Systemic treatment effectiveness in advanced esophagogastric cancer in clinical practice

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SYSTEMIC TREATMENT
EFFECTIVENESS IN ADVANCED
ESOPHAGOGASTRIC CANCER

in clinical practice

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Academisch proefschrift

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Aula der Universiteit

op *vrijdag 25 juni 2021, te 14.00 uur*

door

Wilhelmina Petronella Maria Dijksterhuis

geboren te Kampen

Introduction & articles

General discussion & summary

Appendices

01.

02

General introduction
& outline of thesis
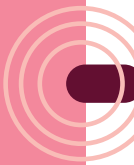
EPIDEMIOLOGY OF ESOPHAGOGASTRIC CANCER

Annually, approximately 1.6 million people are diagnosed with esophageal or gastric cancer worldwide.[1] Together these cancers account for 1.3 million deaths,[1] and are among the top five leading causes of cancer death.[2] In The Netherlands, approximately 4200 patients are diagnosed with esophagogastric cancer per year, and 3100 patients die as a result of these diseases.[3]

The vast majority of gastric cancers are adenocarcinomas (>95%).[4,5] In esophageal cancer, two main histological subtypes with a distinct etiology can be identified, i.e. adenocarcinoma and squamous cell carcinoma.[6] While squamous cell carcinomas account for 84% of esophageal cancers globally, the number of patients with esophageal adenocarcinoma exceeds those with squamous cell carcinoma in multiple high-income countries, including the Netherlands.[1] Three quarter of the Dutch patients with esophageal (including gastroesophageal junction [GEJ]/cardia) cancer have an adenocarcinoma.[7]

The incidence of esophageal cancer, especially adenocarcinoma, has risen over the past decades in high-income countries, including The Netherlands, whereas the incidence of gastric cancer has decreased (Figure 1).[2,3] This decrease has been attributed to improved food preservation due to the introduction of the refrigerator, and better hygiene in general resulting in reduced prevalence of Helicobacter pylori.[2] The rise in number of patients with esophageal adenocarcinoma can mainly be attributed to increasing body weight, in particular central obesity, i.e. accumulation of fat tissue in the abdominal area.[8]

Figure 1. Incidence of esophageal (including GEJ/cardia) and gastric cancer between 1989 and 2020 in The Netherlands.

Incidence of esophageal and gastric cancer in the Netherlands (1989–2020)
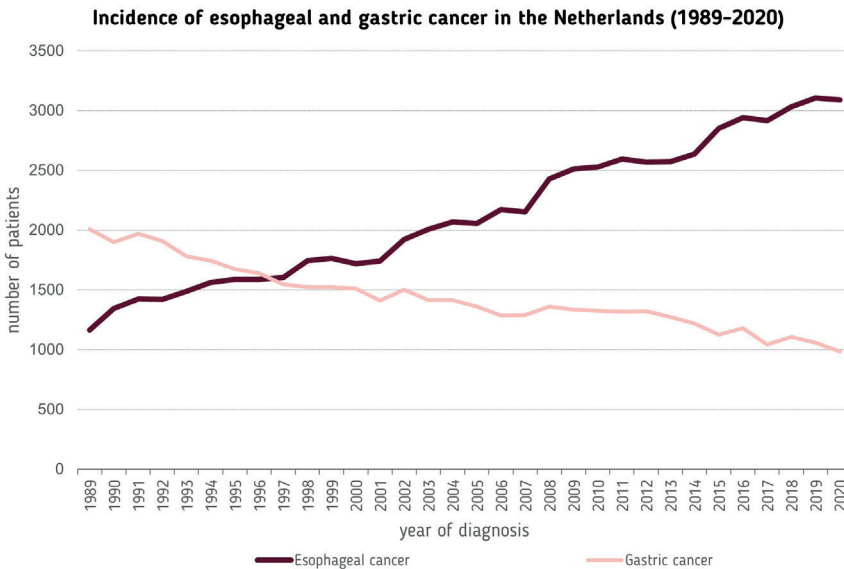
The numbers for 2019 and 2020 are based on estimations. Source: Netherlands Cancer Registry.

