Survival of esophageal and gastric cancer patients with adjuvant and palliative chemotherapy—a retrospective analysis of a register-based patient cohort

Isabella Ekheden1 · Fereshte Ebrahim2 · Halla Ólafsdóttir3 · Pauline Raaschou4 · Björn Wettermark4,5,6 · Roger Henriksson2,7 · Weimin Ye1

Received: 22 November 2019 / Accepted: 24 April 2020 / Published online: 5 May 2020
© The Author(s) 2020

Abstract

Purpose The survival of esophageal and gastric cancer patients treated with chemotherapy is rarely assessed outside of clinical trials. Therefore, we compared the effectiveness of various curative or palliative chemotherapy regimens on the survival of esophageal and gastric cancer patients in a “real world” clinical setting.

Methods We identified a cohort of 966 incident esophageal and gastric cancer patients in Stockholm/Gotland County (a low-risk Western population) during 2008–2013. Patients who received chemotherapy with curative intention (n = 279) and palliative intention (n = 182) were analyzed separately. Using Cox proportional hazards regression models, we estimated hazard ratios (HRs) with 95% confidence intervals (CIs) and adjusted for the potential confounding factors: age, sex, TNM stage, radiotherapy, comorbidity, marital status, education, income, and country of birth.

Results In esophageal cancer patients with curative treatment intention, we observed a higher hazard for death among patients who received carboplatin-fluorouracil compared to patients who received cisplatin-fluorouracil, corresponding to a HR of 2.18 (95% CI 1.09–4.37). Conversely, in patients with cancer in the gastroesophageal junction who had a curative treatment intention at diagnosis, we observed a reduced hazard for death among those who received fluorouracil-oxaliplatin, compared to patients who received cisplatin-fluorouracil (HR 0.28; 95% CI 0.08–0.96).

Conclusion Among patients with esophageal cancer who received treatment with curative intention, cisplatin-fluorouracil was associated with better survival compared to carboplatin-fluorouracil, while patients with gastroesophageal junction cancer who were treated with cisplatin-fluorouracil had worse survival compared to fluorouracil-oxaliplatin.

Keywords Esophageal cancer · Gastric cancer · Chemotherapy · Adjuvant · Palliative · Survival

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-020-02883-3) contains supplementary material, which is available to authorized users.

1 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE171 77 Stockholm, Sweden
2 Regional Cancer Centre Stockholm Gotland, Stockholm County Council, Västgötagatan 2, 102 39 Stockholm, Sweden
3 Cancer Theme, Karolinska University Hospital, 171 64 Stockholm, Sweden
4 Department of Medicine Solna, Clinical Epidemiology Section, Karolinska Institutet, 171 76 Stockholm, Sweden
5 Department of Laboratory Medicine (LABMED), H5, Division of Clinical Pharmacology, C1:68, Karolinska University Hospital, Huddinge, 141 86 Stockholm, Sweden
6 Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden
7 Department of Radiation Sciences, Umeå University, 901 87 Umeå, Sweden
**Introduction**

Patients with esophageal and gastric cancer (EC and GC) have a very poor prognosis with an overall mortality to incidence ratio of 0.89 and 0.76, respectively, according to an IARC (International Agency for Research on Cancer) report [1]. The poor prognosis is mainly due to delayed diagnosis caused by late presentation of symptoms, when the disease usually has reached an advanced, metastatic stage. At this stage, the gold standard treatment, curative surgery, is no longer beneficial for the majority of patients [2]. In fact, only about 20–30% of EC [3] and GC [4] patients are eligible for curative surgery at diagnosis. In addition to radical tumor resection, neoadjuvant chemoradiotherapy or chemotherapy for EC patients and perioperative chemotherapy or adjuvant chemotherapy for GC patients have been established in clinical practice as an add-on treatment alternative to prolong survival [5], except for a minority of patients with cervical EC who can be cured with chemoradiotherapy alone [6]. Despite advances in surgical techniques and addition of chemotherapy over the past decades, the survival of EC and GC patients has not improved substantially and the mortality remains high [7–9]. Many potential new chemotherapies are currently explored in clinical trials, continuously including fit and willing patients [10–14]. However, the majority of patients are excluded from these clinical trials due to their advanced disease, poor physical conditions, and/or co-morbidities [15]. The use and outcome of chemotherapy in these patients can differ both regarding efficacy and safety compared to pre-registration reports from study patients [16]. Furthermore, chemotherapy can be used in other combinations and with other co-medications than previously studied, which might influence the effectiveness and/or safety in these patients. Follow-up data on post-marketing chemotherapy effectiveness and patient survival in the clinical, “real-world” setting are limited. Such information is of interest for regulators, caregivers, and patients. Unfortunately, previous post-marketing studies on EC and GC from the “real-world” setting are few and their results are inconclusive [17–21].

