(Neo)-Adjuvant Chemo(-Radio) Therapy for Adenocarcinomas of the Gastroesophageal Junction and the Stomach in the West

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Abstract
Worldwide, the treatment of adenocarcinomas of the gastroesophageal junction and stomach has changed over the past decades. It is no longer surgery alone. Nowadays, most patients undergo surgery plus pre- and/or postoperative therapies. However, there are still marked differences in surgical procedures between the East and the West which might influence the surgical prognosis and thereby also the choice of perioperative treatment strategies. In the East, with its more extended surgical procedures, including standard D2 dissections, the current treatment philosophy is primary surgery followed by adjuvant chemotherapy. Neoadjuvant approaches are restricted to really advanced tumors, and perioperative chemoradiation is not routinely used (at least to date). This clearly differs from treatment strategies currently recommended in Western countries. In Europe and North America, pre- plus postoperative chemotherapy has become the recommended treatment for locally more advanced tumors, and preoperative chemoradiation is increasingly administered to patients with adenocarcinomas of the gastroesophageal junction (Siewert type I/II). However, the role of postoperative chemotherapy (despite its increasing use) is still under discussion in the West (especially Europe) and not generally recommended/accepted as a standard treatment. Postoperative chemoradiation, which is one standard treatment in North America, is only regarded as a treatment option for patients after ‘inadequate surgery’ (i.e. <D2 dissection) in many European countries.

Introduction
Adenocarcinoma of the gastroesophageal junction and the stomach remain a therapeutic challenge in the West that has remained essentially unchanged over the past decades. Despite improved preoperative staging procedures allowing a better patient selection for ‘curative’ surgery and despite improved surgical techniques and perioperative management strategies, the 5-year survival rates are still less than 30% with a median survival time of approximately 24 months. This is mainly due to the fact that more than 70% of Western patients are diagnosed
with locally advanced tumors and/or distant metastases. Only 10–15% of Western patients primarily present with an early tumor stage compared to more than 50% in Asia, especially in Japan and Korea.

Nevertheless, there is increasing evidence that even patients with locally advanced disease have an improved survival prognosis if perioperative (chemotherapy with/without radiotherapy) therapies are included in the treatment strategies for these tumors. However, the question as to which kind of perioperative treatment should be offered to an individual patient does not only differ between the West and the East, but also within the West.

It is very likely that the differences in the overall outcome of clinical trials in the West and East (surgical trials and trials including pre- and postoperative treatment strategies) and their interpretation concerning further treatment strategies can in part be explained by differences in the way surgery is performed in the East and West. There is no doubt about the value of an R0 resection in the Western countries, but there has been a long discussion about the appropriate extent of lymph node dissection (D1 vs. D2). The surgical and oncological standpoint of view of Eastern oncologists is that a D1 dissection is inadequate and associated with a higher local failure rate. In the West however, based on the results of two larger randomized European trials comparing D1 versus D2 dissection, a D1 dissection was regarded as an appropriate treatment until recently. Meanwhile, long-term follow-up data of a Dutch trial [1] showed a lower locoregional recurrence rate and a longer disease-free survival rate for patients after a D2 dissection compared with those who had a D1 dissection. Nowadays, a D2 dissection is also recommended as the standard surgical procedure in many Western countries [2, 3].

Similar to Asia, multimodal treatment strategies, such as preoperative chemotherapy, pre- plus postoperative chemotherapy, preoperative chemoradiotherapy, postoperative chemotherapy, and postoperative chemoradiotherapy, have been investigated in the West over the past three decades. However, the therapeutic conclusions drawn from many published phase II/III trials and meta-analyses are in part different to what is recommended in Asia.

This review presents and discusses the current status of the Western view of perioperative treatment strategies in adenocarcinomas of the gastroesophageal junction and stomach. The rationale of the different perioperative treatment strategies will not be outlined as they are nicely described in Fujitani’s article [this vol., pp. 119–129].

Pre- plus Postoperative (Perioperative) Chemotherapy

If we accept the statement ‘No cure without adequate surgery’, then treatment strategies with the aim of increasing R0 resection rates are of particular interest. Since the mid-1980s, results of phase II studies with preoperative chemotherapy in patients with surgically (explorative laparotomy) or clinically staged unresectable gastroesophageal adenocarcinomas indicated a downsizing/downstaging effect as well as higher R0 resection and survival rates compared to historical controls [4].

Meanwhile, two positive randomized trials comparing pre-plus postoperative chemotherapy versus surgery alone in patients with gastroesophageal adenocarcinomas (predominantly stage II/III according to the former UICC classification) with nearly identical results have been published [5, 6]. These studies included patients with tumors of the gastroesophageal junction and the stomach. This was and is still an acceptable approach because the efficacy of chemotherapy (i.e. response rates and survival times) was very similar in both tumor localizations.

