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Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study

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The optimal first-line palliative systemic treatment strategy for metastatic esophagogastric cancer is not well defined. The aim of our study was to explore real-world use of first-line systemic treatment in esophagogastric cancer and assess the effect of treatment strategy on overall survival (OS), time to failure (TTF) of first-line treatment and toxicity. We selected synchronous metastatic esophagogastric cancer patients treated with systemic therapy (2010–2016) from the nationwide Netherlands Cancer Registry (n = 2,204). Systemic treatment strategies were divided into monotherapy, doublet and triplet chemotherapy, and trastuzumab-containing regimens. Data on OS were available for all patients, on TTF for patients diagnosed from 2010 to 2016.

Additional Supporting Information may be found in the online version of this article.

Key words: esophageal neoplasms, gastric neoplasms, drug therapy, palliative treatment

Abbreviations: 5-FU: 5-fluorouracil; CapOx: capecitabine/oxaliplatin; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECC: epirubicin/cisplatin/capecitabine; EOX: epirubicin/oxaliplatin/capecitabine; FLOT: docetaxel/oxaliplatin/5-fluorouracil/leucovorin; FOLFOSX: 5-fluorouracil/oxaliplatin; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IQR: interquartile range; NCR: Netherlands Cancer Registry; NOS: not otherwise specified; OS: overall survival; TTF: time to failure

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[Correction added on August 31, 2019 after first online publication: reference list updated.]

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Introduction
Palliative treatment represents an important part of esophagogastric cancer care, since approximately one-third of esophagogastric cancer patients have metastases at initial diagnoses, and curative treatment options are not available.1,2 Systemic therapy can improve both survival and quality of life in these patients.3–6

However, the optimal first-line palliative systemic therapy regimen for metastatic esophagogastric cancer patients has not yet been identified. Currently, first-line systemic treatment usually comprises a fluoropyrimidine and a platinum compound with the addition of trastuzumab in the case of human epidermal growth factor receptor 2 (HER2) overexpression, providing a survival benefit up to 9 months compared to no systemic treatment.7–11 Triplet therapy, in which either an anthracycline or taxane is added to the platinum-fluoropyrimidine doublet, is suggested in international guidelines for patients in good condition,8,10,12,13 but becomes increasingly controversial because of its toxicity.6,14,15 Because of the lack of consensus on optimal palliative systemic treatment, making choices about the best approach for these patients is challenging, which can result in interhospital and interphysician variation in individual systemic treatment. This could eventually affect survival and quality of life, and might be the explanation for stagnating survival rates, despite an increase in the administration of palliative systemic therapy from <10% to 40% of metastatic esophagogastric cancer patients between 1990 and 2011 in the Netherlands.1,2,16–18

Current practice is based on the results of several randomized controlled trials.5–6 Because of, for example, the under-representation of elderly and fragile patients in these trials, the actual patient population may not be adequately reflected. Therefore, more clarity about the administration and effects of palliative systemic therapy in daily clinical practice and evidence for the optimal therapeutic approach are needed. In this nationwide study, we aimed to explore first-line palliative systemic treatment in patients with metastatic esophagogastric cancer and the effect of treatment strategy on survival and toxicity in a real-world setting.

Materials and Methods
Data collection
Patients with an adenocarcinoma or squamous cell carcinoma of the esophagus, gastroesophageal junction or stomach (classified as C15 and C16 according to the third edition of the International Classification of Diseases for Oncology19) diagnosed with synchronous metastases (T1–4aN0–M1) and treated with systemic therapy were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that covers the total Dutch population of more than 17 million people and is directly linked to the pathological archive that comprises all histologically confirmed cancer diagnoses. Data on vital status were obtained by annual linkage to the Dutch Personal Records Database.

All esophagogastric cancer patients with synchronous metastases (metastases diagnosed before or within the first 5 days of the first systemic treatment cycle) treated with systemic therapy were included when diagnosed in a subset of Dutch hospitals between 2010 and 2014, and all hospitals in 2015–2016 (Fig. 1). Due to capacity and financial constraints, we were able to collect additional data of approximately 50% of the patients diagnosed in 2010–2014. For this period, we selected 43 of all 80 hospitals as a representative sample of all
hospitals in terms of annual number of patients, type of hospital and location in the Netherlands, and included all patients diagnosed in these hospitals between 2010 and 2014. This sample can therefore be considered as adequately reflecting the nationwide patient population and hospitals (Supporting Information Table S1). Patient characteristics and data on treatment and follow-up were extracted from the hospital’s electronic health record system or medical records by specially trained data managers.