The increased intra-abdominal pressure causes gastric acid flow in the esophagus, leading to irritation by gastric secretions which can ultimately result in the development of esophageal adenocarcinoma.[8] Smoking and heavy alcohol use are the main risk factors for the development of esophageal squamous cell carcinoma and are responsible for the majority of the cases.[9]

Patients with esophagogastric cancer are predominantly men. The men/women ratio in esophageal cancer is 3:1, and nearly 2:1 in gastric cancer.[3] Although the gender disparity in incidence can be partly attributed to the higher exposure to risk factors such as central obesity, smoking and alcohol in men,[10,11] as well as to differences in sex hormone levels,[12,13] the predominance in men is still not completely understood.

DISEASE STAGES AND TREATMENT OPTIONS

Patients with esophagogastric cancer may present with dysphagia, weight loss or fatigue.[14] However, symptoms are often absent or nonspecific for a long time, with the result that esophagogastric cancer is diagnosed in an advanced stage.[2,3,14] Curative treatment of esophagogastric cancer consists of a surgical resection of the primary tumor, usually preceded and possibly followed by chemo(radio)therapy. A surgical resection is only feasible in patients with a locally resectable tumor, without distant metastases, and who are fit for surgery. In patients with advanced disease, the primary tumor invades surrounding organs or distant metastases are present, with the result that a surgical resection is often not an option. These patients can be treated with palliative systemic treatment. Life expectancy in these patients is poor: approximately one in five patients with advanced disease are still alive one year after diagnosis, with a median overall survival of five months.[7,15] In The Netherlands nearly 40% of esophageal and 50% of gastric cancer tumors are diagnosed in an advanced stage, and this proportion has remained stable over the past decade.[3,7,16] Therefore, treatment options that can improve patient outcomes are urgently needed.

PALLIATIVE SYSTEMIC TREATMENT

Palliative treatment can be administered in patients who are not eligible for treatment with curative intent. The mainstay of tumor targeted palliative treatment is systemic therapy, which includes chemotherapy, targeted therapy and immunotherapy. The aim of systemic treatment administration is to improve survival while maintaining quality of life.[17–20] In the Netherlands, up to 40% of patients with metastatic esophagogastric cancer receive systemic treatment.[7,15]

Currently available evidence on systemic treatment is based on the results of several randomized controlled trials (RCTs), in which median survival benefits between one and a half and seven months were observed compared with no systemic treatment administration, i.e. best supportive care alone.[18–21] RCTs are considered the reference standard for studying the efficacy of interventions since many decades.[22] Although the probability of introducing bias is limited by the randomization, blinding and prospective collection of data, these trials often have strict inclusion criteria regarding a patient's performance status and comorbidities. As a result, they often do not adequately reflect the actual patient population, for example due to the underrepresentation of elderly, fragile and female patients, which hampers the

external validity of these studies.[23,24] Therefore, other study types that include outcomes of patients with esophagogastric cancer who may not be eligible for inclusion in these trials are warranted. Studies on the use and type of palliative treatment and its effect for esophagogastric cancer in daily clinical practice are currently lacking, but could provide useful information complementary to the results of RCTs. Moreover, these population-based studies can give information on guideline adherence in treatment administration as well as on real-world aspects associated with treatment decision-making, e.g. biomarker testing.

Consensus on the exact optimal initial, i.e. first-line, palliative systemic therapy regimen for metastatic esophagogastric cancer patients has not been reached. Despite the rise of targeted agents in the past decade in several tumor types, including esophagogastric cancer,[21,25–27] chemotherapy is still the corner stone of systemic treatment in esophagogastric cancer. Generally, combination chemotherapy is preferred over treatment with single agents.[18–20] For long, national and international guidelines therefore recommend a fluoropyrimidine and platinum doublet in first line, with the addition of an anthracycline or – more recently – a taxane in selected patients.[28–32] Although superior survival rates in patients treated with triplet therapy, in which either an anthracycline or taxane is added to the platinum-fluoropyrimidine doublet, compared to doublet chemotherapy have been reported,[20,33] the use of triplet therapy is questioned because of its higher toxicity rates.[20,33,34]

