Surgery After Neoadjuvant Chemotherapy

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Introduction

Neoadjuvant/perioperative chemotherapy (CT) for locally advanced gastric cancer has become a routine clinical procedure on the base of recent randomized controlled trials. This chapter describes the European prospective randomized controlled trials and focuses on their surgical results. Outcome-related measures are described from a surgical point of view. Numerous aspects are discussed, and the influence of surgical outcomes on oncologic results is critically reviewed.

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Clinical Trials for Neoadjuvant Chemotherapy and Their Surgical Outcomes

Neoadjuvant or perioperative CT is an accepted and recommended therapeutic approach of GC treatment in most European countries [1]. This goes back to the results of the British MAGIC [2] and the French FNLCC/FFCD trial [3], 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 [4]. One 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 like effects on occult metastasis or single tumor cell dissemination (micrometastasis) at the earliest point in time are also discussed.

The MAGIC trial is the presently most recognized landmark study for perioperative CT [2]. Between 1994 and 2002 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

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preoperative and three postoperative cycles of i.v. epirubicin, cisplatin, and continuous 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% vs. 45% and 5.6% vs. 5.9%). 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 to 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 [2].

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 who 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 is uncertain, 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 to 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 [5].

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 [3]. The chemotherapeutic regimen consisted of two to three 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. Two hundred twenty-four patients were randomized to receive either preoperative CT or primary surgery. The R0 resection rate among the patients receiving CT was significantly higher compared to the primary surgery arm (84% vs. 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 match those reported for the MAGIC trial (see above) with 38% in the CT and 24% in the surgery-only arm. [3]

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 [6]. 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, this trial solely relied on preoperative (neoadjuvant) 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% vs. 66.7%; $p = 0.036$). A significant survival benefit could not be shown, but a downstaging and a tendency toward a prolonged OS and DFS for the neoadjuvant treatment arm were observed ($p = 0.113$ and $p = 0.065$). Postoperative complications and deaths were also more common among patients treated with neoadjuvant CT (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 CT 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). 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 [6].

Ronellenfitsch et al. performed an interesting meta-analysis showing an absolute improvement in the survival of 9% at 5 years for patients undergoing perioperative CT [7]. 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. Additionally 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 recently reported German series, 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 [7], an observation which was basically confirmed in the patient population of a specialized German center [8].

There is also evidence in literature that patients with signet ring cell adenocarcinoma do not benefit from perioperative CT. Messager et al. investigated this issue in a multicenter comparative study including 3010 patients from 19 French centers including 1050 patients (34.9%) with signet cell histology [9]. In a patient cohort from the Klinikum rechts der Isar in Munich, Germany including 200 patients with diffuse-type histology having undergone neoadjuvant CT only, 14.5% showed a good histopathologic response (TRG1 according to Becker) [10]. In comparison 27.7% of patients with an intestinal type growth pattern ($n = 331$) showed a TRG1 in the histopathologic workup [unpublished data].

An ongoing British trial presently investigates the safety and efficacy of adding the monoclonal VEGF antibody bevacizumab to ECX CT administered perioperatively in patients with resectable gastric and EGJ adenocarcinomas [11]. 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) [12].

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, like tumors with paraaortal and/or bulky N2 and N3 nodal disease [13], large type 3 (≥8 cm) or 4 (linitis plastica) tumors (JOCG0210 [14], JCOG0501 [15], JCOG1002 [16]), and T2–T3 N+ or T4 tumors (PRODIGY trial) [17], is investigated in Eastern Asia.

Despite promising results in the abovementioned trials, the outcomes appear to be difficult to evaluate due to the fact that the beneficial effects of perioperative chemotherapy are not directly attributed to either the neoadjuvant or the adjuvant part of the respective chemotherapeutic regimens. Therefore, careful consideration of the surgical outcomes within the trials is mandatory. One of the most debated issues regarding surgical technique and oncologic outcome is D2 lymphadenectomy. Recent data revealed the benefits even in the criticized Dutch gastric cancer trial [18]. The long-term results clearly demonstrated that adherence to D2 lymph node dissection resulted in reduced risk of death in gastric cancer patients. Therefore, it is important to review the abovementioned trials in the light of surgical procedures. Despite conceivable differences in ethnicity and biologic properties, survival outcomes between Eastern Asian and European patients appear to be enormous [19]. Whereas 5-year survival rates of around 60%–70% are reported in Japanese gastric cancer trials [20] in the surgery-only arms, a 20–30% 5-year survival rate is notable in the European trials for those patients undergoing surgery only for advanced gastric cancer [2, 3]. Therefore, surgical procedures appear to be relevant regarding the oncologic outcome also in patients having been treated by neoadjuvant or perioperative chemotherapy and have to be evaluated carefully in order to judge oncologic results.