Exclusion

Patients with esophageal, gastroesophageal junction or cardia carcinoma and nonregional lymph node metastases in the head and neck region only (n = 153) were excluded because they could have been eligible for definitive chemoradiotherapy with potential curative intent in cases in which dissemination of metastases was limited to the supraclavicular lymph nodes (Fig. 1). Because the exact location of these head and neck lymph node metastases was unknown, we excluded all of these patients. Moreover, patients who received chemoradiotherapy, defined as chemotherapy with concurrent radiotherapy consisting of ≥23 fractions or a total radiation dose of ≥40 Gy, were excluded (n = 111). Patients who received first-line systemic treatment outside the Netherlands were excluded (n = 29) as were patients without follow-up data on vital status (n = 9), without information on type of administered systemic therapy regimen (n = 10) or who were included in a trial in which they possibly received a placebo (n = 9). Finally, six patients in whom the primary tumor was considered to be other than esophageogastric (n = 6) were excluded.

Systemic therapy

First-line systemic treatment was defined as the first systemic therapy (monotherapy or combination regimen) given until suspension, regardless of reason for discontinuation.
combination regimen was specified as all systemic agents starting within 3 days after the first chemotherapeutic agent started. However, if trastuzumab was added more than 3 days after the start but before the end date of the combination regimen, this was also considered first line (e.g., because of delay in determination of HER2 status). All assumptions regarding first-line treatment can be found in Supporting Information Table S2.

If the same regimen was restarted after a therapy break, regardless of the duration of this break, this was still considered first line. Continuation of first line was also assumed if one of the agents of the initially started regimen was discontinued and the other agent(s) continued (e.g., capecitabine monotherapy after capecitabine/oxaliplatin [CapOx]), as well as in the case of a switch of a single drug within the same drug group (e.g., 5-fluorouracil [5-FU]/oxaliplatin [FOLFOX] to CapOx). If systemic therapy was switched to a regimen containing an agent of a new drug group that was not administered in the first line (e.g., carboplatin/paclitaxel to CapOx) after progression or because of toxicity, or if an agent of a new drug group was added (e.g., oxaliplatin added to 5-FU), this was considered second-line treatment.

The systemic therapy strategy was classified into regimens with one, two or three therapeutic agents (monotherapy, doublet therapy and triplet therapy, respectively; all without targeted therapy), trastuzumab-containing regimens and (nontrastuzumab) targeted therapy-containing regimens. Subsequently, systemic therapy regimens were subdivided based on the number and type of agents, as described previously: monotherapy; fluoropyrimidine (F) doublets (with a platinum [but not cisplatin], taxane [T] or irinotecan [I]); cisplatin (C) doublets (with a fluoropyrimidine, taxane or etoposide); gemcitabine (G) doublets (with a platinum/cisplatin); platinum (P; but not cisplatin)/taxane doublets; anthracycline (A) triplets (with a fluoropyrimidine and platinum/cisplatin); taxane triplets (with a fluoropyrimidine and platinum/cisplatin); trastuzumab-containing regimens; and (nontrastuzumab) targeted therapy-containing regimens (Supporting Information Fig. S2).

Toxicity
grade 3–5 systemic treatment toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0321) was registered in patients diagnosed between 2010 and 2014. If toxicity was registered but the grade was missing and the patient was not deceased, we considered toxicity as grade 3–4, because grades 1 and 2 were not registered in the NCR.

Overall survival and time to failure of first-line treatment
Overall survival (OS) was assessed from start of treatment until death or end of follow-up. Information on vital status was updated until February 1, 2019. Time to failure (TTF) of first-line treatment was available only in patients with complete follow-up (i.e., patients diagnosed between 2010 and 2015). TTF was used as a proxy for progression-free survival and calculated from the start of treatment to the first progression that resulted in termination of the regimen or end of follow-up. All assumptions regarding TTF are included in Supporting Information Table S1.

Statistical analysis
Patient and tumor characteristics are displayed with counts and percentages, or medians and interquartile ranges (IQRs). Differences between groups were analyzed using chi-square tests and Fisher’s exact tests where appropriate. Kaplan–Meier curves for OS and TTF were compared using the log-rank test. Multivariable Cox regression analyses were used to identify independently associated treatment strategies with OS and TTF, with adjustment of age, sex, performance status, number of comorbidities, year of diagnosis, tumor location, histology and metastases locations. Values of $p < 0.05$ were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

Data availability
The data that support the findings of our study are available from the Netherlands Cancer Registry. Restrictions apply to the availability of these data, which were used under license for our study.

Results
Patient characteristics
We included 2,204 patients (Fig. 1), of whom most were male (76%), with a median age of 64 (IQR, 57, 70) years (Table 1). Most patients had a World Health Organisation performance status of 0–1 (55%). Adenocarcinoma was present in 93% of the patients, squamous cell carcinoma in 6% and carcinoma not otherwise specified (NOS) in 1%. Nearly half of the primary tumors were located in the esophagus (46%), followed by noncardia stomach (35%) and gastroesophageal junction or cardia (19%). Most patients had one metastasis location at diagnosis (53%).

