Abstract. The current study presents a retrospective comparison, performed at a single academic center, of preoperative chemoradiation (CRT) and perioperative chemotherapy (CT) in addition to surgery in locally advanced but resectable adenocarcinoma of the esophagogastric junction (AEG). A total of 29 consecutive patients with locally advanced AEGs were retrospectively analyzed. Treatment consisted of preoperative CRT (mean dose, 45.0 Gy) plus two cycles of CT with cisplatin and 5-FU or perioperative CT with epirubicin, cisplatin and capecitabine (three cycles preoperatively and postoperatively). Within four to six weeks following preoperative treatment, surgical therapy was performed. Median overall survival was 21.0 months in the perioperative CT group versus 41.7 months in the CRT group [P=0.36; hazard ratio (HR), 1.50; 95% confidence interval (CI), 0.58-3.84]. Three-year survival rates were 55 and 38%, respectively, in favor of the CRT group, and progression-free survival was 20.0 months in the CT group compared with 24.1 months in the CRT group (P=0.71; HR, 1.19; 95% CI, 0.46-3.05). The total number of major surgical complications was almost equal in the two groups. Margin-free resections were achieved in all patients of the CRT group, but only 76.9% of the CT group (P=0.05). In addition, significantly higher R0 resection rates and an increased number of pathological complete remissions were demonstrated in the CRT group compared with those of the CT group. These results appear to indicate a trend for improved progression-free and overall survival for the CRT group. As postoperative morbidity and mortality rates were similar in the two groups, the results support the use of CRT for patients with advanced AEG tumors.

Introduction

The incidence of adenocarcinomas of the distal esophagus and esophagogastric junction (AEG) is rising notably in Western populations with >480,000 new cases diagnosed annually, accounting for 400,000 mortalities per year (1,2). Despite adequate preoperative staging and improvements in perioperative treatment, the overall prognosis remains poor, with a five-year-survival rate of ~40%. In addition, <30% of patients exhibit potentially operable tumors and the majority of patients already have locally advanced tumor stages with involvement of locoregional lymph nodes on presentation (3). For patients undergoing surgery following neoadjuvant therapy [chemoradiotherapy (CRT) or chemotherapy (CT) alone], three-year survival rates vary between 22 and 55% (4-11). To improve long-term survival rates, multimodal treatment strategies, including preoperative CT and neoadjuvant CRT, for locally advanced AEGs have been considered and investigated widely. In an updated meta-analysis, Sjoquist et al summarized the results of multimodal treatment strategies indicating a trend in favor of neoadjuvant CRT (12). In addition, a current phase III trial from the Netherlands has confirmed the feasibility and superiority of a neoadjuvant CR regimen compared with surgery alone (10). However, a standard of care for patients with AEG tumors has not yet been defined. Recently, the EORTC expert panel voted in favor of neoadjuvant CRT (12). In addition, a current phase III trial from the Netherlands has confirmed the feasibility and superiority of a neoadjuvant CR regimen compared with surgery alone (10). However, a standard of care for patients with AEG tumors has not yet been defined. Recently, the EORTC expert panel voted in favor of neoadjuvant CRT for AEG I and II tumors and recommended perioperative CT for AEG III tumors (13).

The current study presents a retrospective analysis of a single center experience with preoperative CRT or perioperative CT in addition to surgery in locally advanced but resectable AEG. The aim of the study was to identify the advantages and potential disadvantages of the two treatment regimens. Patients who were treated either with perioperative CT or neoadjuvant CRT between the years 2006 and 2012 at
the Johann Wolfgang Goethe University Hospital (Frankfurt, Germany) were included in the analysis. Major surgical and non-surgical complications were evaluated and a Kaplan-Meier survival analysis was performed to compare the overall and progression-free survival-estimates between the two groups.

Patients and methods

Patients and treatment. A retrospective analysis was performed of patients with advanced but resectable AEG, treated in neoadjuvant intention with neoadjuvant CRT or perioperative CT between January 2006 and October 2012. Patients were allocated to the two treatment regimens almost equally by the consensus decision of a multidisciplinary tumor board of the Johann Wolfgang Goethe University Hospital. In total, 29 patients were identified who received identical CRT or CT schedules. Patients with different treatment regimens or who were participants in clinical trials were excluded from the analysis to achieve a homogeneous study population. The study was approved by the ethics committee of the Johann Wolfgang Goethe University Hospital. Written informed consent was obtained from the patients.

