in an Asian population (ACTS-GC-trial) the positive effect of the combination of surgery and chemotherapy seems to be proven for stage II and stage III gastric cancer, in spite of a D2-resection rate of 100%.[11] Another difference between the East and the West most probably lies in the tumor biology, which seems also to be reflected by the tumor location. While the incidence of adenocarcinoma of the lower esophagus and the gastric cardia (AEG I~III) is increasing in most Western populations,[22-24] in Asian countries where gastric carcinoma in the proper sense is more common junctional adenocarcinomas are still rare.[25,26] There is evidence from a metaanalysis and a retrospective analysis of a large single-center cohort, that predominantly patients with cancer of the EGJ seem to benefit from neoadjuvant chemotherapy.[16,27] Also both landmark trials showing a positive effect of neoadjuvant CRT just included adenocarcinomas of the EGJ.[9,10] So a commonly less radical lymphadenectomy and the higher prevalence of junctional adeoncarcinomas in the West as compared to Asia may be an explanation for the different preferences when it comes to multimodal treatment of gastric cancer. Another point is the good experience in Asia with the oral fluoropyrimidine S-1 that is usually employed in the adjuvant setting. The tegafur contained in S-1 is a prodrug of 5-FU, which is metabolized to 5-FU in the body via cytochrome P-450 dependent enzymes. Tegafur is differently metabolized in patients with Asian and European heritage due to polymorphisms of the CYP2A6-Gene,[28] leading to a significantly reduced safety-profile in Western patients, so that S-1 did not acquire widespread acceptance among Western oncologists. Whether EGJ tumors should be treated by CRT or CT and if those results are also applicable to gastric cancer in the proper sense can presently not be answered.

However, a multimodal approach seems to consistently result in a survival benefit when used in operable gastric cancer. The actual dilemma we are facing is that the positive effects of adjuvant chemotherapy have been shown for gastric cancer in the proper sense in an Asian population, while the positive effects of perioperative chemotherapy (with an emphasis on the neodjuvant part) have been shown in an European population of gastric cancer patients with a high percentage of tumors located at the EGJ and a less

radical lymphadenectomy.[6] 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.[9,10] The task for the near future will be to first determine the effect of the adjuvant part of perioperative chemotherapy which still remains unclear since only 54.8% of patients assigned to perioperative chemotherapy in the MAGIC-trial actually received postoperative chemotherapy due to various reasons.[6] In this context future studies should take the patients individual response to the neoadjuvant chemotherapy into consideration when deciding upon the administration of an additional adjuvant treatment. In a second step those patients who benefit from neoadjuvant treatment have to be exactly determined in terms of tumor-location and maybe also Laurén-histotype,[27,29] before the possible advantage of the additional administration of radiotherapy to CT over neoadjuvant CT only can be found out in a third step. The answer to these questions would lead to a more differentiated, individualized use of neoadjuvant and adjuvant treatment strategies in gastric cancer therapy. It is questionable, however, given the accrual problems of previous trials[8,9] if such trials are presently feasible in Europe.

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