Therefore, we compared the effect of chemotherapy on the survival of esophageal and gastric cancer patients in a clinical setting with “real-world” data from retrospective registers in Stockholm and Gotland County during 2008–2016.

**Material and methods**

**Data collection—population, time periods, and variables**

The Stockholm and Gotland region in Sweden was comprised of almost 2.4 million people at the end of 2018 according to the census from Statistics Sweden. Current national guidelines for treatment of patients with esophageal or gastric cancer have been established collaboratively through Regional Cancer Centers (Regionala cancercentrum i samverkan) [22].

A cohort of patients diagnosed with esophageal or gastric cancer between 1 January 2008 and 31 December 2013 was constructed (Supplementary Fig. 1) from the Research Database at Regional Cancer Centre in Stockholm/Gotland, described in detail elsewhere [23–25]. The cohort was followed until death (all-cause mortality), emigration, or end of follow-up (31 December 2016), whichever occurred first. Individual-level data on exposure, outcome, and adjustment variables were obtained using a unique identifier, the National Registration Number, for linkages with the data collected in six national and three regional registers between 1 January 2001 and 31 December 2016 [26] (Supplementary Fig. 2).

We applied the tenth Swedish edition of the International Classification of Diseases (ICD-10), the second edition of the International Classification of Diseases in Oncology (ICD-O) for topography of the tumor, the Swedish version of the Systematized Nomenclature of Medicine II (SNOMED II) for tumor morphology, and the Anatomical Therapeutic Chemical (ATC) classification for exposure to drugs (Supplementary Table 1). We calculated the Charlson Comorbidity Index Score according to previously updated weights [27].

We included patients with curative or palliative treatment intention at diagnosis from the quality register “Nationellt kvalitetsregister för matstrups- och magsäckscancer” (NREV), and excluded patients with no tumor-specific treatment or missing treatment intention from further analyses. We analyzed the curative and palliative treatment groups separately. We divided the cancer patients into three groups depending on cancer site: the esophagus, gastroesophageal junction, or stomach. We excluded patients with tumor stage T0/Tis and missing T stage or Tx. Only chemotherapy treatment initiated within 6 months from diagnosis until 3 weeks after the start of the treatment was included in the analysis.

**Statistical analysis**

Comparisons of patient characteristics between groups were made using Wilcoxon two-sample test for continuous variables, Chi-squared test for categorical variables with ≥5, and Fisher’s exact test for categorical variables with less than five observations.

We used Kaplan-Meier graphs to illustrate survival curves and log-rank test to compare the difference of survival curves. In addition, Cox proportional hazards regression was employed to estimate hazard ratio (HR) with 95% confidence intervals (CI) to compare the effect of chemotherapy on survival separately for patients treated with curative and palliative intention. We tested the proportional hazards assumption and used stratification when this assumption was not met. We adjusted for potential confounding factors such as age.
(continuous), sex (men/women), and tumor stage (T1 + 2/T3 + 4, missing/N−/N+, missing/M−/M+) in a minimally adjusted model and added radiotherapy (unknown or missing/yes), comorbidity (0/1–5), marital status (missing/married/unmarried or divorced or widowed), education (missing/high and medium level/low level), income (missing/below median/equal to or above median), and country of birth (Sweden/other) in the fully adjusted model. We assessed the influence of unknown tumor stage by a sensitivity analysis including patients with unknown tumor stage.

We utilized SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for data management and analyses, and R Studio 1.0.153 (RStudio, Inc.) for producing Kaplan-Meier survival curves.

**Results**

In the final cohort of 966 patients, the mean age at cancer diagnosis was 66.7 years among patients in the curative treatment group and 69.9 among patients in the palliative treatment group (Table 1). More men than women were diagnosed with gastroesophageal cancer both in the curative and in the palliative treatment groups (Table 1).

In the curative treatment group, patients had less advanced tumor stage at diagnosis, a higher proportion with a current occupation (due to younger age), and a longer survival after diagnosis (Table 1). Fewer patients in the curative group received radiotherapy in addition to chemotherapy compared to the palliative group (Table 1).

At the end of follow-up, 31 December 2016, about 30% of the patients in the curative-intention group were alive, while only 3% of the palliative-intention group had survived (Table 1).

The distribution of other demographic variables (Table 1) and use of anti-inflammatory drugs and drugs against peptic ulcer/gastro-esophageal reflux disease (GERD) up to 1 year before diagnosis (Supplementary Table 2) were not statistically different between the curative and palliative treatment groups.

The distribution of TNM stages among patients with different chemotherapy regimens in the curative-treatment group was similar, except for patients with cancer in the esophagus treated with cisplatin-fluorouracil who had more advanced T and N stages at diagnosis. Mean age at diagnosis and percentage of patients who received radiotherapy were different between groups except radiotherapy for patients with stomach cancer, where very few received radiotherapy. There was a higher proportion of male than female patients with cancer in the gastroesophageal junction in the cisplatin-fluorouracil or epirubicin-oxaliplatin-capecitabine group than other chemotherapy groups, while the distribution of males was similar between chemotherapy groups in patients with cancer in the esophagus and stomach (Table 2).

