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Utilization and Efficacy of Palliative Chemotherapy for Locally Advanced or Metastatic Gastroesophageal Carcinoma

RUTH BAUMGARTNER[1,2], HOSSEIN TAGHIZADEH[1,2], GERD JOMRICH[2,3], SEBASTIAN FRIEDRICH SCHOPPMANN[2,3], MATTHIAS PREUSSER[1,3] and AYSEGUL ILHAN-MUTLU[1,3]

[1]*Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria;*
[2]*Comprehensive Cancer Center Vienna, Gastroesophageal Tumor Unit, Medical University of Vienna, Vienna, Austria;*
[3]*Department of Surgery, Medical University of Vienna, Vienna, Austria*

Abstract. *Background/Aim: A standard treatment recommendation for advanced stage gastroesophageal cancer is still missing. Patients and Methods: We retrospectively analyzed clinical data of patients with inoperable locally advanced or metastatic gastroesophageal cancer treated between 2001 and 2017 at the Vienna General Hospital, Austria. Results: Administration of systemic therapy was positively associated with overall survival (OS) (469 days vs. 185 days; p<0.001), while palliative gastrectomy or radiotherapy showed no correlation. OS was significantly longer in patients receiving capecitabine/oxaliplatin (XELOX) vs. leucovorin/5-FU/oxaliplatin (FOLFOX) (600 days vs. 327 days, p<0.05). Comparison of doublet vs. triplet chemotherapies showed no difference in OS, but triplet chemotherapy resulted in more adverse events. The anti-HER2-antibody trastuzumab doubled OS (836 days vs. 399 days, p=0.053). Conclusion: Capecitabine may be preferably used over infused 5-FU and doublet chemotherapy over triplet chemotherapy in the first-line palliative setting of advanced gastroesophageal cancer.*

Cancer of the upper gastrointestinal tract is globally the second leading cause of cancer related death, with about 1.4 million newly diagnosed cases (951,000 cases of gastric cancer and 456,000 cases of esophageal cancer) worldwide in 2012 (1). Gastroesophageal cancer is twice as common in men than in women (1). While the incidence of gastric cancer decreased over the past decades and the incidence of esophageal cancer remained fairly unchanged, a gradual relative increase of gastroesophageal junction cancer on the basis of Barrett's esophagus could be observed (2, 3).

Gastroesophageal cancer is usually asymptomatic in early stages and symptoms such as weight loss, dysphagia, abdominal pain, vomiting or gastrointestinal bleeding develop mostly in advanced tumor stages. Consequently, most patients in the western world are diagnosed very late during the course of the disease, at a locally advanced or metastatic stage. In the US, the proportion of patients diagnosed with regional or distant tumor spread amounts to 71% for esophageal cancer and 62% for gastric cancer. Even though relative survival independent of tumor stage showed a steady increase during the past decades, prognosis remains poor especially in higher stages. 5-year relative survival for esophageal and gastric cancer is 23.6% and 30.6% at regional stages, and 4.8% and 5.2% at distant stages, respectively (2, 3).

Combination chemotherapy remains the mainstay of treatment for this patient collective, although response rates and efficacy are still low (4-8). The management of esophageal cancer is less well-defined and mostly treated based on the recommendations for gastric cancer (6). Currently, the combination of a fluoropyrimidine and a platinum is the recommended standard first-line regimen in advanced gastroesophageal cancer with a reported median OS of around one year (4, 9-12). There is persisting controversy regarding the benefit of triplet regimens because of increased toxicity. According to ESMO 2016 guidelines, an anthracycline (*e.g.* epirubicin) or a taxane (*e.g.* docetaxel) can be added optionally as a third agent (5), while the latest NCCN guidelines no longer recommend three-drug regimens as first-line treatments (7).

Only scarce data are available on the comparison of the different fluoropyrimidine and platinum derivates in the treatment of gastroesophageal cancer. The results from the

Correspondence to: Aysegül Ilhan-Mutlu, MD, PhD, PD, Department of Medicine I, Clinical Division of Oncology, Comprehensive Cancer Center Vienna, Gastroesophageal Tumor Unit, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. Tel: +43 14040044570, Fax: +43 14040044280, e-mail: aysegul.ilhan@meduniwien.ac.at

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REAL II trial suggested that oxaliplatin and capecitabine represent equally effective agents as cisplatin and 5-FU, respectively, in an epirubicin based triplet regimen (9). A German phase III trial provided additional evidence that cisplatin can be exchanged by oxaliplatin (13). Based on this evidence, oxaliplatin is increasingly used in daily practice and in clinical trials.

In Asia, gastroesophageal cancer is especially common and screening programs for gastric cancer have been successfully established in some countries (14). Tumor biology and treatment strategies differ from Western countries; *e.g.* the use of S1 (tegafur/gimeracil/oteracil) is more common in Asian patients (5, 15).

Tumors of the upper gastrointestinal tract with positive human epidermal growth factor receptor 2 (HER2) status represent a special case. Since the approval of the monoclonal antibody trastuzumab in 2010 following the trastuzumab for gastric cancer (ToGA) trial, a first targeted therapy is available for this subgroup of patients with originally possibly worse prognosis (11, 16).

The establishment of a standard therapy for advanced stage gastroesophageal cancer has been proved difficult due to heterogeneity in performance status, age, tumor biology and disease progression. The uncertainty regarding the choice of regimens underlines the importance of retrospective analyses in order to evaluate the efficacy of different treatment strategies (4, 17).

The aim of our retrospective single-center study was to analyze palliative (immuno)chemotherapy and outcomes of patients diagnosed with advanced stage gastroesophageal carcinoma in the clinical setting at the Vienna General Hospital, Austria.