First-line systemic treatment regimens and strategies
A total of 45 different first-line systemic therapy regimens were administered (Supporting Information Fig. S1). The most commonly administered regimen was CapOx (21%), followed by epirubicin, oxaliplatin and capecitabine (EOX; 20%), carboplatin and paclitaxel (13%), epirubicin, cisplatin and capecitabine (ECC; 10%) and capecitabine monotherapy (9%; Supporting Information Table S3). Most patients received doublet chemotherapy (45%), followed by triplet chemotherapy (34%), monotherapy (10%), trastuzumab-containing regimens (10%) and nontrastuzumab targeted therapy-containing regimens (1%). The latter group was not displayed as a subgroup in Table 1, and not included in the Kaplan–Meier curves because of the limited number of patients.
Table 1 Baseline characteristics of all patients subdivided per systemic treatment strategy

| Characteristics          | All patients (n = 2,204) | Monotherapy (n = 228) | Doublet (n = 980) | Triplet (n = 758) | Trastuzumab-containing regimen (n = 215) |
|--------------------------|--------------------------|-----------------------|-------------------|------------------|----------------------------------------|
| Male, n (%)              | 1,670 (75.8%)            | 158 (69.3%)           | 757 (77.2%)       | 564 (74.4%)      | 171 (79.5%)                            |
| Age, years, median (IQR) | 64 (57, 70)              | 71 (65, 76)           | 64 (57, 70)       | 62 (53, 68)      | 63 (55, 69)                            |
| <60                      | 741 (33.6%)              | 32 (14.0%)            | 306 (31.2%)       | 311 (41.0%)      | 81 (37.7%)                             |
| 60–69                    | 856 (38.8%)              | 68 (29.8%)            | 404 (41.2%)       | 292 (38.5%)      | 84 (39.1%)                             |
| 70–79                    | 566 (25.7%)              | 110 (48.2%)           | 251 (25.6%)       | 152 (20.1%)      | 49 (22.8%)                             |
| ≥80                      | 41 (1.9%)                | 18 (7.9%)             | 19 (1.9%)         | 3 (0.4%)         | 1 (0.5%)                               |
| BMI, kg/m², median (IQR) | 24.7 (22.5, 27.7)        | 24.2 (21.4, 27.1)     | 25.0 (22.5, 27.8) | 24.8 (22.6, 27.7)| 24.4 (22.3, 27.7)                     |
| <18.5 (underweight)      | 57 (2.6%)                | 8 (3.5%)              | 26 (2.7%)         | 20 (2.6%)        | 3 (1.4%)                               |
| 18.5–25 (normal weight)  | 829 (37.6%)              | 107 (46.9%)           | 325 (33.2%)       | 311 (41.0%)      | 78 (36.3%)                             |
| >25 (overweight)         | 779 (35.3%)              | 73 (32.0%)            | 337 (34.4%)       | 299 (39.4%)      | 59 (27.4%)                             |
| Unknown                  | 539 (24.5%)              | 40 (17.5%)            | 292 (29.8%)       | 128 (16.9%)      | 75 (34.9%)                             |
| Performance status, n (%)|                          |                      |                   |                  |                                        |
| 0 or 1                   | 1,220 (55.4%)            | 104 (45.6%)           | 549 (56.0%)       | 406 (53.6%)      | 143 (66.5%)                            |
| ≥2                       | 152 (6.9%)               | 33 (14.5%)            | 75 (7.7%)         | 33 (4.4%)        | 10 (4.7%)                              |
| Unknown                  | 832 (37.7%)              | 91 (39.9%)            | 356 (36.3%)       | 319 (42.1%)      | 62 (28.8%)                             |
| Comorbidities, n (%)     |                          |                      |                   |                  |                                        |
| 0                        | 804 (36.5%)              | 61 (26.8%)            | 346 (35.3%)       | 311 (41.0%)      | 77 (35.8%)                             |
| 1                        | 621 (28.2%)              | 69 (30.3%)            | 271 (27.7%)       | 214 (28.2%)      | 63 (29.3%)                             |
| ≥2                       | 702 (31.9%)              | 94 (41.2%)            | 326 (33.3%)       | 207 (27.3%)      | 65 (30.2%)                             |
| Unknown                  | 77 (3.5%)                | 4 (1.8%)              | 37 (3.8%)         | 26 (3.4%)        | 10 (4.7%)                              |
| Tumor location, n (%)    |                          |                      |                   |                  |                                        |
| Esophagus                | 1,014 (46.0%)            | 66 (28.9%)            | 579 (59.1%)       | 241 (31.8%)      | 116 (54.0%)                            |
| Gastroesophageal junction or cardia | 410 (18.6%) | 47 (20.6%) | 148 (15.1%) | 169 (22.3%) | 41 (19.1%) |
| Stomach                  | 780 (35.4%)              | 115 (50.4%)           | 253 (25.8%)       | 348 (45.9%)      | 58 (27.0%)                             |
| Histology, n (%)         |                          |                      |                   |                  |                                        |
| Adenocarcinoma           | 2,056 (93.3%)            | 221 (96.9%)           | 858 (87.6%)       | 739 (97.5%)      | 215 (100.0%)                           |
| Squamous cell carcinoma  | 128 (5.8%)               | 6 (2.6%)              | 107 (10.9%)       | 15 (2.0%)        | 0                                      |
| Carcinoma NOS            | 20 (0.9%)                | 1 (0.4%)              | 15 (1.5%)         | 4 (0.5%)         | 0                                      |
| cT stage, n (%)          |                          |                      |                   |                  |                                        |
| cT1–cT3                  | 1,200 (54.4%)            | 111 (48.7%)           | 543 (55.4%)       | 388 (51.2%)      | 138 (64.2%)                            |
| cT4                      | 206 (9.3%)               | 26 (11.4%)            | 79 (8.1%)         | 88 (11.6%)       | 12 (5.6%)                              |
| cTx                      | 798 (36.3%)              | 91 (39.9%)            | 358 (36.5%)       | 282 (37.2%)      | 65 (30.2%)                             |
| cN stage, n (%)          |                          |                      |                   |                  |                                        |
| cN0                      | 342 (15.5%)              | 45 (19.7%)            | 145 (14.8%)       | 128 (16.9%)      | 21 (9.8%)                              |
| cN1–cN2                  | 1,474 (66.9%)            | 141 (61.8%)           | 659 (67.2%)       | 500 (66.0%)      | 160 (74.4%)                            |
| cN3                      | 192 (8.7%)               | 14 (6.1%)             | 102 (10.4%)       | 53 (7.0%)        | 20 (9.3%)                              |
| cNx                      | 196 (8.9%)               | 28 (12.3%)            | 74 (7.6%)         | 77 (10.2%)       | 14 (6.5%)                              |
| Histologic grade, n (%)  |                          |                      |                   |                  |                                        |
| Well differentiated      | 34 (1.5%)                | 2 (0.9%)              | 19 (1.9%)         | 7 (0.9%)         | 6 (2.8%)                               |
| Moderately differentiated| 400 (18.1%)              | 29 (12.7%)            | 179 (18.3%)       | 127 (16.8%)      | 61 (28.4%)                             |
| Poorly differentiated    | 928 (42.1%)              | 86 (37.7%)            | 410 (41.8%)       | 352 (46.4%)      | 68 (31.6%)                             |
| Unknown                  | 842 (38.2%)              | 111 (48.7%)           | 372 (38.0%)       | 272 (35.9%)      | 80 (37.2%)                             |
| Metastatic sites, n (%)  |                          |                      |                   |                  |                                        |
| 1                        | 1,172 (53.2%)            | 131 (57.5%)           | 517 (52.8%)       | 423 (55.8%)      | 94 (43.7%)                             |
| ≥2                       | 1,032 (46.8%)            | 97 (42.5%)            | 463 (47.2%)       | 335 (44.2%)      | 121 (56.3%)                            |