In early-stage patients with curative treatment intention at diagnosis, initial survival was not significantly different; however, long-term survival seemed to be better in patients without chemotherapy vs. with chemotherapy ($p = 0.0099$) (Fig. 1A). The difference in survival between those who received chemotherapy vs. those without chemotherapy was not statistically significant neither in the curative-intention group with late tumor stage (Fig. 1B) nor in the palliative-intention group with early tumor stage (Fig. 1C). However, patients with late-stage tumor who received chemotherapy in the palliative-intention group had a clearly better survival ($p < 0.0001$) than patients without chemotherapy (Fig. 1D).

We observed a statistically significant survival benefit by choice of chemotherapy (cisplatin-fluorouracil) in the unadjusted Kaplan-Meier graph among esophageal cancer patients in the curative-intention group (Fig. 2), while no such difference existed for patients with cancer in the gastroesophageal junction (Fig. 3). In addition, there was a statistically significant difference in survival among patients with gastric cancer in the curative-intention group by choice of chemotherapy (epirubicin-oxaliplatin-capecitabine or fluorouracil-irinotecan) (Fig. 4).

In the fully adjusted Cox regression model for the curative group, we could demonstrate a higher HR for death of 2.18 (95% CI 1.09–4.37) for patients with cancer in the esophagus who received carboplatin-fluorouracil compared to the reference group (cisplatin-fluorouracil). Similarly, a more than doubled HR for death, 2.23 (95% CI 1.02–4.91), was detected for those patients treated with other, more unusual chemotherapy (Table 3). Among those patients with cancer in the gastroesophageal junction who were treated with fluorouracil-oxaliplatin, we observed a lower HR of 0.28 (0.08–0.96) compared to cisplatin-fluorouracil. Among gastric cancer patients in the curative treatment group, none of the chemotherapy regimens were associated with better or worse survival in the fully adjusted Cox model (Table 3). These associations could not be confirmed in the palliative-intention group (Supplementary Table 3) due to a different choice of treatment than in the curative-intention group. In the palliative-intention group with cancer in the gastroesophageal junction, the fully adjusted Cox regression model showed a trend of higher HR for treatment with other, more unusual chemotherapy, HR 32.53 (95% CI 3.97–266.89) (Supplementary Table 3).

For comparison of chemotherapy choices, we performed separate sensitivity analyses in the curative-intention group (Supplementary Table 4) and palliative-intention group (Supplementary Table 5) including patients with unknown and missing tumor stage. The direction of the estimates did not change except for reduced HR for esophageal cancer patients treated with carboplatin-fluorouracil in the palliative-intention group, which was not statistically significant, and gastric cancer patients in the palliative-intention group treated with other, more unusual chemotherapy where the association was only marginally statistically significant.
Table 1  Characteristics of the study subjects in a register-based cohort study on treatment in esophageal and gastric cancer patients in Stockholm county, Sweden 2008–2016 (n = 966)