Currently, only one targeted agent is available for first-line treatment in esophagogastric cancer, and only indicated in a part of the adenocarcinomas. Since 2010, therapy that targets the human epidermal growth factor receptor 2 (HER2), i.e. trastuzumab, is added to doublet chemotherapy in case of HER2 overexpression of adenocarcinomas, resulting in a median survival of 13.8 months compared to 11.1 months in doublet chemotherapy only.[21] The use of trastuzumab is recommended in both HER2 positive esophageal and gastric adenocarcinomas in international guidelines, and HER2 testing is indicated in every patient with an esophagogastric adenocarcinoma eligible for palliative systemic treatment.[28–31] However, the uptake of HER2 testing after publication of the landmark ToGA trial in 2010[21] and subsequent trastuzumab administration in case of HER2 overexpression have not been investigated in a real-world population. It is therefore unknown if testing and treatment administration are actually performed in daily practice in patients with esophagogastric cancer.

If first-line treatment fails, for example if the disease progresses or if the treatment is not tolerated, several options for sequential, i.e. beyond first-line, treatment are available.[35] The type of second-line treatment is largely dependent on the agents that are administered in first-line treatment, as similar agents, i.e. from the same drug group, are usually not used. Current recommendations on second-line treatment are a combination of a taxane with ramucirumab (a VEGF inhibitor), or monotherapy with ramucirumab or irinotecan for adenocarcinomas, or a taxane alone in adenocarcinomas and squamous cell carcinomas.[35–38] Evidence on the administration beyond first-line treatments in clinical practice is scarce, but could add valuable information alongside the trial results as well.

Despite increased systemic treatment administration from approximately 10% in 1989 to 40% in 2014 in all metastatic esophagogastric cancer patients in the Netherlands, median overall survival only increased from 18 to 22 weeks in these 26 years.[7] The reason for the very modest increase in survival is incompletely understood, but may at least partly be

a result of the lack of a standard first-line regimen. Moreover, although the current Dutch gastric cancer guideline includes specific recommendations on systemic treatment in first and second line,[32] the current national esophageal cancer guideline[39] as well as the gastric cancer guideline that was used until 2016[40] do not specify regimens, but only mention the indication for systemic treatment in general for patients with a good performance status. This may have resulted in variety in the type of systemic treatment that was used. However, the present status regarding palliative systemic regimens that are administered in first and beyond first-line in clinical practice is unknown. Moreover, real-world outcomes and treatment-related toxicity for the different systemic treatment strategies have not been explored in this patient population yet.

FACTORS ASSOCIATED WITH SYSTEMIC TREATMENT ADMINISTRATION AND OUTCOMES

In patients with esophagogastric cancer who are eligible for treatment with curative intent, an association between the number of patients that is diagnosed with esophagogastric cancer in a hospital annually, i.e. hospital volume, and the probability of receiving this treatment has been observed.[41–43] Patients who were diagnosed in a Dutch hospital that treated a high volume of patients with esophagogastric cancer were more likely to receive a curative treatment than patients diagnosed in low-volume hospital, and had a longer overall survival.[42,43] In the palliative setting, a high hospital treatment volume resulted in improved overall survival in patients who received first-line systemic treatment compared to low-volume hospitals.[15] The hospital volume is hypothesized to serve as a proxy for its experience with diagnosing or treating a tumor type. The experience in palliative systemic treatment for esophageal and gastric cancer may be limited, especially beyond first-line as not even half of the patients with metastatic esophagogastric cancer receive first-line treatment, and only a limited number will be eligible for beyond first-line treatment. Moreover, since only a part of patients has overexpression of HER2, familiarity with testing of this biomarker and the administration of HER2 targeted therapy among physicians may be limited. With the aim to assess the effect of hospital volume on treatment decisions in the palliative setting as well, two studies that investigate the association between hospital volume and the probability of receiving beyond first-line or HER2 targeted treatment, and outcomes of patients treated with systemic therapy, are included in this thesis.

A patient-related factor that may influence treatment outcomes is cachexia. Cachexia is a multifactorial syndrome characterized by involuntary weight loss due to ongoing loss of skeletal muscle mass, and is common among cancer patients.[44] Cancer patients with major weight loss or sarcopenia, i.e. skeletal muscle mass depletion, are assumed to have cachexia.[44] It is associated with poor outcomes and worse treatment tolerability in cancer patients.[44–46] Patients with esophagogastric cancer may experience more weight loss compared to other tumor types due to mechanical obstruction of the primary tumor, which may hamper food intake and induce weight loss. However, it is unknown to what extent cachexia affects the outcomes of patients with esophagogastric cancer, as the number of patients that presents with cachexia at initial diagnosis is unknown, and the effect of it on overall survival and treatment toxicity has not been investigated in clinical practice.