Patients and Methods

This retrospective analysis is based on clinical information including patient demographics, therapy regimens, adverse events, tumor marker profiles and survival outcomes obtained from the patient database of the General Hospital Vienna, Austria.

We identified patients diagnosed between January 2001 and September 2017 with inoperable locally advanced or metastatic (stage IV) gastroesophageal cancer according to the current edition (6^{th} or 7^{th}) of the tumor–node–metastasis (TNM) classification of the International Union against Cancer (UICC) (18, 19), who were in a solely palliative treatment setting.

All patients underwent tumor staging prior to therapy according to the local hospital standard practices, including history taking, physical examination, routine hematologic tests, upper gastrointestinal endoscopy with histological biopsy and computed tomography of the chest and abdomen. Depending on the administered chemotherapy additional examinations were conducted as required. Only patients with histologically confirmed diagnosis were included.

HER2 status was evaluated in all patients potentially eligible for trastuzumab treatment after November 2010. Carcinomas with immunohistochemical intensity score 3+ or 2+ with additional positive fluorescence *in situ* hybridization were classified as HER2 positive and consequently eligible for anti-HER2 treatment (20). Patients were treated according to the individual decision of an interdisciplinary tumor board, which ensured the best possible treatment according to the respective standard of knowledge at the time of diagnosis. As all treatments were in a palliative setting due to the advanced tumor stage, the prolongation of OS and the reduction of symptoms were the main goals.

The treatment included systemic (immuno)chemotherapy and/or palliative gastrectomy and/or radiation therapy of the primary tumor, lymph nodes or metastatic sites. Some patients participated in clinical trials. Patients with neoadjuvant treatment of the same tumor in an initially curative setting were excluded from the study.

Routine re-evaluation of the tumor status was performed at least every three months with computed tomography or magnetic resonance imaging. Evaluation of the response was performed according to the current RECIST criteria by experienced radiologists (21, 22).

Whenever available, serum levels of the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were analyzed prior to therapy and 6 months after the initiation of therapy.

The study was conducted in accordance with the guidelines for good scientific practice of the Medical University of Vienna and approved by the local ethics committee.

Statistical analysis. Chi-squared test was utilized for the analysis of the distribution of dichotomized variables. ANOVA test was applied where multiple testing was necessary.

Patients without an event (death) were censored at the date that they were last known to be alive. OS was calculated from the date of the initial diagnosis to the death of the patient or the patient`s last follow-up date. PFS was measured from the first administration of the first-line systemic anti-tumor treatment to the date of disease progression confirmed by CT scans. Analyses of OS and PFS were performed with Kaplan–Meier survival estimates with log-rank test and Cox regression.

Using Cox-regression analysis, the following parameters were correlated with outcome: age, gender, family history of cancer, family history of gastrointestinal cancer, prior cancer, smoking, primary tumor site, histologic carcinoma type, tumor grade, number and location of metastatic sites.

Differences between tumor marker levels before and after chemotherapy were calculated using paired *t*-test.

Two-tailed *p*-values of ≤ 0.05 were considered to indicate statistically significant differences. All statistics were calculated using statistical package for the social sciences (SPSS) 24.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics. Patient and tumor characteristics are summarized in Table I. In total, 244 patients with gastroesophageal cancer met the criteria and were included into this retrospective analysis. About one third of the patients [78 (31.97%)] were women and the median age at diagnosis was 61 years (range=27-91 years). Nearly half of the patients [119 (48.77%)] were diagnosed with gastric cancer, and all of those with adenocarcinoma. Of the 66 patients (27.05%) with cancer of the gastroesophageal junction, histopathologic examination showed a similar

Table I. *Patient and tumor characteristics*.

Patient/tumor characteristics, n=244, unless otherwise stated*	Value
Age, years, median (range)	61 (27-91)
Female gender, n (%)	78 (31.97)
Family history of cancer, n (%)	42 (17.21)
Family history of gastrointestinal cancer, n (%)	26 (10.66)
Prior cancer, n (%)	28 (11.48)
Smoking, n (%)	108 (44.26)
Primary tumor site, n (%)	
Stomach	119 (48.77)
Adenocarcinoma	119 (100.00)
Squamous cell carcinoma	0 (0)
Gastroesophageal junction	66 (27.05)
Adenocarcinoma	64 (96.97)
Squamous cell carcinoma	2 (3.03)
Esophagus	59 (24.18)
Adenocarcinoma	31 (52.54)
Squamous cell carcinoma	28 (47.45)
Tumor Grade, n (%) (n=161)	
I	1 (0.62)
II	55 (34.16)
III	103 (63.98)
IV	2 (1.24)
HER2 positivity, n (%) (n=119)	23 (16.67)
Number of metastatic sites, n (%) (n=237)	
1	137 (57.81)
2	75 (31.65)
≥3	25 (10.55)
Metastatic sites, n (%) (n=237)	
Liver	94 (39.66)
Peritoneum	82 (34.6)
Lymph nodes	82 (34.6)
Lung	37 (15.61)
Bones	20 (8.44)
Omentum	18 (7.59)
Muscle	9 (3.8)
Pancreas	9 (3.8)
Krukenberg tumor	4 (1.69)
Adrenal glands	3 (1.27)
Colon	3 (1.27)
Brain	2 (0.84)
Kidney	2 (0.84)
Palliative treatment modality, n (%)	
Systemic therapy†	218 (89.34)
Radiotherapy†	17 (6.97)
Gastrectomy†	39 (15.98)
Best supportive care only	22 (9.02)

*Due to the retrospective character of the study, not all information was available for all patients. †Irrespective of additional treatment modalities.

distribution with an overweighing majority of 64 (96.97%) adenocarcinomas in comparison to 2 (3.03%) squamous cell carcinomas. Of the 59 patients (24.18%) with esophageal cancer, adenocarcinoma [31 (52.54%)] and squamous cell carcinoma [28 (47.45%)] were about equally common.