MAGIC

The MAGIC trial was conducted in 104 centers in the UK, the Netherlands, Germany, Singapore, New Zealand, and Brazil between 1994 and 2002 [2]. Only 66–69% of the patients received curative resections, whereas 18–28% of all patients underwent palliative resection. The D2 dissection rates ranged from 40% to 43% of the patients, and 22–27% of the patients underwent esophagogastrectomy for cardia cancer. Seventy-four percent of the patients suffered from stomach cancer, whereas all other patients had cancer of the lower esophagus or the cardia. The authors state that the extent of lymphadenectomy was left to the surgeons' discretion not making D2 dissection a prerequisite for the surgical procedure. The original paper does not report on preclinical stages but states that one of the inclusion criteria was at least stage II. The preoperative workup was not prescribed. Staging laparoscopy was not mandatory for the trial, and distant metastases were ruled out by CT scan. Additionally procedures involving the esophagus were not standardized regarding approach, luminal extent of resection, and lymphadenectomy.

ACCORD

The ACCORD trial was conducted in 28 French centers from 1995 to 2003 [3]. Seventy-five percent of the patients suffered from lower esophageal or gastric cardia cancer, whereas 25% of the patients had locally advanced gastric cancer. Forty-nine percent of the patients received esophagectomies, whereas gastrectomies were performed on 51% of the cases. D2 dissection was recommended for the study cohort, but the paper does not report on the success of D2 lymph node dissection. However, a median number of 19 dissected lymph nodes were reported. Preclinical stages were not reported in the original paper, and there is no data available if staging laparoscopy was performed in order to rule out peritoneal metastasis. Further surgical data is not available from the original publication.

EORTC

The EORTC trial was performed in ten experienced centers in Germany, Belgium, Portugal, the UK, and the Netherlands [6]. In contrast to the aforementioned trials, 96% of all patients had laparoscopic staging for pretherapeutic tumor classification. 51–54% of the patients revealed cancers of the GE junction or the proximal third of the stomach. All patients received gastrectomy (+/− transhiatal extension), and the D2 dissection rate was 93–96% with a median number of 31–33 dissected lymph nodes. Despite laparoscopic staging, 13–16% of the patients revealed metastatic disease in the final pathologic workup. The curative resection rate was 82% in those patients undergoing neoadjuvant chemotherapy compared to 67% for those patients undergoing surgery only. However, this effect did not translate into improved survival rates.

Implications of Surgical Outcomes After Neoadjuvant Chemotherapy

Regarding the heterogeneous (European) results derived from randomized controlled trials investigating the role of neoadjuvant/perioperative chemotherapy, it has to be stated that surgical quality reporting is underrepresented in the respective publications. Therefore, interpretation of the results, especially when it comes to comparisons with Eastern Asian data, has to be conducted carefully. First of all, reporting of preclinical data is insufficient. The landmark trials do not sufficiently report on the staging process. The EORTC trial may be considered an exemption, although only clinical T-stage is being reported. There is no information on the clinical N-stage, which may be related to the fact that not all centers perform endoscopic ultrasound. However, this factor could be negligible due to the fact that endoscopic N-staging did not demonstrate to be a reliable method, especially in cT2 cancers. Another point of criticism in the reported trials is that surgical procedures in the MAGIC and ACCORD trials did not adhere to