Moreover, differences in outcome between men and women with esophagogastric cancer have been described.[11,47,48] Also, it is known that women are less often enrolled for participation in oncological trials.[49] Currently, it is unclear if gender differences in treatment administration and survival are observed in clinical practice in The Netherlands.

DATA SOURCES

Data used in the majority of the studies included in this thesis are retrieved from the Netherlands Cancer Registry (NCR). The NCR is a nationwide registry that was established in 1989, and covers cancer diagnoses of the entire Dutch population of approximately 17 million inhabitants. Notification of newly diagnosed malignancies is obtained from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA), which is a pathological archive that contains all histologically confirmed cancer diagnoses. The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). Information on patient, tumor and treatment characteristics is collected by specially trained registrars. Details on systemic treatment i.e. type and duration of treatment, number of cycles, response and adverse events, as well as data on progressive disease are collected in the NCR in patients diagnosed from 2015 onwards. Additionally, these treatment and progression of disease data are collected in approximately half of synchronous metastatic esophagogastric cancer patients diagnosed in 2010-2014 for the purpose of the studies included in this thesis. The selection of hospitals is made due to logistic constraints, and based on the hospital in which patients were diagnosed, in order to obtain an adequate representation of the whole patient population. Data on patients' vital status are obtained by annual linkage to the Dutch Personal Records Database. Information of HER2 testing was extracted from PALGA reports.

In addition to data retrieved from the NCR, clinical data and patient reported outcomes collected in the Prospective Observational Cohort study of Oesophageal-gastric cancer Patients (POCOP) are used. POCOP was established in 2013 as a part of a nationwide, multidisciplinary research infrastructure with the aim to facilitate research in gastrointestinal cancer patients.[47] Patient-reported outcomes including results of health-related quality of life, weight loss parameters and diet quality, were obtained from questionnaires that were completed after informed consent of the patients.

OUTLINE OF THIS THESIS

This thesis includes studies that focus on the daily practice management of patients with advanced esophagogastric cancer. The main aims are to explore the use and effectiveness of systemic treatment in advanced esophagogastric cancer on the basis of population-based data, and identify factors that are associated with the administration of palliative systemic treatment and treatment outcomes. Furthermore, patient characteristics that may influence (survival) outcomes, such as skeletal muscle mass depletion and health-related quality of life, will be explored.

CHAPTER 2 focuses on the use and heterogeneity of first-line palliative systemic treatment administration in Dutch clinical practice, in particular the effect of different first-line treatment strategies on overall survival and toxicity.

In CHAPTER 3, the real-world testing of HER2 status in esophagogastric cancer patients is analyzed. We investigated which factors are associated with an increased probability of testing, and improved overall survival.

In CHAPTER 4, the association between hospital treatment volume and the probability of receiving beyond first-line treatment is assessed. Moreover, the efficacy of second-line systemic treatment regimens on overall survival is analyzed.

CHAPTER 5 AND 6 focus on patients with esophageal and gastric cancer who were diagnosed with interval distant metastases during treatment with curative intent. We explore the clinical characteristics, management and overall survival of these patients.

The effect of body composition on the tolerability of chemotherapy and outcomes in patients treated with first-line systemic treatment is discussed in CHAPTER 7. The prognostic significance of cachexia at initial diagnosis and subsequent dietetic interventions are determined in CHAPTER 8.

In CHAPTER 9, the prognostic value of health-related quality of life in esophagogastric cancer patients is assessed, using patient-reported outcomes of POCOP.
Gender differences in the incidence of esophageal and gastric cancer are acknowledged regularly, but it is unknown whether disparities in management and outcomes exist as well. Therefore, we analyzed if treatment and outcomes differ between men and women with incurable esophagogastric cancer and discuss the results in CHAPTER 10.

Lastly, possible implications of the results of this thesis, and differences between treatment efficacy in randomized controlled trials and effectiveness in real world, are discussed in CHAPTER 11, as well as opportunities to bridge this gap.