The most common metastatic sites were the liver [94 (39.66%)] and peritoneal carcinomatosis [82 (34.6%)], followed by the lung [37 (15.61%)], bone structures [20 (8.44%)] and the omentum [18 (7.59%)]. Positive lymph nodes at the time of diagnosis were detected in slightly more than a third of the patients [82 (34.6%)].

Treatments. Altogether, systemic (immuno)chemotherapy was administered to 218 patients (89.34%), with 166 patients (68.03%) receiving only this treatment modality. Further, 17 patients (6.97%) were treated with radiation therapy of the primary tumor, 16 of which also received systemic therapy. Thirty-nine patients (15.98%) underwent palliative gastrectomy, 36 of which received adjuvant systemic therapy. Twenty-two patients (9.02%) received best supportive care only.

Eight main chemotherapy regimens dominated the first-line treatment and were administered to 182 patients (Table II). Thirty-eight patients (15.57%) received docetaxel/cisplatin/5-FU (DCF), 46 patients (18.85%) epirubicin/oxaliplatin/capecitabine (EOX), 21 patients (8.61%) cisplatin/5-FU, 20 patients (8.20%) leucovorin/5-FU/oxaliplatin (FOLFOX), 15 patients (6.15%) capecitabine/oxaliplatin (XELOX), 12 patients (4.92%) oxaliplatin/docetaxel and 11 patients (4.51%) capecitabine. Nineteen patients (7.79%) received trastuzumab-containing regimens, mostly cisplatin/capecitabine/trastuzumab according to the ToGA protocol (16), two patients received trastuzumab in combination with DCF and three in combination with FOLFOX. Systemic first-line chemotherapies other than those named, including etoposide/leucovorin/5-FU (ELF), irinotecan/mitomycin, cisplatin/docetaxel, docetaxel mono, 5 FU/leucovorin/epirubicin/cisplatin (FLEP) and 5-FU/leuco-vorin/oxaliplatin/docetaxel (FLOT), were administered to 62 patients (25.41%). Because of tumor progression during or after first-line treatment, second-, third- and fourth-line treatments were administered to 86, 30 and 7 patients (39.45%, 13.76% and 3.21% of patients receiving systemic therapy), respectively. The distribution of patients receiving second-, third- or fourth-line chemotherapy did not differ between the main chemotherapy groups.

Survival outcome. Median OS in the total study population was 448 days (95%CI=368-528). Median OS of patients who received systemic therapy, irrespective of other additional treatment modalities, was 469 days (95%CI=378-560) in comparison to a median OS of 185 days (95%CI=115-255) of patients without systemic therapy ($p<0.001$) (Figure 1a). Palliative gastrectomy, irrespective of other additional treatment modalities, was not associated statistically significantly with prolonged OS, although a tendency could be seen [582 days (95%CI=402-762) *vs*. 398 days (95%CI=312-483), $p=0.07$] (Figure 1b). Administration of palliative radiation of the primary tumor, irrespective of other additional treatment modalities, was not correlated with a significantly longer OS (Figure 1c).

Table II. *Main chemotherapy regimens and tolerability.*

	DCF	EOX	Cis/5-FU	Trastuzumab*	FOLFOX	XELOX	Oxa/doc	Capecitabine	*p*-Value
n (% of all chemotherapies)	38 (15.57)	46 (18.85)	21 (8.61)	19 (7.79)	20 (8.20)	15 (6.15)	12 (4.92)	11 (4.51)	
No. of cycles, median (range)	4.47 (1-6)	4.57 (1-7)	3 (1-8)	4.53 (1-10)	4.11 (1-8)	6.27 (1-20)	6.18 (2-12)	3.17 (1-6)	0.000
Adverse events, n (%)									
Gastrointestinal	4 (10.53)	6 (13.04)	4 (19.05)	5 (26.31)	1 (5.00)	4 (26.67)	1 (8.33)	1 (9.09)	0.428
Hematological	5 (13.16)	0 (0.00)	0 (0.00)	3 (14.29)	0 (0.00)	1 (6.67)	1 (8.33)	0 (0.00)	0.049
Allergic	0 (0.00)	2 (4.35)	0 (0.00)	4 (21.05)	0 (0.00)	1 (6.67)	0 (0.00)	1 (9.09)	0.014
Renal toxicity	2 (5.26)	1 (2.17)	3 (14.29)	2 (10.53)	1 (5.00)	0 (0.00)	0 (0.00)	0 (0.00)	0.342
Infections	5 (13.16)	2 (4.35)	0 (0.00)	1 (5.26)	1 (5.00)	1 (6.67)	1 (8.33)	0 (0.00)	0.556
Polyneuropathy	1 (2.63)	2 (4.35)	0 (0.00)	4 (21.05)	0 (0.00)	3 (20.00)	0 (0.00)	0 (0.00)	0.007
Fatigue	0 (0.00)	2 (4.35)	0 (0.00)	2 (10.53)	0 (0.00)	2 (13.33)	0 (0.00)	0 (0.00)	0.119
2nd-line CTx, n (%)	15 (39.47)	17 (36.96)	7 (33.33)	10 (52.63)	9 (45.00)	6 (40.00)	5 (41.67)	2 (18.18)	0.756
3rd-line CTx, n (%)	6 (15.79)	5 (10.87)	3 (14.29)	2 (10.53)	3 (15.00)	3 (20.00)	1 (8.33)	1 (9.09)	0.976
≥4th-line CTx, n (%)	0 (0.00)	2 (4.35)	1 (4.76)	0 (0.00)	1 (5.00)	0 (0.00)	0 (0.00)	1 (9.09)	0.639
OS, days, median (95%CI)	362 (290-434)	469 (164-774)	406 (140-672)	836 (264-1408)	327 (218-436)	600 (211-989)	322 (0-785)	211 (188-234)	0.047
PFS, days, median (95%CI)	267 (240-294)	320 (224-416)	382 (240-524)	354 (215-493)	245 (206-284)	408 (267-549)	978 (0-1989)	341 (140-542)	0.060