| Variables                                      | Palliative treatment (n = 453) N (%) | Curative treatment (n = 513) N (%) | p value     |
|------------------------------------------------|------------------------------------|------------------------------------|-------------|
| Mean age (S.D.), years at diagnosis            | 69.9 (12.7)                        | 66.7 (11.0)                        | < 0.0001*   |
| Sex                                            |                                    |                                    | 0.2040**    |
| Male                                           | 297 (65.6)                         | 356 (69.4)                         |             |
| Female                                         | 156 (34.4)                         | 157 (30.6)                         |             |
| Tumor site                                     |                                    |                                    | <0.0001**   |
| Esophagus                                      | 229 (50.6)                         | 184 (35.9)                         |             |
| Gastroesophageal junction                      | 66 (14.6)                          | 94 (18.3)                          |             |
| Stomach                                        | 158 (34.9)                         | 235 (45.8)                         |             |
| Cancer subtype                                 |                                    |                                    | <0.0001**   |
| Esophageal squamous cell carcinoma             | 110 (24.3)                         | 84 (16.4)                          |             |
| Esophageal adenocarcinoma                      | 110 (24.3)                         | 98 (19.1)                          |             |
| Adenocarcinoma in gastroesophageal junction    | 62 (13.7)                          | 90 (17.5)                          |             |
| Gastric adenocarcinoma                         | 155 (34.2)                         | 226 (44.1)                         |             |
| Missing                                        | 16 (3.5)                           | 15 (2.9)                           |             |
| T stage                                        |                                    |                                    | <0.0001**   |
| T1                                             | 11 (2.4)                           | 57 (11.1)                          |             |
| T2                                             | 30 (6.6)                           | 97 (18.9)                          |             |
| T3                                             | 220 (48.6)                         | 282 (55.0)                         |             |
| T4                                             | 192 (42.4)                         | 77 (15.0)                          |             |
| N stage                                        |                                    |                                    | <0.0001**   |
| N negative                                     | 81 (17.9)                          | 192 (37.4)                         |             |
| N positive                                     | 313 (69.1)                         | 315 (61.4)                         |             |
| Unknown/not assessed/missing (Nx or missing)   | 59 (13.0)                          | 6 (1.2)                            |             |
| M stage                                        |                                    |                                    | <0.0001**   |
| M negative                                     | 166 (36.6)                         | 464 (90.5)                         |             |
| M positive                                     | 270 (59.6)                         | 44 (8.6)                           |             |
| Unknown/not assessed/missing (Tx or Nx)        | 17 (3.8)                           | 5 (1.0)                            |             |
| Occupation                                     |                                    |                                    | <0.0001**   |
| White collar                                   | 40 (8.8)                           | 64 (12.5)                          |             |
| Blue collar                                    | 53 (11.7)                          | 134 (26.1)                         |             |
| Pink collar<sup>4</sup>                        | 79 (17.4)                          | 165 (32.2)                         |             |
| Age ≥ 65 years                                 | 211 (46.6)                         | 98 (19.1)                          |             |
| Missing                                        | 70 (15.5)                          | 52 (10.1)                          |             |
| Survival time<sup>a</sup>, days. Median (IQR)  | 167 (255)                          | 776 (1383)                         | <0.0001*    |
| Palliative/curative radio-chemotherapy         |                                    |                                    | 0.0412**    |
| Yes                                            | 176 (37.6)                         | 167 (32.6)                         |             |
| No or missing                                   | 277 (61.1)                         | 346 (67.4)                         |             |
| Status at end of follow-up, 31 December 2016   |                                    |                                    | <0.0001*    |
| Alive                                          | 15 (3.3)                           | 151 (29.4)                         |             |
| Died 2015–2016, missing cause of death         | 9 (2.0)                            | 39 (7.6)                           |             |
| Died from other causes                         | 42 (9.3)                           | 38 (7.4)                           |             |
| Died from esophageal and junction cancer       | 213 (47.0)                         | 138 (26.9)                         |             |
| Died from gastric cancer                       | 174 (38.4)                         | 147 (28.7)                         |             |
| Follow-up time<sup>2</sup>, days. Median (IQR) | 210 (298)                          | 654 (1194)                         | <0.0001*    |
| Education                                      |                                    |                                    | 0.244**     |
| Low (primary school)                           | 143 (31.6)                         | 147 (28.7)                         |             |
| Middle (upper secondary school)                | 164 (36.2)                         | 219 (42.7)                         |             |
| High (university)                              | 110 (24.3)                         | 134 (26.1)                         |             |
| Missing                                        | 36 (8.0)                           | 13 (2.5)                           |             |
Discussion

Our results show that patients with curative treatment intention were younger than those with palliative treatment intention. This could reflect a better performance status, which is an essential part of being able to benefit from and tolerate multimodal curative treatment. The fact that these patients also received less radiotherapy than the palliative treatment group may have also contributed to shorten the time to curative surgery. We could confirm the large difference in survival between curative and palliative treatment patients, which is probably due to the effect of multimodal treatment including tumor resection, but the impact of tumor burden and metastatic pattern could not be excluded. We did not find a statistically different distribution of demographic variables between the curative and palliative treatment groups which is an indication of health care equity.

We found that chemotherapy (vs no chemotherapy) influenced survival for patients with early-stage tumors in the curative treatment group and late-stage tumors in the palliative treatment group, but not late cancer stage patients in the curative treatment group and early cancer stage patients in the palliative treatment group. A reason for an advantage in long-term survival among patients with early-stage tumors in the curative treatment group was likely due to a shorter median time to surgery among those without chemotherapy vs.
with chemotherapy. On the contrary, patients in the late stage palliative treatment group did not have curative surgery and therefore the effect of chemotherapy is clearer. Similarly, the influence of curative surgery seems to attenuate the effect of chemotherapy in the late-cancer-stage patients with curative treatment. Very few patients with early cancer stage had a palliative treatment intention at diagnosis, probably since they were not eligible for curative treatment due to various reasons such as patient characteristics (frailty, age, and comorbidities) or tumor characteristics (bulky tumor, lymph node metastases, cellular/molecular markers). These characteristics also seem to attenuate the effect of chemotherapy.