(Continues)
Overall survival of synchronous metastatic esophagogastric cancer patients. Kaplan–Meier curves displaying overall survival in patients treated with one, two or three chemotherapeutic agents (monotherapy, doublet and triplet, respectively) and in patients treated with a trastuzumab-containing regimen, diagnosed between 2010 and 2016 (n = 1,981). Survival curve of patients treated with a regimen containing (nontrastuzumab) targeted therapy (n = 23) is not displayed.
analyses (Figs. 2 and 3; Table 2a). The OS and TTF of patients treated with doublet therapy did not differ from patients treated with triplets after adjustment for confounding (OS: adjusted hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.83–1.02; TTF: HR 0.92, 95% CI 0.82–1.04).

Neither cisplatin, gemcitabine or platinum–taxane doublets nor anthracycline triplets showed survival benefit over fluoropyrimidine doublets in multivariable analyses (Table 2b). OS and TTF of taxane triplets were significantly better than in fluoropyrimidine doublets (HR 0.63, 95% CI 0.46–0.86; HR 0.67, 95% CI 0.45–1.00). Both trastuzumab- and targeted therapy-containing regimens showed significantly better OS and TTF than fluoropyrimidine doublets as well.

Of note, if we performed a predictive model and added only additional variables with \( p < 0.1 \) on univariable analysis, this did not influence statistically significance of the hazard ratios of systemic therapy strategies or regimens in the multivariable models.

**Toxicity**

Of 1,221 patients diagnosed in 2010–2014, systemic treatment toxicity grade 3–5 was reported in 27% (Table 3). Trastuzumab-containing regimens induced the highest complication rate (45%), followed by triplets (33%), doublets (21%) and monotherapy (17%). The complication rate differed significantly between the four subgroups (\( p < 0.001 \)).