Preoperative staging. Initial staging included endoscopy of the upper gastrointestinal tract with multiple biopsies, computed tomography scan of the thorax and abdomen and an endoscopic ultrasound. Other diagnostics, including positron emission tomography/computed tomography or diagnostic laparotomy, were optional. Physical examination and laboratory testing were routinely performed in all patients.

CRT group. The CRT group included 16 patients. Radiation therapy planning was based on three-dimensional computed tomography scans of the chest and upper abdomen with a resolution of 3-mm slice reconstructions. The planning target volume was delineated as the macroscopic gross tumor volume plus the safety margins of 15 mm in the circumferential, 30 mm in the oral and 50 mm in the aboral extension. Patients received a median cumulative dose of 45.0 Gy (range, 45.0-50.4 Gy) in single fractions of 1.8 Gy/day. In addition, patients received two cycles of cisplatin and 5-Fluorouracil (5-FU) in the first and fifth week of radiotherapy. Cisplatin was administered at a dose of 20 mg/m² from day one to five of each cycle. 5-FU was administered at a dose of 600 mg/m² as a continuous infusion from day one to five of each cycle.

CT group. The CT group included 13 patients who received a maximum of six three-week cycles of epirubicin, cisplatin and capecitabine (three cycles preoperatively and postoperatively). On day one of every three-week cycle, 50 mg/m² epirubicin was administered to each patient, followed by the administration of 60 mg/m² cisplatin. Between days one and 14, 1,000 mg/m² capecitabine was orally administered twice daily. Following surgical resection, patients underwent adjuvant treatment with the same CT regimen.

Surgery and follow-up. Surgery in the two groups was performed between four and six weeks following preoperative treatment. Extended gastrectomy and distal esophagectomy, with Roux-en-Y esophageojejunostomy and two-field D2-lymph node dissection, was performed in patients with AEG II/III. Transthoracic esophagectomy and proximal gastrectomy with en bloc removal of the esophagus and adjacent lymph nodes were performed in patients with AEG I. Patients were first seen for physical examination six to eight weeks following the termination of therapy. Technical examination (esophagogastrroduodenoscopy or computed tomography) was performed at the discretion of the attending physician. For follow-up, patients were observed every three months in the first year and every six months in the following years. Medical reports and information from the attending physicians were also taken into account for analysis.

Statistical analysis. Data were analyzed and compiled using BiAS software for Windows (version 9.11; Epsilon-Verlag, Darmstadt, Germany), SPSS version 20 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 for Windows (version 5; GraphPad Software Inc., La Jolla, CA, USA). P<0.05 was considered to indicate a statistically significant difference. Follow-up time was defined as the time between initiation of preoperative therapy and mortality or final contact. The primary endpoint of the study was overall survival (OS), calculated between initiation of preoperative therapy and mortality. Progression-free survival (PFS) was calculated between the initiation of neoadjuvant treatment and reported initial reaction (defined as locoregional relapse or distant metastases) or mortality.

Acute hematological side effects were recorded according to Common Toxicity Criteria, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). For TNM staging, the current TNM classification at diagnosis was used respecting the 2009 revision of TNM classification for esophageal cancer (www.uicc.org).

Results

Patient follow-up. Median follow-up was 25.5 months (range, 6.0-73.3 months) in the CRT group versus 22.0 months in the CT group (range, 5.3-64.7 months). Patients and tumor characteristics are shown in Table I.

Acute side effects and feasibility of perioperative and preoperative therapy. In the two groups, no acute non-hematological adverse events ≥ grade 3, leading to treatment modifications, were recorded. Acute hematological toxicity grade 3 or 4 was reported more frequently in the CRT group [eight of the 16 patients (50%)] compared with the CT group [two of the 13 patients (15%)] (P=0.02). Therefore, a dose reduction of CT was necessary in 50% of CRT patients and 15% of CT patients. In 15 of the 16 patients (94%) in the CRT group and 12 of the 13 patients (92%) in the CT group, all scheduled preoperative CT cycles were able to be administered. In the CT group, eight of the 13 patients (62%) were unable to receive adjuvant CT due to prolonged hematological toxicity or deterioration of general condition (Table II).

Major surgical and non-surgical postoperative complications and associated mortality. Postoperative pulmonary and pleural complications, including pneumonia, pneumothorax,
relevant pleural-effusion and pleural empyema, occurred more frequently in the CRT group than in the CT group (44 vs. 8%, respectively; P=0.04). One patient in each group succumbed to their condition during hospitalization due to septic complications following anastomotic leakage (Table III). The two groups did not differ significantly in the number of major surgical complications (CRT group, 69% vs. CT group, 77%; P=0.63; Table IV).