In our unadjusted Kaplan-Meier graph, esophageal cancer patients in the curative treatment group had a higher survival rate if treated with cisplatin-fluorouracil and gastric cancer patients had a better prognosis if treated with epirubicin-oxaliplatin-capecitabine and fluorouracil-irinotecan compared with other chemotherapy regimens. There was no statistically significant difference in the Kaplan-Meier graph between the various curative chemotherapy regimens among patients with gastroesophageal junction cancer. A similar trend, although not statistically significant, was observed in the palliative treatment group. We are only aware of two previous clinical trials that have made a head-to-head comparison between some of the chemotherapy regimens in our study. The first is a randomized trial among esophageal cancer patients not eligible for surgery and they did not find a statistically significant increase of progression-free survival for patients who received cisplatin-fluorouracil compared to FOLFOX (oxaliplatin-fluorouracil-leucovorin) [28], which was in line with our results in the palliative-treatment group, but is contrary to our findings in the curative treatment group. Furthermore, the OE05 trial [29] did not find an increased survival in esophageal adenocarcinoma patients treated with neoadjuvant ECX (epirubicin-cisplatin-capecitabine) compared to cisplatin-fluorouracil, which is in line with our results for epirubicin-oxaliplatin-capecitabine in the gastroesophageal junction cancer patients. Unfortunately, it is unlikely that any future clinical trial will make a head-to-head comparison of the chemotherapy regimens in our study since they are outdated in the Western world. The combination of cisplatin-fluorouracil for esophageal cancer has been practiced in Sweden since the 1980s when proven effective in head and neck squamous cell carcinoma patients [30], and is the most common regimen in our study period, followed by the combination EOX (epirubicin-oxaliplatin-capecitabine), which is an equivalent [31] of the ECF/ECX regimen (epirubicin-cisplatin-fluorouracil/capecitabine) which was reported in 2006 in the MAGIC trial [13] to significantly improve disease-free and overall survival in gastroesophageal cancer patients compared to surgery alone. Since then, the clinical treatment practice has been changed to use preoperative chemoradiotherapy treatment according to the CROSS trial (carboplatin-paclitaxel) which was published in 2012 [11] or the neoadjuvant FLOT regimen

### Table 2

Characteristics for patients with cancer in the esophagus, gastroesophageal junction, and stomach who received chemotherapy with curative intention within 6 months from diagnosis ($n=279$)

| Cancer site and chemotherapy groups | Cohort | Stage Mean age (SD) | %Radiotherapy | %Male |
|----------------------------------|--------|-------------------|--------------|-------|
| Esophagus, N                     | 132    | (T1 + T2)/ (T3 + T4) | %Npos %Mpos | p value |
| Cisplatin-fluorouracil           | 85     | 14/71             | 81 6        | 63.3 (7.5) 78 74 |
| Fluorouracil-oxaliplatin         | 23     | 4/19              | 61 4        | 67.6 (6.0) 65 78 |
| Carboxplatin-oxaliplatin         | 14     | 3/11              | 64 7        | 67.9 (6.7) 93 79 |
| Other chemotherapy               | 10     | 3/7               | 50 0        | 71.4 (6.4) 70 70 |
| p value                          | p = 0.01 | p < 0.01 p = 1.00 | p < 0.01 p < 0.01 p = 0.98 |
| Gastroesophageal junction, N     | 59     | 6/28              | 76 12       | 60.4 (9.4) 82 91 |
| Cisplatin-fluorouracil           | 34     | 2/11              | 54 0        | 64.5 (9.0) 54 69 |
| Fluorouracil-oxaliplatin         | 13     | 2/5               | 86 14       | 69.1 (4.7) 14 100 |
| Epirubicin-oxaliplatin-capecitabine | 7   | 3/2               | 20 0        | 70.2 (11.3) 40 40 |
| Other chemotherapy               | 5      | 3/2               | 20 0        | 70.2 (11.3) 40 40 |
| p value                          | p = 0.09 | p = 0.12 p = 0.75 | p = 0.05 p < 0.01 p = 0.03 |
| Stomach, N                       | 88     | 24/47             | 54 7        | 58.7 (10.4) 3 61 |
| Epirubicin-oxaliplatin-capecitabine | 71 | 0/8               | 88 0        | 66.9 (7.2) 0 88 |
| Fluorouracil-irinotecan          | 8      | 4/5               | 56 33       | 70.3 (9.0) 0 56 |
| Other chemotherapy               | 9      | 4/5               | 56 33       | 70.3 (9.0) 0 56 |
| p value                          | p = 0.17 | p = 0.18 p = 0.20 | p < 0.01 p = 0.40 p = 0.48 |
which showed a superior survival rate to ECF/ECX in a publication in 2016 [12]. In the meanwhile, fluoropyrimidine/platinum (fluorouracil-cisplatin) based perioperative regimens are recommended for patients with gastroesophageal junction or gastric cancer according to the FFCD trial [5, 14]. Our study period precedes the large clinical trials such as CROSS and FLOT that have shaped current treatment guidelines. We therefore found a larger variation in treatment than one can probably find in more recent data. The older chemotherapy (fluorouracil-leucovorin-oxaliplatin-docetaxel) which showed a superior survival rate to ECF/ECX in a publication in 2016 [12]. In the meanwhile, fluoropyrimidine/platinum (fluorouracil-cisplatin) based perioperative regimens are recommended for patients with gastroesophageal junction or...
Regimens that we have compared to each other in this study are most likely used in a much lesser extent today than during the study period but may still be in clinical use and gives important insight into the impact on survival of various chemotherapy regimens. Esophageal and gastric cancer patients with curative treatment who were eligible to receive the most common chemotherapy regimens (cisplatin-fluorouracil in esophageal cancer and epirubicin-oxaliplatin-capecitabine or fluorouracil-irinotecan in gastric cancer patients) had a higher survival rate than those patients who received other chemotherapies. The explanation may be that these patients were more fit with regard to patient and tumor characteristics so that they were perceived...
by the treating physician as being able to benefit from the standard treatment and to be able to tolerate it, which seems to be a very good prognostic marker. Patients who received more uncommon chemotherapy regimens had lower survival possibility, but since they were not eligible for the most common chemotherapy, maybe their prognosis should rather be compared with palliative treatment patients.