*Trastuzumab-containing regimens (mostly cisplatin/capecitabine/trastuzumab, 3× FOLFOX/trastuzumab, 1× DCF/trastuzumab). DCF: Docetaxel/cisplatin/5-fluorouracil; EOX: epirubicin/oxaliplatin/capecitabine, cis/5-FU: cisplatin/5-fluorouracil; FOLFOX: leucovorin/5-fluorouracil/oxaliplatin; XELOX: capecitabine/oxaliplatin; oxa/doc: oxaliplatin/docetaxel; CTx: chemotherapy; OS: overall survival; PFS: progression-free survival.

Comparison of the eight main chemotherapies (n=182) showed a significant difference in OS (p=0.047), although PFS was not diverging significantly (Figure 2). There was a significant difference between the number of received chemotherapy cycles. Patients receiving DCF (n=38) had a median OS of 362 days (95%CI=290-434) *vs*. 469 days (95%CI=164-774) for EOX (n=46) *vs*. 406 days (95%CI=140-672) for cisplatin/5-FU (n=21) *vs*. 327 days (95%CI=218-436) for FOLFOX (n=20) *vs*. 836 days (95%CI=264-1408) for trastuzumab-based regimens (n=19) *vs*. 600 days (95%CI=211-989) for XELOX (n=15) *vs*. 322 days (95%CI=0-785) for oxaliplatin/docetaxel (n=12) and 211 days (95%CI=188-234) for capecitabine (n=11). No statistically significant correlation was observed between the administration of the individual chemotherapy substances and survival outcome.

There was no association of OS with age and even the comparison of young (<40 years) and very old (>70 years) patients showed no significant difference in OS. No association of OS with gender, family history of cancer, family history of gastrointestinal cancer, prior cancer, smoking, primary tumor site, histologic carcinoma type, tumor grade or number of metastatic sites could be detected. Among the metastatic sites, only Krukenberg tumors were associated with significantly shorter OS (HR=3.2); metastases in the colon showed a tendency towards worse OS (HR=4.1).

Patients treated with cisplatin/5-FU had no significantly different OS from patients receiving FOLFOX [406 days (95%CI=140-672) *vs*. 327 days (95%CI=218-436), p=0.078] (Figure 3a).

OS was significantly longer in patients administered XELOX *vs*. FOLFOX [600 days (95%CI=211-989) *vs*. 327 days (95%CI=218-435), p=0.014] (Figure 3b).

The overall comparison of doublet *vs*. triplet treatment strategies showed no significant difference in OS [459 days (95%CI=295-605) *vs*. 433 days (312-554), p=0.668] (Figure 4a). In particular, there was no significant difference in OS in patients treated with DCF in comparison to oxaliplatin/docetaxel [362 days (95%CI=290-434) *vs*. 322 days (95%CI=0-785), p=0.486], DCF in comparison to cisplatin/5-FU [362 days (95%CI=290-434) *vs*. 406 days (95%CI=140-672), p=0.884] or EOX in comparison to XELOX [469 days (95%CI=164-774) *vs*. 600 (95%CI=211-989), p=0.653] (Figure 4b-d).

Since 2010, trastuzumab is available as a standard treatment of HER2 positive gastroesophageal cancer. The median OS of patients who received trastuzumab-based therapies was about twice as long as that of the other patients