More than 500 patients were randomized into the MAGIC trial, receiving either perioperative chemotherapy [epirubicin, cisplatin, 5-fluorouracil (ECF); 3 cycles were planned before and after the operation] or surgery only [5]. The postoperative complication (46%) and 30-day mortality rates (6%) were similar in both treatment arms. Compared with the surgical alone arm, preoperative chemotherapy resulted in a significant reduction of the initial tumor extent (5 vs. 3 cm) and significantly lower T and N categories. The progression-free survival rates (p = 0.001) and the absolute survival rates at 5 years (36 vs. 23%, p = 0.009) were significantly better in the perioperative ECF arm.

Nearly identical results were achieved in the French FNCLCC/FFCD trial (224 patients), which compared pre- (2–3 cycles) and postoperative (1–4 cycles) cisplatin/5-fluorouracil (CF) with surgery alone [6]. The R0 resection rate was significantly higher after preoperative CF and fewer advanced T and N categories were observed. Postoperative complication and mortality rates were not different. The 5-year disease-free survival rate was significantly better in the perioperative chemotherapy arm as well as the survival rate with an absolute difference of 13 and 14%, respectively. The use of perioperative chemotherapy was an independent and prognostic favorable variable in both studies, underlining its importance for the positive outcome. Table 1 summarizes the relevant results of the MAGIC and FNCLCC/FFCD trial.
The results of a recent meta-analysis of seven randomized trials (1,249 patients) comparing neoadjuvant chemotherapy versus surgery alone in patients with locally advanced gastroesophageal adenocarcinomas come to the following conclusions supporting the positive study results of the MAGIC and FNCLCC/FFCD trial [7]. A fluorouracil-based neoadjuvant chemotherapy significantly improves overall survival rates (OR: 1.40, \( p = 0.005 \)), 3-year progression-free survival rate (OR: 1.62, \( p = 0.001 \)), tumor downstaging rate (OR: 1.77, \( p = 0.0009 \)), and R0 resection rate (OR: 1.38, \( p = 0.03 \)). No obvious safety concerns were raised based on a nearly identical perioperative mortality rate (5.08 vs. 4.86%).

Monochemotherapy was inferior to combination chemotherapy and intravenous administration was more advantageous than the oral route.

The use of pre- plus postoperative chemotherapy for gastric and gastroesophageal junction adenocarcinomas has gained increasing interest in the Western world and is nowadays regarded as the preferred treatment modality at least for locally advanced tumors [8].

**Preoperative Chemoradiotherapy**

Based on a couple of meta-analyses in esophageal cancer, preoperative chemoradiotherapy with surgery proved superior to surgery alone in localized disease [9]. The hazard ratios (HR) for overall survival ranged from 0.53 to 0.87, thus emphasizing the significant improvement of about 25% with multimodal treatment. These analyses evaluating survival for subgroups clearly show that the benefit of preoperative chemoradiotherapy was even more pronounced in adenocarcinomas [10]. It can be concluded from the single trials that most of the patients in these studies had adenocarcinoma of the gastroesophageal junction.

Sjoquist et al. [11] reviewed studies with preoperative chemoradiotherapy and those with preoperative chemotherapy alone in patients with localized gastroesophageal adenocarcinomas. Three randomized trials including 345 patients were evaluated for chemoradiotherapy. The HR for overall survival was 0.75 (95% CI: 0.59–0.95) and the log-rank \( p \) value reached 0.02. In comparison, another three trials including 976 patients were evaluated for chemotherapy. Overall survival was also significantly improved by preoperative treatment, but to a lower extent (HR: 0.83, 95% CI: 0.71–0.95, \( p = 0.007 \)).

Until now, only two randomized trials have been performed to compare preoperative chemoradiotherapy and chemotherapy, respectively, in gastroesophageal adenocarcinomas [12, 13]. Stahl et al. [12] randomized 126 patients with locally advanced adenocarcinoma of the gastroesophageal junction based on extended diagnostic procedures including endoscopic ultrasound and laparoscopy. The addition of radiotherapy led to significantly less incomplete resections and increased the number of patients with a pathologic complete tumor remission. This improved the 3-year survival rate from 28% without preoperative chemotherapy to 48% with preoperative chemoradiotherapy. Unfortunately, the study was stopped early due to low recruitment and therefore this clinically important increase in survival was not statistically significant (\( p = 0.07 \)). Burmeister et al. [13] randomized 75 patients with adenocarcinoma of the esophagus or gastroesophageal junction in a phase II trial and the majority had resectable stage II disease. Also different from the German study, they used significantly less chemotherapy in both arms. Again the addition of radiotherapy significantly increased the rate of pathologic complete remission (13 vs. 0%, \( p = 0.02 \)) and reduced the rate of R1 resection (0 vs. 4%, \( p = 0.04 \)). However, only a trend in favor of preoperative chemoradiotherapy, but no statistical differences, were observed in progression-free and...
overall survival (5-year survival rate: 45 vs. 36%, p = 0.6). Of note, both studies did not show a significant increase in postoperative mortality due to preoperative radiotherapy.