Of 486 reported adverse events, the most common causes were gastrointestinal complications (43%), followed by blood and lymphatic system disorders, including infections (21%), general disorders (fatigue, pain) and administration site conditions (7%), cardiovascular (6%) and metabolism and nutrition disorders (5%).

Eighteen patients died due to complications of systemic therapy, of whom 7 were treated with a triplet, 5 with a doublet, 2 with monotherapy and 3 with a trastuzumab-containing regimen. Causes of death were blood and lymphatic system (\( n = 7 \)), cardiovascular (\( n = 6 \)) and gastrointestinal (\( n = 5 \)) disorders.

**Discussion**

In this nationwide cohort of 2,204 synchronous metastatic esophagogastric cancer patients, we found a strikingly wide variation of 45 different systemic therapy regimens that were administered between 2010 and 2016. This heterogeneity in treatment is undesirable, especially in case of unconventional
| Systemic treatment strategy                  | Patients No. | Median OS (months) | Univariable analyses | Multivariable analyses | Time to failure of first-line treatment (n = 1,700) |
|----------------------------------------------|--------------|--------------------|----------------------|------------------------|-----------------------------------------------|
| Monotherapy                                  | 228          | 4.1                | 1.71 1.48–1.98 <0.001 | 1.67 1.43–1.96 <0.001  | 205 205 1.51 1.29–1.77 <0.001 1.65 1.39–1.96 <0.001 |
| Doublet                                      | 980          | 7.4                | Ref                  | Ref                    | 683 683 Ref Ref 683 683 Ref Ref |
| Triplet                                      | 758          | 7.7                | 0.94 0.85–1.03 0.188 | 0.92 0.83–1.02 0.110  | 666 666 0.89 0.79–0.99 0.027 0.92 0.82–1.04 0.179 |
| Trastuzumab-containing regimen                | 215          | 11.2               | 0.62 0.53–0.72 <0.001 | 0.63 0.54–0.74 <0.001  | 126 126 0.62 0.51–0.76 <0.001 0.62 0.51–0.76 <0.001 |
| Targeted therapy-containing regimen (nontrastuzumab) | 23          | 11.9               | 0.73 0.48–1.11 0.142 | 0.67 0.44–1.03 0.068  | 20 20 0.54 0.35–0.86 0.009 0.53 0.33–0.83 0.006 |
| Age, years                                   |              |                    |                      |                        |                                              |
| <60                                          | 741          | 7.8                | Ref                  | Ref                    | 581 581 Ref Ref 581 581 Ref Ref |
| 60–69                                        | 856          | 7.5                | 1.03 0.93–1.14 0.542 | 1.01 0.91–1.12 0.901  | 669 669 0.99 0.89–1.11 0.904 0.95 0.85–1.07 0.432 |
| 70–79                                        | 566          | 7.0                | 1.06 0.95–1.19 0.280 | 1.01 0.89–1.14 0.893  | 417 417 1.00 0.88–1.13 0.937 0.92 0.80–1.06 0.227 |
| ≥80                                          | 41           | 6.5                | 1.26 0.92–1.74 0.153 | 1.03 0.74–1.43 0.873  | 33 33 1.19 0.84–1.69 0.330 0.94 0.65–1.35 0.721 |
| Sex                                          |              |                    |                      |                        |                                              |
| Male                                         | 1,670        | 7.5                | Ref                  | Ref                    | 1,290 1,290 Ref Ref 1,290 1,290 Ref Ref |
| Female                                       | 534          | 7.5                | 1.02 0.93–1.13 0.645 | 0.92 0.83–1.03 0.135  | 410 410 1.01 0.90–1.13 0.909 0.93 0.83–1.05 0.251 |
| Performance status                           |              |                    |                      |                        |                                              |
| 0 or 1                                       | 1,220        | 8.3                | Ref                  | Ref                    | 902 902 Ref Ref 902 902 Ref Ref |
| ≥2                                           | 152          | 4.7                | 1.73 1.46–2.06 <0.001 | 1.61 1.36–1.92 <0.001  | 114 114 1.53 1.26–1.87 <0.001 1.39 1.14–1.70 0.001 |
| Unknown                                      | 832          | 6.8                | 1.20 1.09–1.31 <0.001 | 1.16 1.06–1.27 0.002  | 684 684 1.14 1.10–1.26 0.011 1.14 1.02–1.26 0.016 |
| Comorbidities                                |              |                    |                      |                        |                                              |
| 0                                            | 805          | 7.6                | Ref                  | Ref                    | 652 652 Ref Ref 652 652 Ref Ref |
| 1                                            | 621          | 7.0                | 0.94 0.84–1.04 0.233 | 0.94 0.84–1.05 0.272  | 475 475 0.95 0.85–1.08 0.442 0.97 0.85–1.10 0.600 |
| ≥2                                           | 702          | 7.6                | 1.00 0.90–1.11 0.975 | 0.96 0.86–1.07 0.460  | 538 538 0.97 0.87–1.09 0.654 0.95 0.84–1.07 0.414 |
| Unknown                                      | 76           | 10.5               | 0.69 0.54–0.88 0.003 | 0.70 0.54–0.89 0.004  | 35 35 0.77 0.55–1.09 0.140 0.74 0.52–1.05 0.088 |
| Tumor location                               |              |                    |                      |                        |                                              |
| Esophagus                                    | 1,014        | 7.8                | Ref                  | Ref                    | 772 772 Ref Ref 772 772 Ref Ref |
| Gastroesophageal junction or cardia           | 410          | 7.6                | 0.95 0.85–1.07 0.395 | 0.95 0.84–1.08 0.417  | 316 316 0.90 0.79–1.03 0.131 0.92 0.80–1.06 0.268 |
| Stomach                                      | 780          | 6.9                | 1.08 0.98–1.18 0.132 | 1.02 0.91–1.15 0.698  | 612 612 0.98 0.88–1.09 0.691 0.98 0.85–1.12 0.729 |
| Histology                                    |              |                    |                      |                        |                                              |
| Adenocarcinoma                               | 2,056        | 7.6                | Ref                  | Ref                    | 1,580 1,580 Ref Ref 1,580 1,580 Ref Ref |
| Squamous cell carcinoma                      | 128          | 6.5                | 1.24 1.03–1.48 0.021 | 1.22 1.01–1.48 0.040  | 104 104 1.40 1.15–1.71 0.001 1.13 1.08–1.67 0.008 |
| Carcinoma NOS                                | 20           | 4.6                | 1.54 0.99–2.40 0.054 | 1.44 0.92–2.25 0.112  | 16 16 1.27 0.77–2.07 0.347 1.03 0.73–2.00 0.452 |