Our main finding is that, in our fully adjusted Cox model, patients with esophageal cancer who were treated with cisplatin-fluorouracil in the curative treatment group experienced
a better survival compared to patients treated with carboplatin-fluorouracil, while patients with cancer in the gastroesophageal junction who received cisplatin-fluorouracil had worse survival than patients treated with fluorouracil-oxaliplatin. Since carboplatin has a more favorable toxicity profile than cisplatin, we interpret the result where carboplatin-fluorouracil–treated patients had a lower survival rate than those treated with cisplatin-fluorouracil as an effect of their underlying diminished capacity to tolerate the cisplatin-based regimen. It is possible that gastroesophageal junction cancer patients might tolerate the fluorouracil-oxaliplatin regimen better than cisplatin-fluorouracil, and so the better delivery of the chemotherapy regimen might result in the higher survival rate among these patients.

The implication of these findings is that the choice of chemotherapy may predict survival in patients with tumors in the esophagus and gastroesophageal junction that are treated with curative intention. Yet, we have no previous studies to compare these associations with and therefore would need to interpret these results cautiously until they have been validated in future studies.

**Table 3** Cohort size and hazard ratios for chemotherapy with curative intention within 6 months from diagnosis with cancer in the esophagus, gastroesophageal junction, or stomach (n = 279)

| Chemotherapy groups by cancer site | Cohort N | Adjusted HR<sup>a</sup> | p value | Adjusted HR<sup>b</sup> | p value |
|-----------------------------------|----------|-------------------------|---------|-------------------------|---------|
| **Esophagus, N**                  |          |                         |         |                         |         |
| Cisplatin-fluorouracil            | 85       | Ref.                    | Ref.    | Ref.                    | Ref.    |
| Fluorouracil-oxaliplatin          | 23       | 1.53 (0.90–2.60)        | 0.12    | 1.28 (0.70–2.35)        | 0.43    |
| Carboplatin-fluorouracil          | 14       | 2.33 (1.24–4.38)        | 0.01    | 2.18 (1.09–4.37)        | 0.03    |
| Other chemotherapy                | 10       | 2.77 (1.34–5.73)        | 0.01    | 2.23 (1.02–4.91)        | 0.05    |
| **Gastroesophageal junction, N**  |          |                         |         |                         |         |
| Cisplatin-fluorouracil            | 34       | Ref.                    | Ref.    | Ref.                    | Ref.    |
| Fluorouracil-oxaliplatin          | 13       | 0.45 (0.16–1.25)        | 0.12    | 0.28 (0.08–0.96)        | 0.04    |
| Epirubicin-oxaliplatin-capecitabine| 7       | 0.76 (0.27–2.11)        | 0.60    | 0.34 (0.07–1.73)        | 0.20    |
| Other chemotherapy                | 5        | 1.00 (0.25–4.06)        | 1.00    | 0.72 (0.15–3.46)        | 0.68    |
| **Stomach, N**                    |          |                         |         |                         |         |
| Epirubicin-oxaliplatin-capecitabine| 71      | Ref.                    | Ref.    | Ref.                    | Ref.    |
| Fluorouracil-irinotecan           | 8        | 2.64 (1.13–6.18)        | 0.03    | 2.26 (0.92–5.53)        | 0.07    |
| Other chemotherapy                | 9        | 0.45 (0.15–1.36)        | 0.16    | 0.45 (0.14–1.40)        | 0.17    |

<sup>a</sup> Adjusted for age (continuous), sex, and TNM stage

<sup>b</sup> Additionally adjusted for radiotherapy, comorbidity, marital status, education, income, and country of birth

![Kaplan-Meier graph of survival in days after chemotherapy among patients with cancer in the stomach who received treatment with curative intention (n = 88)](image-url)
Strengths and limitations