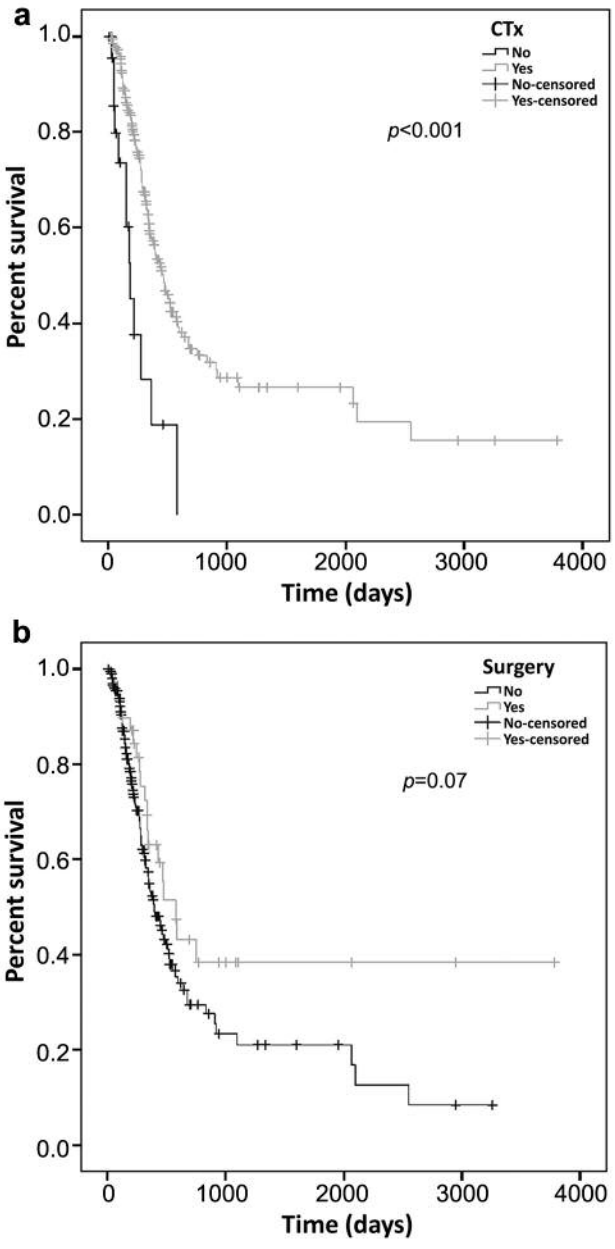

Figure 1. *Comparison of the different treatment modalities. Kaplan–Meier estimates of overall survival for a) patients treated with and without systemic therapy (CTx), b) with and without palliative surgery and c) with and without radiation therapy (RTx) of the primary tumor.*

[836 days (95%CI=264-1408) *vs*. 399 days (95%CI=314-484), p=0.053] (Figure 5a). HER2 status was documented in 119 patients. A significant prolongation of OS could be observed in patients with a positive HER2 status [836 days (95%CI=9-1663) *vs*. 345 days (95%CI=298-392), p=0.003; HR=0.29] (Figure 5b).

OS of the five patients who received the anti-VEGFR2 antibody ramucirumab alone or in combination with paclitaxel as second- or third-line treatment was not different from the other patients.

Adverse events. Registered adverse events for each main chemotherapy are summarized in Table II. Events with statistical significance between the therapies included blood count deviations, allergic reactions and polyneuropathy. The highest incidence of each of these symptom categories occurred in trastuzumab-based regimens.

Tumor markers. Serum CEA levels were known for 144 patients before and for 77 patients after chemotherapy. Serum CA 19-9 levels were known for 138 patients before and for 73 patients after chemotherapy. The serum levels of CEA before chemotherapy were significantly associated with OS (p=0.008), however with a hazard ratio of 1. There was no significant change after the administration of chemotherapy. CA 19-9 levels before chemotherapy were not associated with outcome and did not change significantly after chemotherapy.

Discussion

Despite ongoing efforts to establish a standard therapy for patients with advanced inoperable or metastatic gastroesophageal carcinoma, there remains much controversy and uncertainty regarding the optimal strategy (17). Systemic chemotherapy not only prolongs patients' survival, but also reduces cancer-related symptoms and hence is the recommended treatment strategy (4-8).

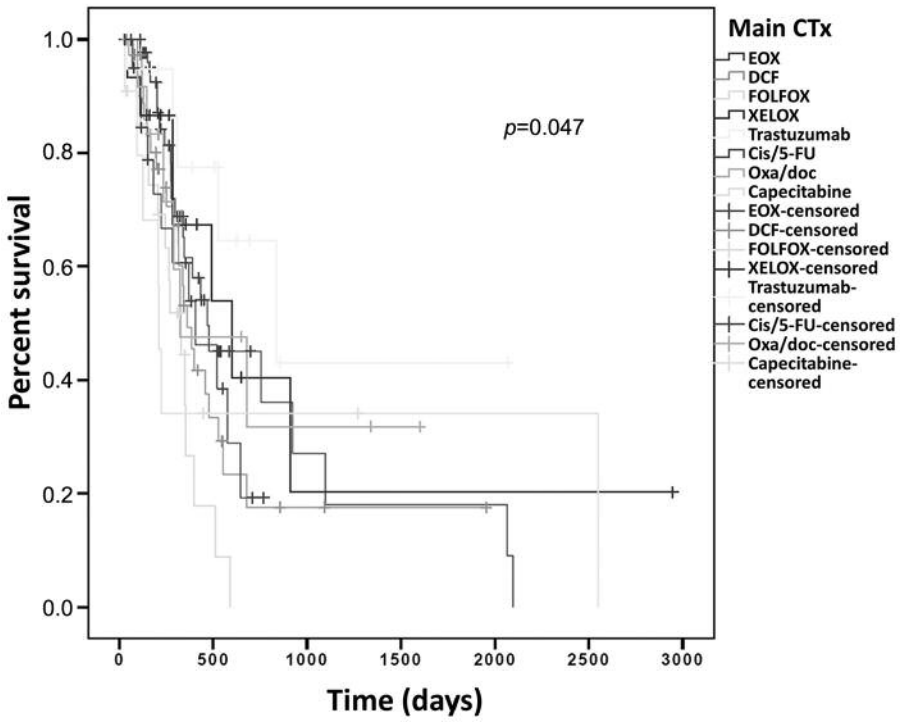

Figure 2. *Kaplan–Meier estimates of overall survival for the eight main chemotherapies (CTx). EOX: Epirubicin/oxaliplatin/capecitabine; DCF: docetaxel/cisplatin/5-fluorouracil; FOLFOX: leucovorin/5-fluorouracil/oxaliplatin; XELOX: capecitabine/oxaliplatin; cis/5-FU: cisplatin/5-fluorouracil; oxa/doc: oxaliplatin/docetaxel.*

European and American guidelines do not generally recommend gastrectomy in the non-curative treatment setting. In our cohort, we observed a tendency towards prolonged OS in patients subjected to palliative gastrectomy, but the results did not reach statistical significance. Additionally, bias must be expected due to the selection of patients deemed suitable for surgery, *e.g.* regarding their fitness or tumor burden. Since the results of the prospective REGATTA trial did not support gastrectomy prior to chemotherapy, the Japanese guidelines likewise excluded surgery without the indication of urgent symptoms in their recommendations (23, 24). However, a reverse therapy sequence with chemotherapy prior to adjuvant surgery might present a beneficial treatment strategy (25).