(Continues)
| Overall survival (n = 2,204) | Time to failure of first-line treatment (n = 1,700) |
|----------------------------|-----------------------------------------------|
|                           | Patients | Median OS (months) | Univariable analyses | Multivariable analyses | Patients | Median TTF (months) | Univariable analyses | Multivariable analyses |
|                           | No.      |                  | HR     | 95% CI | p value | HR     | 95% CI | p value |
| Liver metastasis          | 1,169    | 7.4              | 0.98   | 0.90–1.07 | 0.628 | 1.17   | 1.06–1.29 | 0.002 |
| Distant lymph node         | 890      | 7.2              | 1.06   | 0.97–1.15 | 0.226 | 1.17   | 1.07–1.29 | 0.001 |
| Peritoneal metastasis      | 524      | 6.9              | 1.22   | 1.11–1.35 | <0.001 | 1.42   | 1.25–1.61 | <0.001 |
| Lung metastasis           | 430      | 7.0              | 1.09   | 0.98–1.21 | 0.122 | 1.16   | 1.04–1.29 | 0.010 |
| Other metastases locations | 499      | 6.6              | 1.25   | 1.13–1.39 | <0.001 | 1.35   | 1.22–1.50 | <0.001 |
| Year of diagnosis         |          |                  | 0.95   | 0.93–0.97 | <0.001 | 0.97   | 0.95–0.99 | 0.009 |

Cox regression analyses in patients diagnosed between 2010 and 2016 for overall survival and patients between 2010 and 2015 for time to failure of first-line treatment. Both univariable and multivariable analyses are displayed for first-line systemic therapy subdivided in strategies (Table 2a) as well as regimens (Table 2b). Hazard ratios were adjusted for age, sex, performance status, number of comorbidities, tumor location, histology, metastases locations and year of diagnosis. Systemic treatment strategies were divided in chemotherapy regimens (monotherapy, doublet and triplet); trastuzumab-containing regimens and nontrastuzumab targeted therapy-containing regimens. Systemic treatment regimens were divided as follows: monotherapy; fluoropyrimidine doublets (with a platinum [but not cisplatin], taxane or irinotecan); cisplatin doublets (with a fluoropyrimidine, taxane or etoposide); gemcitabine doublets (with a platinum/cisplatin); platinum (but not cisplatin)/taxane doublets; anthracycline triplets (with a fluoropyrimidine and platinum/cisplatin); taxane triplets (with a fluoropyrimidine and platinum/cisplatin); trastuzumab-containing regimens; and (nontrastuzumab) targeted therapy-containing regimens. Abbreviations: A, anthracycline; C, cisplatin; CI, confidence interval; E, etoposide; F, fluoropyrimidine (capecitabine or 5-FU); G, gemcitabine; HR, hazard ratio; I, irinotecan; NOS, not otherwise specified; OS, overall survival; P, platinum compound (oxaliplatin or carboplatin); T, taxane; TTF, time to failure.