Pathological complete remission and rate of R0 resection. Pathological complete remission (pCR) of the tumors was observed in three patients in the CT group (CT group, 19%...
Table III. Surgical complications and mortality.

| Complication                                         | Chemoradiotherapy, n (%) | Chemotherapy, n (%) | P-value\(^a\) |
|------------------------------------------------------|--------------------------|---------------------|--------------|
| Patients                                             | 11 (69)                  | 10 (77)             | NS           |
| Type of major surgical complication                  |                          |                     |              |
| Anastomotic leakage                                  | 4 (25)                   | 4 (31)              | NS           |
| Mediastinitis/sepsis                                 | 1 (6)                    | 1 (8)               | NS           |
| Implantation of esophageal stent                      | 2 (13)                   | 2 (15)              | NS           |
| Pulmonary complications                              | 7 (44)                   | 1 (8)               | 0.04         |
| Secondary surgery                                    | 3 (19)                   | 1 (8)               | NS           |
| Necrosis of intrathoracic gastric tube/neoesophagus   | 1 (6)                    | 0 (0)               | NS           |
| Lymphatic fistula                                     | 1 (6)                    | 0 (0)               | NS           |
| Other                                                | 5 (31)                   | 3 (23)              | NS           |
| Complication-associated mortality                     | 1 (6)                    | 1 (8)               | NS           |

\(^a\)Determined by Fisher's exact test. NS, not significant.

Table IV. Surgical outcome and survival data.

| Outcome                                             | Chemoradiotherapy | Chemotherapy | P-value\(^a\) |
|-----------------------------------------------------|-------------------|--------------|--------------|
| R0 resection\(^b\)                                  | 16 (100)          | 10 (77)      | 0.05         |
| pCR\(^c\)                                           | 3 (19)            | 0 (0)        | 0.23         |
| Median OS, months                                   | 41.7              | 21.0         | 0.36         |
| 3-year OS rate, %                                   | 55.0              | 38.0         | NS           |
| Median PFS, months                                  | 24.1              | 20.0         | 0.71         |
| Pattern of recurrence                               |                   |              |              |
| Locoregional                                        | 2 (13)            | 4 (31)       | NS           |
| Distant                                             | 7 (44)            | 4 (31)       | NS           |
| Locoregional and distant                            | 1 (6)             | 1 (8)        | NS           |

\(^a\)Determined by Fisher's exact test; \(^b\)all resection margins clear in postoperative specimen; \(^c\)Absence of any viable tumor cells in postoperative specimen. Values are presented as n, (%), unless specified otherwise. pCR, pathological complete regression; OS, overall survival; PFS, progression-free survival; NS, not significant.

vs. CRT group, 0%; P=0.11). In addition, the R0 resection rate (complete tumor-free resection margins) was significantly higher in the CRT group compared with the CT group (100 vs. 77%, respectively; P=0.05; Table IV).

OS and PFS. Median OS time was 21.0 months in the CT group versus 41.7 months in the CRT group [P=0.36; hazard ratio (HR), 1.50; 95% confidence interval (CI), 0.58-3.84]. Three-year survival rates were 38% in the CT group and 55% in the CRT group. Median PFS time was 20.0 months in the CT group compared with 24.1 months in the CRT group (P=0.71; HR, 1.19; 95% CI, 0.46-3.05) (Table IV; Figs. 1 and 2).

Patterns of recurrence and secondary malignancies detected during the follow-up period. The rate of local and/or distant recurrence during the follow-up period was 56% in the CRT and 69% in the CT group (Table IV). In the CRT group, three patients were diagnosed with secondary malignancies, including non-small cell lung cancer, colon carcinoma and cholangiocarcinoma. At least one patient in the CRT group succumbed to a secondary malignancy and not to the AEG tumor. In the other two cases, the cause of mortality was not clearly identifiable.

Discussion

Although modern perioperative treatment regimens have shown improved outcomes for patients with advanced AEG tumors, there remains a lack of profound data to define the most effective treatment approach. The current study compared the outcome of a homogeneous patient population treated with neoadjuvant CRT or perioperative CT at a single center. An updated meta-analysis in 2011 analyzing the administration of neoadjuvant CT or CRT in addition to surgery was unable to determine a clear advantage between the treatment regimens, although, a proportionately larger
Table V. Studies on multimodal treatment strategies in AEG.