These two trials were included in a meta-analysis [11] showing a trend for superior survival of chemoradiotherapy compared to chemotherapy prior to surgery (HR: 0.77, 95% CI: 0.53–1.12) with some heterogeneity between the studies precluding to calculate the p value [11].

In conclusion, preoperative chemoradiotherapy significantly improves the prognosis of patients with localized gastroesophageal adenocarcinoma compared to surgery alone. It also appears that this advantage is more pronounced than with preoperative chemotherapy alone, but this remains a matter of debate and further well-designed clinical trials. Nevertheless, based on published data, the EORTC St. Gallen International Expert Consensus Conference recommended preoperative chemoradiotherapy as the preferred treatment for AEG type I/II tumors (Siewert classification) [8]. Other national guidelines support this statement [14] and preoperative chemoradiotherapy is increasingly used in this indication in the West.

**Adjuvant Chemotherapy**

Independent of the fact that adjuvant chemotherapy after gastric cancer resection is used in Western countries, data from Western studies are less convincing than data from East Asia [15, 16]. Only a few single trials have suggested a survival advantage for adjuvant treated patients in non-Asian countries. Meanwhile, several meta-analyses have been published [17–21]. As indicated by the OR and the CI, 4 out of 5 meta-analyses have demonstrated a moderate but statistically significant effect in favor of adjuvant chemotherapy (table 2). But several restrictions should be taken into account. First, many of the trials from Western countries have a relatively high baseline mortality rate. Therefore, the OR 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 Western 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. Finally, many Western trials have been underpowered to show smaller survival benefits.

<p>| Table 2. Meta-analysis of randomized adjuvant chemotherapy studies in gastric cancer |
|------------------------------------------|-------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Studies, n</th>
<th>Patients, n</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans et al. [17]</td>
<td>11</td>
<td>2,096</td>
<td>0.88 (0.78–1.08)</td>
</tr>
<tr>
<td>Earle and Maroun [18]</td>
<td>13</td>
<td>1,990</td>
<td>0.80 (0.66–0.97)</td>
</tr>
<tr>
<td>Mari et al. [19]</td>
<td>21</td>
<td>3,658</td>
<td>0.82 (0.75–0.89)</td>
</tr>
<tr>
<td>Janunger et al. [20]</td>
<td>21</td>
<td>3,962</td>
<td>0.84 (0.74–0.96)</td>
</tr>
<tr>
<td>Gastric Group [21]</td>
<td>17</td>
<td>3,838</td>
<td>0.82 (0.75–0.90)</td>
</tr>
</tbody>
</table>

In 2002, a Scandinavian group published a meta-analysis, the largest known to date, which showed the advantage of adjuvant chemotherapy seemed to be restricted to studies performed in Asia [20]. The cause of this difference could not be explained. The GASTRIC Group recently published a meta-analysis in which they investigated heterogeneity among the regions where the trials were conducted (Europe, Asia, and the United States) [21]. Interestingly, they reported an absence of interaction with the region, which speaks against a definitive difference between study results from Asia and the Western world. The authors also saw no interaction with four different chemotherapy regimen groups (e.g. mono- vs. polychemotherapy and anthracycline-containing vs. anthracycline-free chemotherapy). This observation is in line with a couple of studies that found no difference between fluoropyrimidine monotherapy and much more toxic polychemotherapy regimens [22–24]. Of note, in one of the subgroup analyses from the Scandinavian group, a trend towards a larger magnitude of the effect of adjuvant chemotherapy was shown when the analysis was restricted to trials in which at least two thirds of the patients had node-positive disease [20]. This finding is interesting because it is consistent with adjuvant treatment in other gastrointestinal cancers and with effects seen in Asian studies [16]. In line with this finding, authors of a negative randomized Italian multicenter trial did an analysis of their patients included with nodal involvement >6 lymph nodes. These patients had a clinically meaningful benefit from adjuvant chemotherapy following gastrectomy and D2 lymphadenectomy (5-year survival: 42 vs. 22%) [25]. As these findings are based on subgroups, they should not guide definitive treatment recommendations. Nevertheless, they suggest that patients at higher risk of recurrence, especially a positive nodal status, may have a greater benefit from adjuvant chemotherapy.