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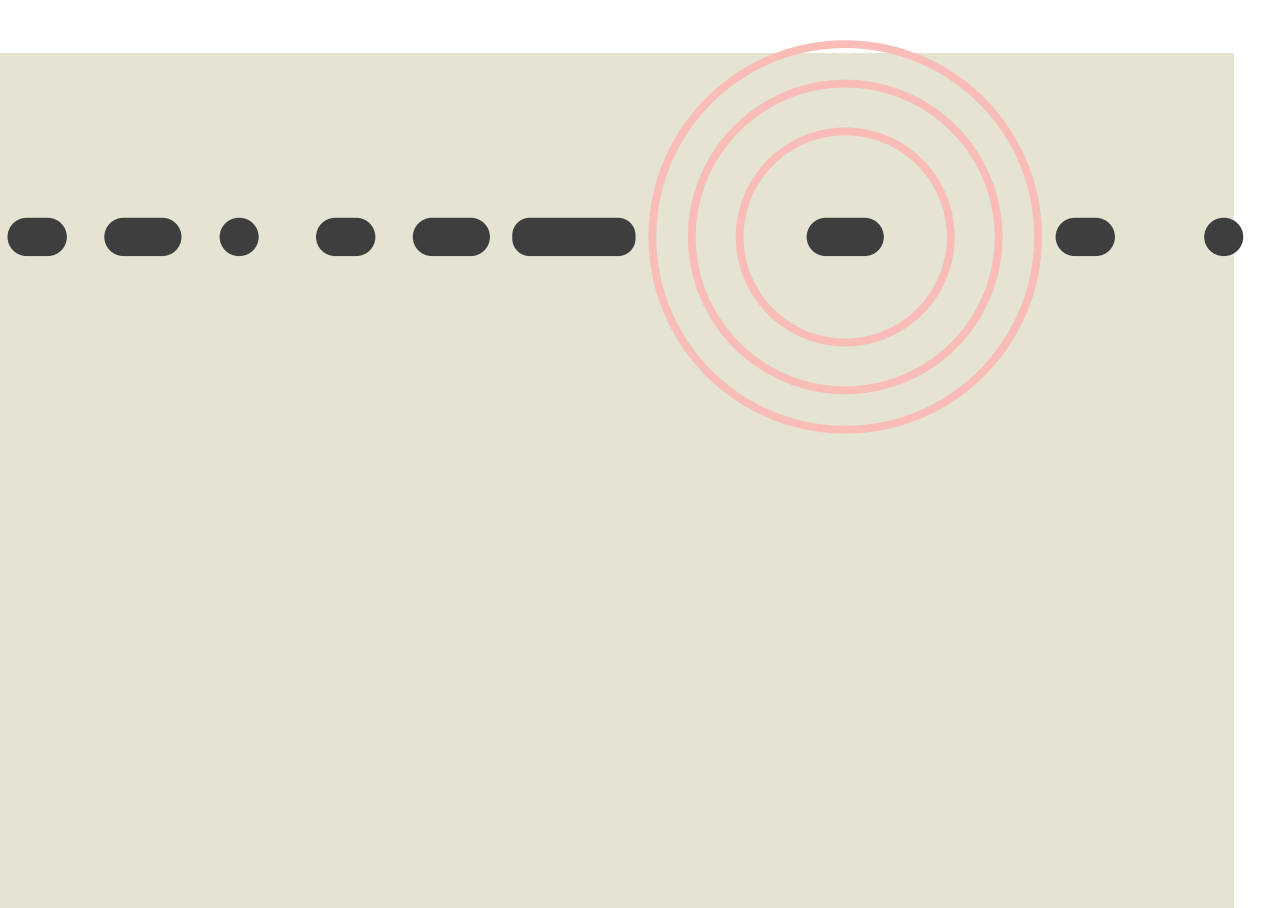
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03

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

International Journal of Cancer, 2020.

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ABSTRACT

Background: 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.

Methods: 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 2015 (n = 1,700), and on toxicity for patients diagnosed from 2010 to 2014 (n = 1,221). OS and TTF were analyzed using multivariable Cox regression, with adjustment for relevant tumor and patient characteristics.