In our study, patients who did not receive palliative chemotherapy had a significantly reduced OS of 185 days. The treatment guidelines changed rapidly during the past years due to the introduction of new effective drugs and better evaluation of combination therapies. Nevertheless, the recommendations for HER2-negative patients remain vague, specifying neither the exact substances nor the combinations (5, 7).

Increased toxicity has been reported for some regimens and the choice of drugs should therefore mainly consider toxicity profiles of the agents and co-morbidities of the patients. As expected, our study revealed most allergic events in patients treated with trastuzumab. DCF led to a considerable number of hematological effects. Overall, triple regimens resulted in more adverse events than doublets.

The REAL II trial investigated the exchangeability of cisplatin by oxaliplatin in the ECF regimen, as oxaliplatin is associated with markedly less nephrotoxic effects and requires no additional hydration. As a further benefit, oxaliplatin led to a significantly lower number of adverse events such as venous thrombosis and neutropenia (9). These results and a recent meta-analysis suggest that oxaliplatin may even prolong OS slightly more than cisplatin (4, 9). We analyzed OS of patients treated with FOLFOX in comparison to cisplatin/5-FU and according to our findings oxaliplatin seems to represent an equally effective alternative to cisplatin in a 5-FU-based doublet regimen.

Recently, doublet regimens with oxaliplatin and a fluoropyrimidine are preferentially used (5, 7). Interestingly, in our study patients treated with XELOX had a significantly better OS in comparison to patients treated with FOLFOX. These results suggest a better efficacy of the oral pyrimidine capecitabine than 5-FU infusions. However, as this study represents therapy decisions based on the needs of the individual patients, selection bias can be at least partially responsible for this result. Patients still able to take oral medication are likely to be in a better performance and

nutrition status. Nevertheless, results of the REAL II trial and a subsequent meta-analysis showed superior OS in capecitabine combination-treated patients in comparison to 5-FU combinations (9, 26).

During the past years the use of triplet regimens became less popular in the palliative setting due to evidence of increased toxicity and no clearly proven benefit. The 2016 ESMO guidelines indicate controversy regarding the actual value of triplets (5), while the 2016 NCCN guidelines state that doublets should be preferred (7). A recent Cochrane meta-analysis could not resolve the question, whether the addition of fluoropyrimidines to taxane-platinum doublets improves OS (4). In our study, there was no significant prolongation of OS in patients treated with DCF in comparison to docetaxel/oxaliplatin. Additionally, we observed no significant differences in OS between the combination regimens cisplatin/5-FU with (*versus* without) docetaxel, although prolonged median OS has been reported (27). A recent meta-analysis casts doubt on whether the addition of epirubicin to the doublet oxaliplatin/capecitabine (EOX) results in extended OS (4). When comparing those two regimens in our patient cohort, epirubicin did not prolong OS significantly. Although a novel triplet combination of 5-FU/leucovorin/oxaliplatin/docetaxel (FLOT) was associated with a survival benefit in the perioperative setting of resectable gastroesophageal cancer patients and this regimen is increasingly considered also in the palliative first-line setting, a direct comparison with a doublet regimen and further data on the toxicity profile are missing (28). In summary, our study hence suggests that triplet regimens might not provide a clear survival advantage in comparison to doublets in the clinical first-line setting.

If this recognition proves right in the future, this might not only simplify choice of first-line regimens, but even impact second-line treatment. Most patients will progress under first-line treatment and the value of second-line therapies is only recently being recognized (29-31). In our study, 86 (39.45%) of the patients with systemic therapy received second- or further-line treatment. Tumor progression is usually addressed to resistance development; consequently, it must be kept in mind that the use of doublets instead of triplets as first-line treatment spares an efficient drug for second-line treatment.

Evaluation of HER2 status revealed HER2 positivity in 16.67% of the tested patients, a percentage similar to what is known from the ToGA trial and other studies (11, 16, 32). Compared to all the other investigated chemotherapy regimens, the introduction of trastuzumab as the first targeted therapy caused the most considerable change in OS in our cohort. However, other anti-HER2 treatments including lapatinib, pertuzumab and T-DM1 demonstrated no survival benefit (33-36).

Recently, further promising results were reached with immunotherapies, including the anti-PD-1 antibodies pembrolizumab and nivolumab, the anti-PD-L1-antibodies avelumab and durvalumab and the anti-CTLA-4 antibody ipilimumab. Nivolumab and Pembrolizumab are approved as salvage treatments for Asian and Western patients, respectively (37, 38). In our cohort five patients received immunotherapy,