**Table 2a. (Continued)**

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## Cox regression analyses for overall survival and time to failure of first-line treatment per systemic treatment regimen

| Overall survival (n = 2,204) | Univariable analyses | Multivariable analyses | Time to failure of first-line treatment (n = 1,700) | Univariable analyses | Multivariable analyses |
|-----------------------------|----------------------|------------------------|-----------------------------------------------|----------------------|------------------------|
| **Patients No.** | **Median OS (months)** | **HR 95% CI p value** | **Median TTF (months)** | **HR 95% CI p value** | **HR 95% CI p value** |
| **Systemic therapy regimen** | | | | | |
| Monotherapy | 228 | 4.1 | 1.72 1.47–2.00 <0.001 | 1.68 1.42–1.98 <0.001 | 205 | 2.5 | 1.51 1.27–1.79 <0.001 | 1.63 1.35–1.96 <0.001 |
| F-doublet (FP, FT, FI) | 611 | 7.3 | Ref Ref | 369 | 4.4 | Ref Ref |
| C-doublet (CF, CT, CE) | 26 | 6.7 | 0.97 0.65–1.47 0.901 | 369 | 4.4 | Ref Ref |
| G-doublet (GP, GC) | 50 | 4.7 | 1.84 1.38–2.45 <0.001 | 46 | 3.0 | 1.71 1.26–2.33 <0.001 | 1.65 1.20–2.27 0.002 |
| PT-doublet | 293 | 8.2 | 0.93 0.81–1.08 0.342 | 248 | 5.5 | 0.91 0.78–1.07 0.272 | 0.86 0.72–1.03 0.093 |
| A-triplet (ACF, AFOx) | 708 | 7.4 | 0.97 0.87–1.09 0.620 | 638 | 4.8 | 0.89 0.78–1.02 0.805 | 0.91 0.80–1.05 0.197 |
| T-triplet (TCF, FOxT) | 50 | 11.8 | 1.38 0.84–2.26 <0.001 | 28 | 6.0 | 0.67 0.45–0.99 0.047 | 0.67 0.45–1.00 0.047 |
| Trastuzumab-containing regimen | 215 | 11.2 | 0.62 0.53–0.73 <0.001 | 126 | 6.7 | 0.62 0.50–0.76 <0.001 | 0.60 0.49–0.75 <0.001 |
| Targeted therapy-containing regimen (nontrastuzumab) | 23 | 11.9 | 0.73 0.48–1.12 0.145 | 20 | 9.2 | 0.54 0.34–0.86 0.009 | 0.51 0.32–0.81 0.005 |
| **Age, years** | | | | | |
| <60 | 741 | 7.8 | Ref Ref | 581 | 4.8 | Ref Ref |
| 60–69 | 856 | 7.5 | 1.03 0.93–1.14 0.542 | 669 | 4.6 | 0.99 0.89–1.11 0.904 | 0.96 0.86–1.09 0.551 |
| 70–79 | 566 | 7.0 | 1.06 0.95–1.19 0.280 | 417 | 4.3 | 1.00 0.88–1.13 0.937 | 0.92 0.80–1.06 0.236 |
| ≥80 | 41 | 6.5 | 1.26 0.92–1.74 0.153 | 33 | 4.1 | 1.19 0.84–1.69 0.330 | 0.92 0.64–1.32 0.664 |
| **Sex** | | | | | |
| Male | 1,670 | 7.5 | Ref Ref | 1,290 | 4.6 | Ref Ref |
| Female | 534 | 7.5 | 1.02 0.93–1.13 0.645 | 410 | 4.6 | 1.01 0.90–1.13 0.909 | 0.93 0.83–1.05 0.270 |
| **Performance status** | | | | | |
| 0 or 1 | 1,220 | 8.3 | Ref Ref | 902 | 4.8 | Ref Ref |
| ≥2 | 152 | 4.7 | 1.73 1.46–2.06 <0.001 | 114 | 2.9 | 1.53 1.26–1.87 <0.001 | 1.37 1.12–1.68 0.002 |
| Unknown | 832 | 6.8 | 1.20 1.09–1.31 <0.001 | 684 | 4.3 | 1.14 1.03–1.26 0.011 | 1.15 1.04–1.28 0.010 |
| **Comorbidities** | | | | | |
| 0 | 805 | 7.6 | Ref Ref | 652 | 4.8 | Ref Ref |
| 1 | 621 | 7.0 | 0.94 0.84–1.04 0.233 | 475 | 4.1 | 0.95 0.85–1.08 0.442 | 0.96 0.85–1.09 0.542 |
| ≥2 | 702 | 7.6 | 1.00 0.90–1.11 0.975 | 538 | 4.7 | 0.97 0.87–1.09 0.654 | 0.95 0.84–1.07 0.371 |
| Unknown | 76 | 10.5 | 0.69 0.54–0.88 0.003 | 35 | 6.2 | 0.77 0.55–1.09 0.140 | 0.74 0.52–1.05 0.091 |
| **Tumor location** | | | | | |
| Esophagus | 1,014 | 7.8 | Ref Ref | 772 | 4.6 | Ref Ref |
| Gastroesophageal junction or cardia | 410 | 7.6 | 0.95 0.85–1.07 0.395 | 316 | 5.0 | 0.90 0.79–1.03 0.131 | 0.90 0.78–1.04 0.158 |
A relatively high rate of grade 3–5 toxicity (45%) was seen in patients who received trastuzumab-containing regimens. In the ToGA trial, trastuzumab did not induce more toxicity compared to chemotherapy only.\textsuperscript{11} We did not observe the expected increase in cardiovascular toxicity due to trastuzumab. Possibly, the cytotoxic backbone induced the toxicity, since a toxicity rate of 56% was observed in patients who received a triplet backbone, compared to 43% with a doublet backbone. Moreover, lower toxicity rates were found in doublet backbones containing oxaliplatin (33%) compared to cisplatin-containing doublet backbones (48%), which confirms previously described findings.\textsuperscript{32}