Results: Up to 45 different systemic treatment regimens were found to be administered, with a median TTF of 4.6 and OS of 7.5 months. Most patients (45%) were treated with doublet chemotherapy; 34% received triplets, 10% monotherapy and 10% a trastuzumab-containing regimen. The highest median OS was found in patients receiving a trastuzumab-containing regimen (11.9 months). Triplet chemotherapy showed equal survival rates compared to doublets (OS: hazard ratio 0.92, 95% confidence interval 0.83−1.02; TTF: hazard ratio 0.92, 95% confidence interval 0.82−1.04) but significantly more grade 3−5 toxicity than doublets (33% vs. 21%, respectively).

Conclusion: Heterogeneity of first-line palliative systemic treatment in metastatic esophagogastric cancer patients is striking. Based on our data, doublet chemotherapy is the preferred treatment strategy because of similar survival and less toxicity compared to triplets.

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.[4–6] Because of, for example, the underrepresentation 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.

MATERIAL 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 Oncology[19]) diagnosed with synchronous metastases (T1–4bNallM1) 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 (Supplementary Table 1). 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).[19, 20] 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 first considered to have a different origin than the esophagus or stomach were excluded.

Figure 1. Flowchart of patient selection.

Subset of patients with metastatic esophagogastric cancer ($T_{1-4b}N_{all}M_1$) treated with systemic therapy diagnosed in 2010-2014 N=1386

All patients with metastatic esophagogastric cancer ($T_{1-4b}N_{all}M_1$) treated with systemic therapy diagnosed in 2015-2016 N=1145

Patients with metastatic esophagogastric cancer treated with systemic therapy N=2531

Included patients N=2204

Excluded (N=327):
- Patients with oesophageal, GEJ or cardia carcinoma and non-regional head and neck lymph node metastases only (N=153)
- Patients treated with chemoradiotherapy (N=111)
- Patients that received chemotherapy abroad (N=29)
- Patients in which systemic therapy regimen was not specified (N=10)
- Patients without follow-up data on vital satus (N=9)
- Patients that participated in a trial and possibly received a placebo (N=9)
- Patients that started with systemic therapy and in which the primary tumor was then considered to be other than esophagogastric (N=6)

GEJ, gastroesophageal junction.

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. A 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 Supplementary Table 2.

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[6]: 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 (Supplementary Figure 2).

Toxicity

Grade 3−5 systemic treatment toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03[21]) 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 Supplementary Table 1.

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).

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 (Supplementary Figure 1). 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%; Supplementary Table 3). 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.
All but one patient treated with a trastuzumab-containing regimen had a HER2-positive tumor. One patient received trastuzumab monotherapy; all other patients received trastuzumab with chemotherapy. Doublet chemotherapy backbones were used in the majority of the patients (n = 167), of which CapOx (n = 73) and capecitabine/cisplatin (n = 65) were administered most often.

Survival
The median OS was 7.5 (IQR, 3.7, 12.9) months. In 1,700 patients, diagnosed between 2010 and 2015 with complete follow-up, the median TTF of first-line systemic treatment was 4.6 (IQR, 2.0, 7.9) months.

Monotherapy resulted in lower survival rates compared to all other treatment strategies in univariable and multivariable 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 add 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.

Table 1. Baseline characteristics of all patients subdivided per systemic treatment strategy.