A. Studies on perioperative CT followed by OP versus OP alone.

| Author (year) [ref] | Years of accrual | n/OS rate, % | CT and OP | OP | Postoperative toxicity |
|---------------------|------------------|--------------|-----------|----|------------------------|
| Kelsen et al (1998) [7] | 1990-1995 | 124/23 (3-year) | 120/26 (3-year) | No difference in morbidity/mortality |
| Allum et al (2009) [4] | 1992-1998 | 265/22.6 (3-year) | 268/17.6 (3-year) | No difference in morbidity/mortality |
| Cunningham et al (2006) [14] | 1994-2002 | 65/38 absolute | 66/31 absolute | No difference in morbidity/mortality |
| Ychou et al (2011) [15] | 1995-2003 | 109/38 (5-year) | 110/24 (5-year) | No difference in morbidity/mortality |

B. Studies on preoperative CRT followed by OP versus OP alone.

| Author (year) [ref] | Years of accrual | n/OS rate, % | CRT and OP | OP | Postoperative toxicity |
|---------------------|------------------|--------------|-----------|----|------------------------|
| Urba et al (2001) [8] | 1989-1994 | 37/30 (3-year) | 38/16 (3-year) | No difference in morbidity/mortality |
| Walsh et al (1996) [9] | 1990-1995 | 58/32 (3-year) | 55/6 (3-year) | No difference in morbidity/higher mortality for CRT |
| Burmeister et al (2005) [5] | 1994-2000 | 78/28 (3-year) | 83/30 (3-year) | No difference in morbidity/mortality |
| Tepper et al (2008) [16] | 1997-2000 | 23/39 (5-year) | 19/16 (5-year) | No difference in morbidity/mortality |
| van Hagen et al (2012) [10] | 2004-2008 | 134/~55° (3-year) | 141/~45° (3-year) | No difference in morbidity/mortality |

C. Studies on preoperative CRT followed by surgery versus preoperative CT followed by OP.

| Author (year) [ref] | Years of accrual | n/OS rate, % | CRT and OP | OP | Postoperative toxicity |
|---------------------|------------------|--------------|-----------|----|------------------------|
| Stahl et al (2009) [11] | 2000-2005 | 60/47.4 (3-year) | 59/27.7 (3-year) | Postoperative mortality was not significantly increased for CRT group |
| Burmeister et al (2011) [6] | 2000-2006 | 39/52 (3-year) | 36/49 (3-year) | No difference in morbidity/mortality |
|                      |                  | 39/45 (5-year) | 39/36 (5-year) |                  |

*Extracted from Kaplan-Meier survival curves. AEG, adenocarcinoma of the gastroesophageal junction; CT, chemotherapy; CRT, chemoradiation; OP, surgery.
In the current study, a significant difference was observed in the frequency of hematological side effects, with 50% of the patients in the CRT group experiencing pathological downstaging (R0 resection) compared with those who received CT (15.6% vs. 2%, respectively). Notably, all patients with pCR survived (11). Similarly, Burmeister et al. was unable to demonstrate a significant survival benefit with the addition of radiation therapy to preoperative CT. The authors reported a prolonged time to progression, a significantly higher pCR rate and a trend to an improved R0 resection rate in the CRT group. By contrast, preoperative CT was noted to decrease the incidence of distant metastasis by 31 versus 44% in the CRT group. Overall, these results reflect the results of the only two randomized trials that have directly compared preoperative CT with preoperative CRT. However, the two trials closed prematurely due to poor accrual. Stahl et al. reported three-year OS rates of 47.4% in the CRT group and 27.7% in the CT group, with an increased number of patients in the CRT group experiencing pathological downstaging and pCR compared with the CT group (15.6 vs. 2%, respectively). Notably, all patients with pCR survived (11).

To determine the best multimodal treatment regimen, further studies are required. At present, an ongoing study, the international phase III TOPGEAR trial (launched in 2012), is investigating whether preoperative CRT (two cycles of ECF followed by 45 Gy of radiation with concurrent 5-FU) or preoperative CT (three cycles of ECF) alone is more effective.
in patients with resectable gastric and esophagogastric cancer. Following surgery, the two groups were scheduled to receive three additional cycles of ECF (unpublished data).

Despite the major limitations of the present small and retrospective analysis, the results confirmed the results of recent randomized trials addressing the issue of whether preoperative CT or CRT is superior for the treatment of AEG tumors. The current study demonstrated significantly higher R0 resection rates and an increased number of pCR in the CRT group. These results appear to indicate a trend for improved PFS and OS for the CRT group. As postoperative morbidity and mortality rates were similar in the two groups, the results of the current study support the use of CRT for patients with advanced AEG. Nevertheless, large trials integrating the best available treatment schedules are required to define a standard treatment approach for this increasingly common tumor entity.

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