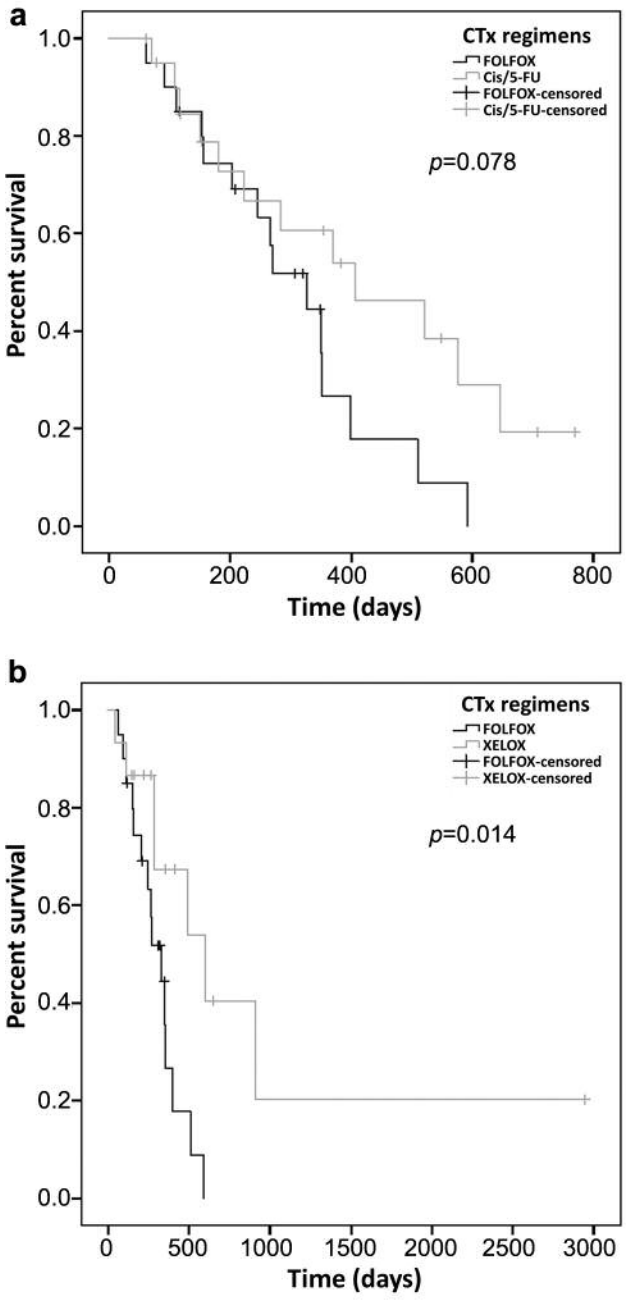

Figure 3. *Comparison of platinum and fluoropyrimidine-based doublet regimens. Kaplan–Meier estimates of overall survival. CTx: Chemotherapy; FOLFOX: leucovorin/5-fluorouracil/oxaliplatin; cis/5-FU: cisplatin/5-fluorouracil; XELOX: capecitabine/oxaliplatin.*

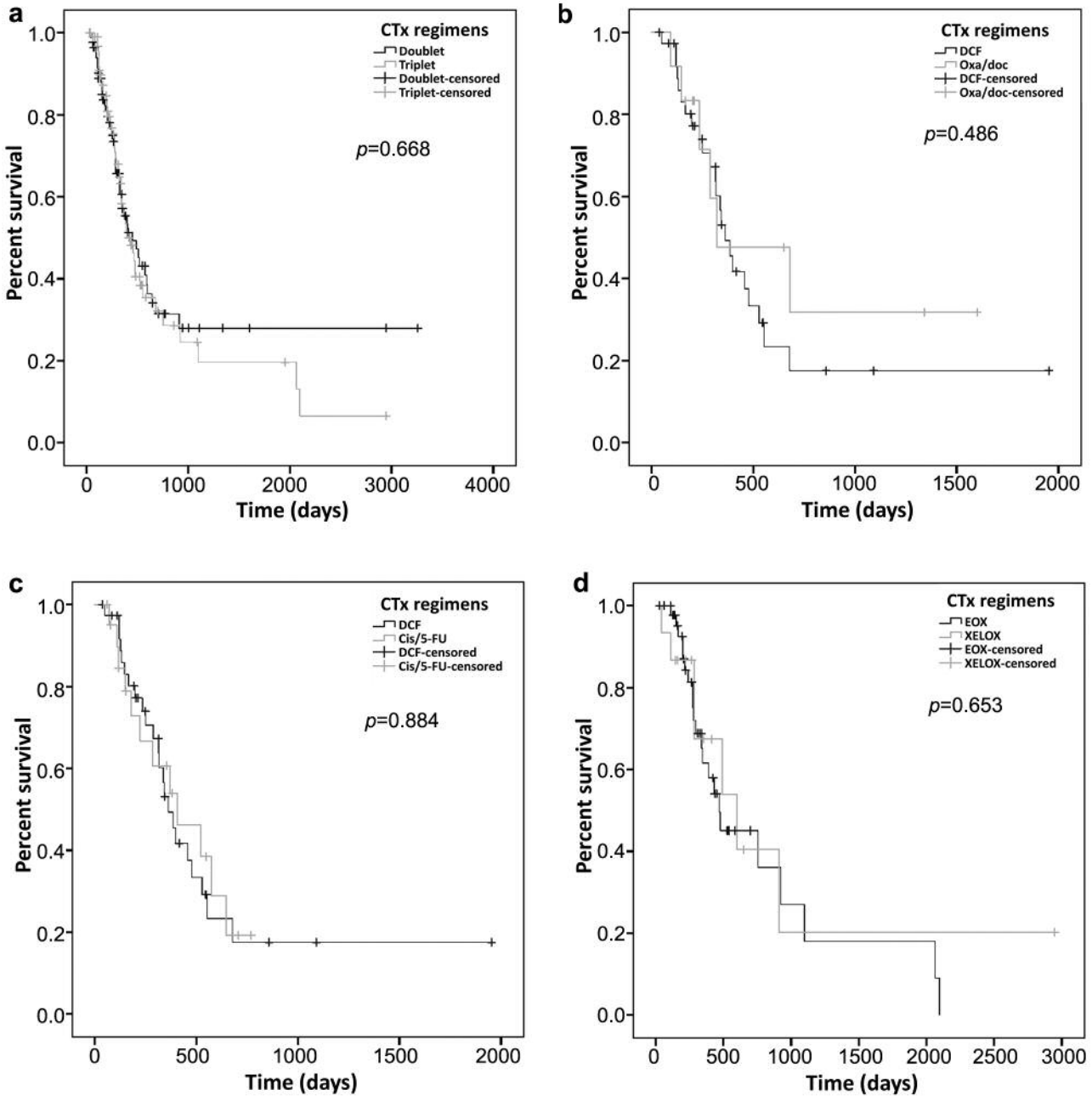

Figure 4. *Comparison of doublet and triplet regimens. Kaplan–Meier estimates of overall survival. CTx: Chemotherapy; DCF: docetaxel/cisplatin/5-fluorouracil; oxa/doc: oxaliplatin/docetaxel; cis/5-FU: cisplatin/5-fluorouracil; EOX: epirubicin/oxaliplatin/capecitabine; XELOX: capecitabine/oxaliplatin.*