Confounding by indication could explain the observed results although we have tried to decrease this risk by several methods, such as restricting the analysis to patients with known tumor stage. To further reduce the risk of confounding by indication, we looked at the curative-intention and palliative-intention groups separately. Thirdly, the study cohort is only from the Stockholm/Gotland area with reasonably similar treatment routines although small differences between hospitals may remain (80% of the patients were however treated at the three largest hospitals “Karolinska University Hospital Huddinge”, “Danderyd Hospital” and “Södersjukhuset”). Lastly, we classified the chemotherapy groups according to use of chemotherapy until 6 months after diagnosis. Analyzing chemotherapy used a longer time after diagnosis would have introduced a greater risk of confounding by indication since clinicians would have even more clinical information available to guide their chemotherapy regimen choice, an information that we could not access through registers.

The risk of differential misclassification of the main exposure and outcome is low since we collected data from registers that have high coverage and accuracy. Misclassification of the treatment intention at diagnosis is possible but we believe the risk for this will be low. Missing data on some of the exposures such as smoking, radiotherapy, and occupation as well as tumor stage was however an issue that we could not overcome. Due to missing data, we chose not to include smoking and occupation in the fully adjusted Cox regression model. This may lead to differential misclassification and either under- or overestimation of the association. Stratification by radiotherapy did not change hazard ratios significantly in the curative treatment group. We could unfortunately not analyze radiotherapy any further since we had no information about doses and regimens. We could not stratify the patients with the same chemotherapy according to dose and duration due to the large underlying variability. The large variability in dose and duration of chemotherapy is to try to reach similar exposures despite inter-individual differences in metabolism, elimination, tolerance, and effect. We tried to limit the effect of this by only including the first cycle of chemotherapy.

This study expands the current field in several aspects. To the best of our knowledge, this is the first study to make a head-to-head comparison of various “real-life” chemotherapy regimens on the survival of gastroesophageal cancer patients. It is not likely that any future clinical trial will make head-to-head comparisons of these chemotherapy regimens since they are not part of currently established guideline recommendations. However, they may still be in clinical use and comparing their effect on survival is of interest for both regulators, caregivers, and patients. Unique and high-quality information about which parenteral chemotherapy has been used in esophageal and gastric cancer patients in Stockholm/Gotland is one of the advantages of this study; this information is unfortunately not available in the nationwide Swedish registers. Another strength is the study base of clinical “real-world” patients, which includes patients commonly excluded from clinical trials. The time period 2008–2013 was of special interest as we believe there was a larger variation of chemotherapy than currently. Lastly, we could gather information about important prognostic factors such as tumor stage, comorbidities, and socioeconomic status.

We conclude that esophageal cancer patients who received carboplatin-fluorouracil had a twofold higher HR for death compared to patients treated with cisplatin-fluorouracil in Stockholm/Gotland 2008–2013. Moreover, patients with cancer in the gastroesophageal junction treated with fluorouracil-oxaliplatin had a reduced HR for death compared to patients treated with cisplatin-fluorouracil.

Acknowledgements Open access funding provided by Karolinska Institute.

Authors’ contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Isabella Ekhaleden and Fereshte Ebrahim. The first draft of the manuscript was written by Isabella Ekhaleden and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Funding information This work was supported by the Swedish Cancer Society (2016/510 to W. Ye) and the Swedish Research Council (2015-02625 to W. Ye). I. Ekhaleden is partly supported by a scholarship from the Karolinska Institutet MD/PhD program.

Availability of data and material The data that support the findings of this study are available from Regional Cancer Center Stockholm/Gotland but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Regional Cancer Center Stockholm/Gotland.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Ethical Review Board in Stockholm (Dnr 2012/1236-31-4, 2012/1726-32, 2014/849-32, 2017/597-32).

Consent to participate Not applicable.