Population-based data represent a wide variation of patients, including frail patients and patients with comorbidity who are usually not included in conventional clinical trials. Real-world evidence, if well analyzed and interpreted, is therefore highly potent in efficiently adding information about systemic treatment, alongside the results of these trials.\textsuperscript{33}

We are aware that our study has possible limitations. Although the data have been checked and improved regularly, there could still have been some errors due to misinterpretations by data managers or inadequate reporting by physicians. Because of incomplete medical records, some variables were missing, which may have impaired adjustment for possible confounding. Furthermore, patients with solely head and neck lymph node metastases were excluded, because treatment could have consisted of definitive chemoradiotherapy with curative intent in the case of only positive supravacuicular lymph nodes, as well as patients who had long-term radiotherapy alongside systemic treatment, since radiotherapy could affect survival rates.\textsuperscript{20,34} Nevertheless, the vast majority of the metastatic esophagogastric cancer patient population who received systemic treatment is represented.

Our population-level findings support doublet chemotherapy as the preferred first-line treatment strategy in terms of survival rates and toxicity. A trastuzumab-containing regimen should be considered in patients with HER2 overexpression. Future studies comparing first-line palliative (doublet) treatment strategies, such as the LyRICX study (NCT03764553), should also focus on quality of life, since this is an important outcome in these patients. Moreover, possible predictive and prognostic characteristics that influence treatment outcomes should be taken into account to improve patient selection and personalize treatment strategies.\textsuperscript{35}

In conclusion, in this nationwide study including real-world evidence in first-line systemic treatment of patients with synchronous metastatic esophagogastric cancer, doublet chemotherapy was associated with equal survival rates compared to triplet chemotherapy with a better toxicity profile. Patients treated with a trastuzumab-containing regimen had the best survival. A remarkable heterogeneity of 45 different systemic therapy regimens was observed, which is

| Table 2b. (Continued) |
|-----------------------|
| Overall survival (n = 2,204) | Time to failure of first-line treatment (n = 1,700) |
| Median | Multivariable analyses | Median | Univariable analyses |
| No. | OS (months) | HR | 95% CI | p value | HR | 95% CI | p value |
| Stomach | 780 | 6.9 | 1.08 | 0.98–1.18 | 0.012 | 1.00 | 0.89–1.13 | 0.995 |
| Histology | Adenocarcinoma | 2,056 | 7.6 | 1.24 | 1.03–1.48 | 0.021 | 1.24 | 1.02–1.51 | 0.032 |
| | Squamous cell carcinoma | 128 | 6.5 | 1.54 | 0.99–2.40 | 0.054 | 1.59 | 0.99–2.53 | 0.053 |
| | Carcinoma NOS | 20 | 4.6 | 0.98 | 0.68–1.43 | 1.6 | 3.1 | 1.27 | 0.75–2.10 | 0.364 |
| | Liver metastasis | 1,169 | 7.4 | 1.06 | 0.97–1.15 | 0.322 | 1.16 | 1.06–1.28 | 0.025 |
| | Distant lymph node metastasis | 890 | 7.2 | 1.06 | 0.97–1.15 | 0.787 | 1.16 | 1.06–1.28 | 0.025 |
| | Peritoneal metastasis | 524 | 6.9 | 1.22 | 1.11–1.35 | 0.073 | 1.22 | 1.11–1.35 | 0.073 |
| | Lung metastasis | 430 | 7.0 | 1.09 | 0.98–1.21 | 0.322 | 1.09 | 0.98–1.21 | 0.322 |
| | Other metastases | 499 | 6.6 | 1.25 | 1.13–1.39 | 0.001 | 1.25 | 1.13–1.39 | 0.001 |
| | Year of diagnosis | 0.95 | 0.93–0.97 | 0.001 | 0.95 | 0.93–0.97 | 0.001 |

\textsuperscript{Dijksterhuis et al. 1899 Int. J. Cancer: 146, 1889–1901 (2020) © 2019 The Authors. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC}
undesirable since it may negatively affect outcomes in these patients.

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