mostly within the context of clinical trials. Several phase III clinical trials in the first- and later-line settings investigating various immunotherapies for gastroesophageal cancer are underway, which probably will change the treatment armamentarium of this entity in the near future.

Regarding the early diagnosis of tumor diseases, the measurement of circulating tumor markers plays a very promising role. Serum concentrations of CEA and CA 19-9 were available for some patients before and six months after the initiation of the first anti-tumor therapy. Although there were no associations of the change in circulating serum levels pre- and post-therapy, pre-chemotherapy CEA concentrations showed a tendency to associate significantly with outcome. Due to the size of our cohort, no clear conclusion regarding

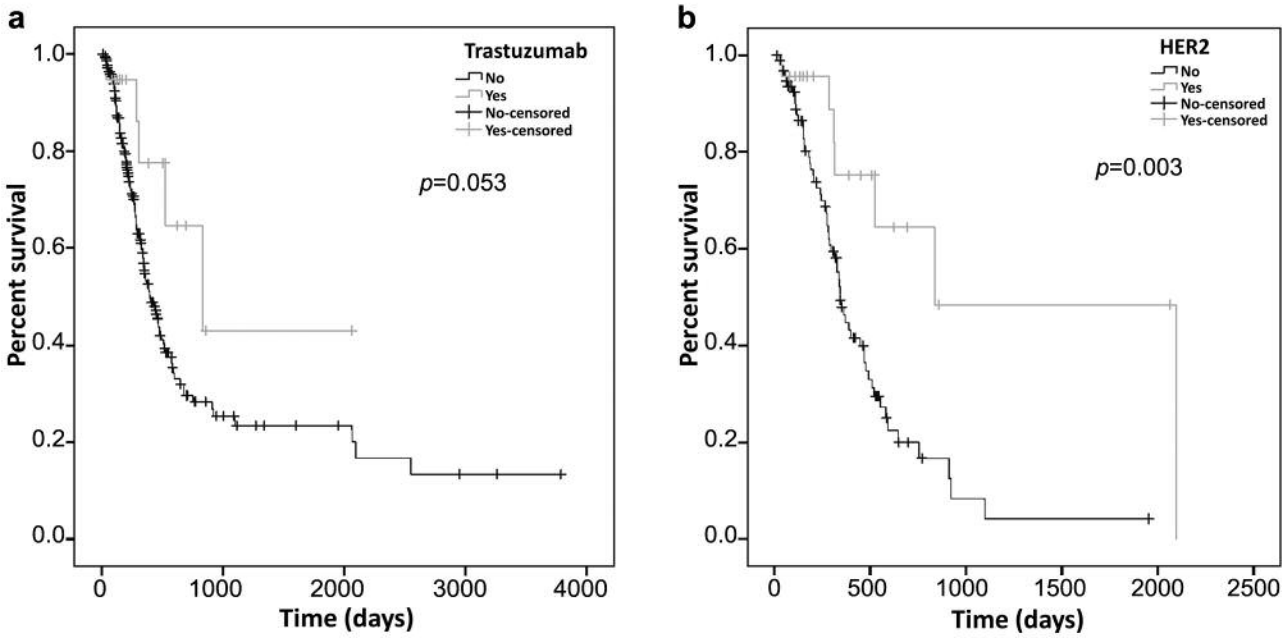

Figure 5. *Kaplan–Meier estimates of overall survival. a) Trastuzumab treatment and b) Human epidermal growth factor receptor 2 (HER2) status.*

this finding can be reached; however, this observation should be investigated in larger prospective cohorts, particularly in longitudinal analysis during treatment follow-up.

An important limitation of this study is the non-central radiological evaluation of the response rate of the patients, which might bias the PFS. Since the patients are usually discussed within the interdisciplinary tumor board of our institution, this bias is minimized. Furthermore, due to the retrospective nature of the study, the documentation of treatment-related adverse events and the patients' general condition must be treated with caution. Especially the performance status was documented insufficiently in older data and, therefore, could not be evaluated, although this is a critical parameter in advanced stage cancer patients.

Gastroesophageal cancers are especially heterogenous and it cannot be expected to find a one-fits-all drug that is suitable for the majority of patients. Additionally, patients with advanced stage cancer of the upper gastrointestinal tract are a very diverse group, which by itself makes individual treatment indispensable. The success of trastuzumab and recent results of immunotherapies point in a new and promising direction. At the same time, the evaluation of existing chemotherapy regimens should be enforced to establish clarity in the treatment recommendations.

Conflicts of Interest

MP has received research support from Boehringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Merck Sharp & Dome.

Authors' Contributions

All Authors contributed significantly to the manuscript. RB, AIM and MP were involved in the conception and design of the study, the analysis and interpretation of data and the drafting of the article and critical revision. HT, GJ and SFS were involved in the conception of the study, interpretation of data and revision of the article.

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