Future trials of adjuvant chemotherapy in Western populations should probably focus on the groups of pa-
tients with particular risk of relapse. The right clinical selection could be based on prognostic nomograms like the New York Memorial Sloan Kettering Cancer Center score [26] 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 [27].

**Adjuvant Chemoradiation**

Locoregional relapse is a significant problem in resected gastric cancer [28]. After the publication of the Southwest Oncology Group 9008/Intergroup 0116 study, adjuvant chemoradiation after curative gastric resection became a standard of care in some European countries and in many US centers [29]. The 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 cycle of chemotherapy. At first glance, the statistically significant survival advantage in the adjuvant treatment arm would justify the general use of adjuvant chemoradiation (table 3). However, one has to keep in mind that the results were obtained in a group of patients who had undergone subradical surgical resection. Although the study protocol recommended D2 lymphadenectomy 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 [30]. Therefore, one may presume that adjuvant chemoradiation did not more than compensate to a certain extent for the sequelae of inadequate surgery. This assumption is supported by observations from well-documented patients treated in phase I/II trials of adjuvant chemoradiation in the Netherlands [31] and also by the recently published long-term results of the SWOG 9008/Intergroup 0116 study showing in a subgroup analysis that patients who underwent D2 lymphadenectomy did not derive any benefit from adjuvant chemoradiation [32]. While the absolute number of local relapses (21 patients after surgery alone vs. 7 patients after surgery plus chemoradiation) and regional relapses (109 vs. 62 patients) was higher in the surgery alone group, no difference was observed in the number of distant relapses (49 vs. 46 patients). The improvement in survival after chemoradiation observed in this study therefore arises solely from better locoregional tumor control. Moreover, compared to other studies, the magnitude of locoregional relapses seems to be particularly high in the SWOG 9008/Intergroup 0116 study.

Another matter of concern is the toxicity associated with adjuvant chemoradiation. The SWOG 9008/Intergroup 0116 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 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 the numbers usually seen during adjuvant treatment in many malignancies. The most commonly reported severe toxicities were hematologic (54% of patients) and gastrointestinal (33%) side effects. It was brought up that the relatively large radiation volumes being applied in the SWOG 9008/Intergroup 0116 study may account for the mediocre survival of the patients. Published data suggest that

| Table 3. Results of the randomized phase III SWOG 9008/INT 0116 trial assessing the role of adjuvant chemoradiation (CRT) after curative gastric cancer resection compared to surgery alone [29] |
|--------------------------------------------------|-----------------|-----------------|-----------------|
| Median duration of survival, months | 36 27 | 0.005 |
| 3-Year survival rate, % | 50 41 | 1.35 1.09–1.66 0.005 |
| HR for death | 1.0 1.52 | 1.23–1.86 0.001 |
| Median relapse-free survival, months | 30 19 | |
| 3-Year relapse-free survival, % | 48 31 | |
| HR for relapse | 1.0 | |
late renal toxicity after postoperative chemoradiation in gastric cancer also merits thorough attention [33].

In summary, the role of adjuvant chemoradiation in gastric cancer is controversially discussed in the West. Based on the findings of the SWOG 9008/Intergroup 0116 study, postoperative chemoradiation should only be recommended when the surgical objective of an extended (D2) lymphadenectomy is missed [34]. The situation of microscopically incomplete resection (R1) has not been sufficiently studied to draw definitive conclusions. Adjuvant chemoradiation is currently being studied in the quality-controlled Dutch CRITICS prospective randomized multicenter study (fig. 1). This study aims to obtain an improved overall survival for patients treated with preoperative chemotherapy and surgery by incorporating radiotherapy concurrently with chemotherapy postoperatively [35]. To date, 551 out of 788 planned patients have been accrued and other European countries have joined this study. Hopefully, enough patients will complete the planned postoperative treatment in both treatment arms (approx. 50% of patients treated in the MAGIC and the FNCLCC/FFCD trials) in order to answer such an important question.

Summary

To date, perioperative treatment strategies are widely used in the West. In contrast to Asia where most patients undergo primary surgery followed by adjuvant chemotherapy, more and more Western patients undergo pre-plus postoperative chemotherapy, especially in the case of locally advanced tumors [8]. The use of preoperative chemoradiation should be restricted for Siewert type I/II tumors [8]. After primary surgery, the role of adjuvant chemotherapy is still under discussion as well as the role of postoperative chemoradiation. Postoperative chemoradiation is frequently used in North America, but not accepted as a general approach in Europe.

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