Consent for publication Not applicable.
Code availability Available from the corresponding author upon reasonable request.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 38 cancers in 185 countries. CA Cancer J Clin 68(6):394–424
2. Recio-Boiles A, Babiker HM (2018) Cancer, gastric. In: StatPearls. StatPearls Publishing StatPearls Publishing LLC, Treasure Island (FL)
3. Klevenbro F (2016) Aspects of neoadjuvant therapy in the curative treatment of cancer in the esophagus or gastroesophageal junction. Inst för kliniskvetenskap, intervention och teknik/Dept of Clinical Science, Intervention and Technology
4. Janunger KG, Hafström L, Nygren P, Glimelius B (2001) The role of systemic therapy in advanced gastric and gastro-oesophageal junction cancer. Curr Treat Options in Oncol 4(2–3):309–326
5. Cartwright E, Cunningham D (2017) The role of systemic therapy in resectable gastric and gastro-oesophageal junction cancer. Curr Oncol 14(3):194–198
6. Hoeber A, Polak J, Van De Voorde L, Hoebers F, Grabsch Hl, De Vos-Geelen J (2016) Cervical esophageal cancer: a gap in cancer knowledge. Ann Oncol 27(9):1664–1674
7. Anderson LA, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT et al (2015) Survival for oesophageal, stomach and small intestine cancers in Europe 1999–2007: results from EUROCARE-5. Eur J Cancer 51(15):2144–2157
8. Howlader NNA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2014) SEER cancer statistics review, 1975-2014. National Cancer Institute, Bethesda
9. Sankaranarayanan R (2011) Cancer survival in Africa, Asia, the Caribbean and Central America. Introduction. IARC Sci Publ 162:1–5
10. Cohen DJ, Leichman L (2015) Controversies in the treatment of local and locally advanced gastric and esophageal cancers. J Clin Oncol 33(16):1754–1759
11. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Berghuis HM, Bussch OR, ten Kate F, Creemers OJ, Punt CJ, Phakker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen M, Rozema T, Biernann K, Beukema JC, Piet AH, van Rij C, Reinders JG, Tilaun HW, van der Gaast A, CROSS Group (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366(22):2074–2084
12. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB et al (2016) Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 17(12):1697–1708
13. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355(11):11–20
14. Ychou M, Boige V, Pignon JP, Comoy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCDC multicenter phase III trial. J Clin Oncol 29(13):1715–1721
15. Glimelius PNB (2001) The Swedish Council on Technology Assessment in Health Care (SBU) report on cancer chemotherapy - project objectives, the working process, key definitions and general aspects on cancer trial methodology and interpretation. Acta Oncol 40(2–3):155–165
16. Prasanna T, Beith J, Kao S, Boyer M, MeNeil CM (2018) Dose modifications in adjuvant chemotherapy for solid organ malignancies: a systematic review of clinical trials. Asia Pac J Clin Oncol 14(3):125–133
17. Aznab M, Beiki O, Pia KE, Setayeshi K, Hesami MA, Vrae H (2017) Evaluation the survival of patients with gastric cancer treated with adjuvant or palliative chemotherapy. J Gastrointest Cancer 48(1):31–37
18. Higgins E, Poon-King A, Prosser A, Kasto D, Gwyne Y (2017) Real-life experience of using definitive chemoradiotherapy for oesophageal cancer: a 5 year retrospective review. Eur J Surg Oncol 43(11):2229
19. Crosby T, Hurt CN, Falk S, Collins S, Mukherjee S, Staffurth J, Ray R, Bashir N, BridgeWater JA, Geh J, Cunningham D, Blazey J, Roy R, Maughan T, Griffiths G (2013) Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 14(7):627–637
20. Hultman B, Gunnarsson U, Nygren P, Sundborn M, Glimelius B, Mahteme H (2017) Prognostic factors in patients with loco-regionally advanced gastric cancer. World J Surg Oncol 15(1):172
21. Klevebro F, Lindblad M, Johansson J, Lundell L, Nilsson M (2016) Outcome of neoadjuvant therapies for cancer of the oesophagus or gastro-oesophageal junction based on a national data registry. Br J Surg 103(13):1864–1873
22. RCC (2017) Vårdprogram masttrops-och magsäckscancer [Available from: https://www.cancercentrum.se/samverkan]
23. Lilja B, Miranda J, Ljunggren G, Lööv S-Ä, Wettermark B, Lissmats A et al (2015) A study on cancer patients in the region of Stockholm by linking data from multiple sources, p 1
24. Bergqvist J, Iderberg H, Mesterton J, Bengtsson N, Wettermark B, Henriksson R (2017) Healthcare resource use, comorbidity, treatment and clinical outcomes for patients with primary intracranial tumors: a Swedish population-based register study. Acta Oncol 56(3):405–414
25. Bergqvist J, Iderberg H, Mesterton J, Henriksson R (2018) The effects of clinical and sociodemographic factors on survival, resource use and lead times in patients with high-grade gliomas: a population-based register study. J Neuro-Oncol 139(3):599–608
26. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A (2009) The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 24(11):659–667
27. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V (2011) Updating and validating the Charlson
Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173(6):676–682

28. Conroy T, Galais MP, Raoul JL, Bouche O, Gourgou-Bourgade S, Douillard JY et al (2014) Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 15(3):305–314

29. Alderson D, Cunningham D, Nankivell M, Blazey JM, Griffin SM, Crellin A, Grabsch HI, Langer R, Pritchard S, Okines A, Krysztopik R, Coxon F, Thompson J, Falk S, Robb C, Stenning S, Langley RE (2017) Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol 18(9):1249–1260

30. Mercke C, Albertsson M, Hambraeus G, Tennvall J, Lillo-Gil R, Samuelsson L et al (1991) Cisplatin and 5-FU combined with radiotherapy and surgery in the treatment of squamous cell carcinoma of the esophagus. Palliative effects and tumor response. Acta Oncol 30(5):617–622

31. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR, Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358(1):36–46

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.