Eastern Asian standards, either D2 dissection rates are not reported or the number of dissected lymph nodes is too low in order to allow for sufficient surgical quality. The MAGIC trial reported that only 40% of the patients received D2 dissection and the ACCORD trial did not report on D2 dissection rates at all. However, adequate lymph node dissection was performed in the EORTC trial with a D2 dissection rate of 96% which is remarkable for European standards. Compared to results from Japanese trials, these results appear to be improvable in future trials. Here D2 dissection rates are 100%, and 5-year survival rate for the standard treatments for advanced gastric cancer accounts for over 60%. Nonetheless, D2 dissection cannot be considered as the only culprit for these survival differences. The Japanese trialists rigorously excluded patients from their trials when curative resections are not reached. In the S1 trials, for example, patients were even excluded when peritoneal washing cytology was not done. At least staging laparoscopy was performed in the EORTC trial to rule out occult peritoneal metastasis in contrast to the French and the British trial. Another issue could be the frequency of postoperative complications. In the MAGIC trial, a complication rate of over 40% was reported, whereas postoperative morbidity accounted for 20–30% in the ACCORD and EORTC trials. The postoperative complication rate in the S1 trial, for example, was below 20% [20]. Several groups reported that survival of postoperative complications leads to worsened long-term outcomes after oncologic surgery [21–23]. Toner et al. reported that survival of postoperative complications leads to worsened long-term outcomes after oncologic surgery [21]. The differences in postoperative complication rates could also be related to the various distributions of tumor location within the reported trials. At least half of the patients in all European trials had GE junction cancer. This stands in stark contrast to Eastern Asian patients where GE junction cancers rarely occur. This also leads to a higher amount of total gastrectomies or even esophagectomies leading to increased morbidity rates compared to Eastern Asian patients who usually undergo subtotal gastrectomy for cancer. Another issue could be the influence of obesity in the Western world. Another reason for higher complication rates in Western patient collectives could be the significantly higher BMI compared to Asians. Kodera et al. published that in Japanese patients higher BMIs were significantly related to postoperative complications after gastric cancer surgery [23].

Comparing the three European landmark studies, it appears remarkable that there could be a relation between surgical quality and the number of participating centers. The lower the number of trial sites became, the better the outcome in the surgery-only arm was. Surgery-related morbidity was highest in the MAGIC trial where over 100 centers took part, whereas the morbidity rate was lowest in the EORTC trial with only 10 participating trial centers. Several analyses in the past demonstrated a centralization effect for esophageal and gastric cancer surgery. One study reported specifically on gastric cancer which demonstrated that 30-day mortality could be reduced by over 7% per additional case in surgeons with an annual volume of at least 14 gastrectomies [24]. Another analysis from England reported that increasing hospital volume resulted in lower mortality, especially in the first 30 days after the surgical procedure [25]. Interestingly this effect was also detected in long-term outcomes leading to the intriguing suspicion that oncologic outcome could possibly be influenced just by hospital and individual surgeon's case volume. This also leads to the conclusion that the design of future trials should consider these facts and include only centers with the respective expertise in gastric cancer surgery.

Conclusions

In general, surgery after neoadjuvant chemotherapy should not be different from surgical procedures without multimodal treatments especially in advanced gastric cancer patients. The obvious advantages of D2 lymphadenectomy and radical surgery for complete tumor removal have been

demonstrated in the past. Especially Eastern Asian surgical principles demonstrated their effectiveness before and should not be abandoned for Western patients undergoing treatment for locally advanced gastric cancers. The European trials on neoadjuvant/perioperative chemotherapy produced heterogeneous results regarding oncologic outcomes. Generally speaking, surgical aspects are underrepresented in these multicenter trials that led to the adoption of neoadjuvant chemotherapy in clinical routine for locally advanced gastric cancer. These trials are difficult to evaluate in their efficacy due to the heterogeneous surgical outcomes. This may be related to either an underreporting of surgical aspects or due to non-compliance with surgical (Eastern Asian) principles or to a non-efficient surgical quality control. The optimal staging modalities are still not defined yet and have to be consented on an international scale. From the author's point of view, EGD, endoscopic ultrasound, CT scans, and staging laparoscopy are considered to be mandatory for defining a clinical stage. Surgical quality controls of the respective trial participant should be mandatory before enrolling patients into clinical trials. This was demonstrated before by Korean trialists who claimed a surgical quality control study for the participating surgeons in order to demonstrate proficiency with the required techniques. A rigorous quality control by photo or video documentation or peer-reviewed trainings should be a prerequisite for future trials investigating on the outcome of neoadjuvant or perioperative chemotherapy for advanced gastric cancer. Centralization to trial sites with high surgical expertise should be held in mind to improve surgical outcomes. Therefore, interpretation of the respective trials in an international context and especially in comparisons with Eastern Asian trials will be difficult to perform. Nonetheless, Eastern Asian data from randomized controlled trials investigating the role of neoadjuvant/perioperative chemotherapy are not yet available and are desperately awaited to evaluate its value in a highly trained surgical community.

Most of the European landmark trials on perioperative CT were headed by medical oncologists. The lion's share of points of criticism on those trials could have been avoided by a closer involvement of surgeons when those trials were planned. These surgeons should not only be experienced in the performed procedures but also in the development of clinical trials. This is likewise a plea to all academic surgeons to involve themselves more in the conduct and initiation of clinical trials dealing with multimodal treatment strategies, not leaving this field solely to medical oncologists and/or radiooncologists.

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