Characteristics	All patients (n = 2204)	Monotherapy (n = 228)	Doublet (n = 980)	Triplet (n = 758)	Trastuzumab-containing regimen (n = 215)
Male, No. (%)	1670 (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)	42 (1.9%)	6 (2.6%)	18 (1.8%)	16 (2.1%)	2 (0.9%)
18.5-25 (normal weight)	844 (38.3%)	109 (47.8%)	333 (34.0%)	315 (41.6%)	79 (36.7%)
>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, No. (%)					
0 or 1	1220 (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, No. (%)					
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, No. (%)					
Esophagus	1014 (46.0%)	66 (28.9%)	579 (59.1%)	241 (31.8%)	116 (54.0%)
Gastro-esophageal 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, No. (%)					
Adenocarcinoma	2056 (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, No. (%)					
cT1-3	1200 (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, No. (%)					
cN0	342 (15.5%)	45 (19.7%)	145 (14.8%)	128 (16.9%)	21 (9.8%)
cN1-2	1474 (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, No. (%)					
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, No. (%)					
1	1172 (53.2%)	131 (57.5%)	517 (52.8%)	423 (55.8%)	94 (43.7%)
≥2	1032 (46.8%)	97 (42.5%)	463 (47.2%)	335 (44.2%)	121 (56.3%)
Location metastases, No. (%)[1]					
Liver	1169 (53.0%)	120 (52.6%)	519 (53.0%)	375 (49.5%)	142 (66.0%)
Distant lymph nodes	890 (40.4%)	93 (40.8%)	403 (41.1%)	287 (37.9%)	94 (43.7%)
Peritoneum	524 (23.8%)	62 (27.2%)	191 (19.5%)	235 (31.0%)	30 (14.0%)
Lung	430 (19.5%)	41 (18.0%)	195 (19.9%)	123 (16.2%)	66 (30.7%)
Other	499 (22.6%)	39 (17.1%)	236 (24.1%)	163 (21.5%)	51 (23.7%)

Baseline characteristics of all patients, divided per systemic therapy regimen. Characteristics of patients who received targeted (nontrastuzumab) therapy (n = 23) were not displayed as a subgroup.
[1]More than one location per patient possible; percentages do not add up to 100.
Abbreviations: IQR, interquartile range; BMI, body mass index; NOS, not otherwise specified; cT stage, clinical tumor stage; cN status, clinical lymph node stage.

Figure 2. Overall survival of synchronous metastatic esophagogastric cancer patients.
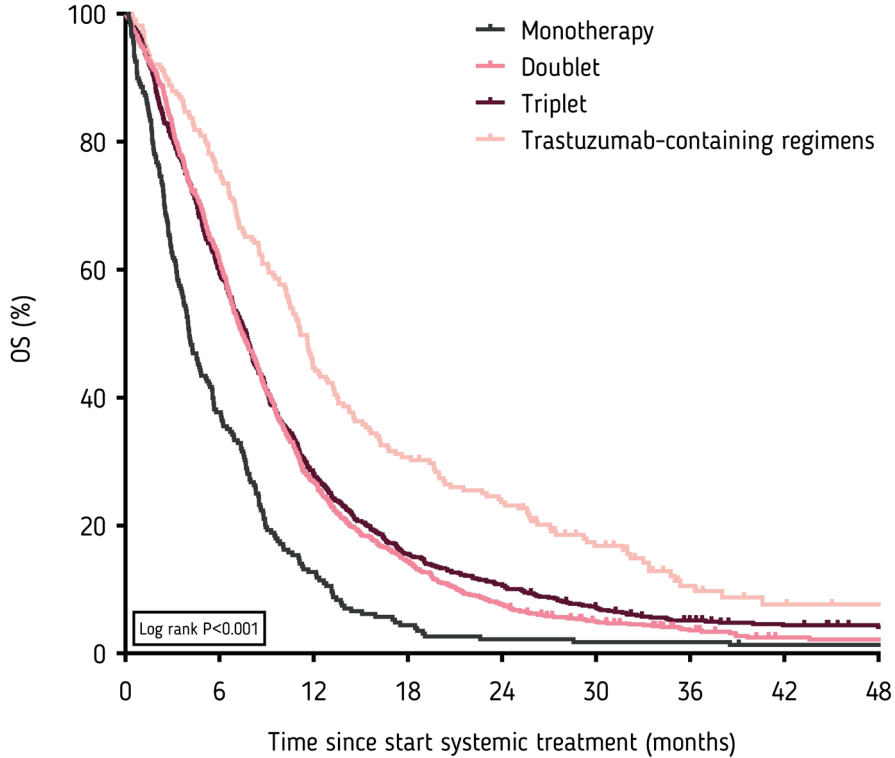
Number at risk

Monotherapy	228	87	30	11	6	5	5	3	3
Doublet	980	605	265	142	76	39	21	9	8
Triplet	758	456	214	119	83	53	32	23	17
Trastuzumab	215	163	97	67	51	30	14	8	6

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.

Figure 3. Time to failure of first-line therapy in synchronous metastatic esophagogastric cancer patients.
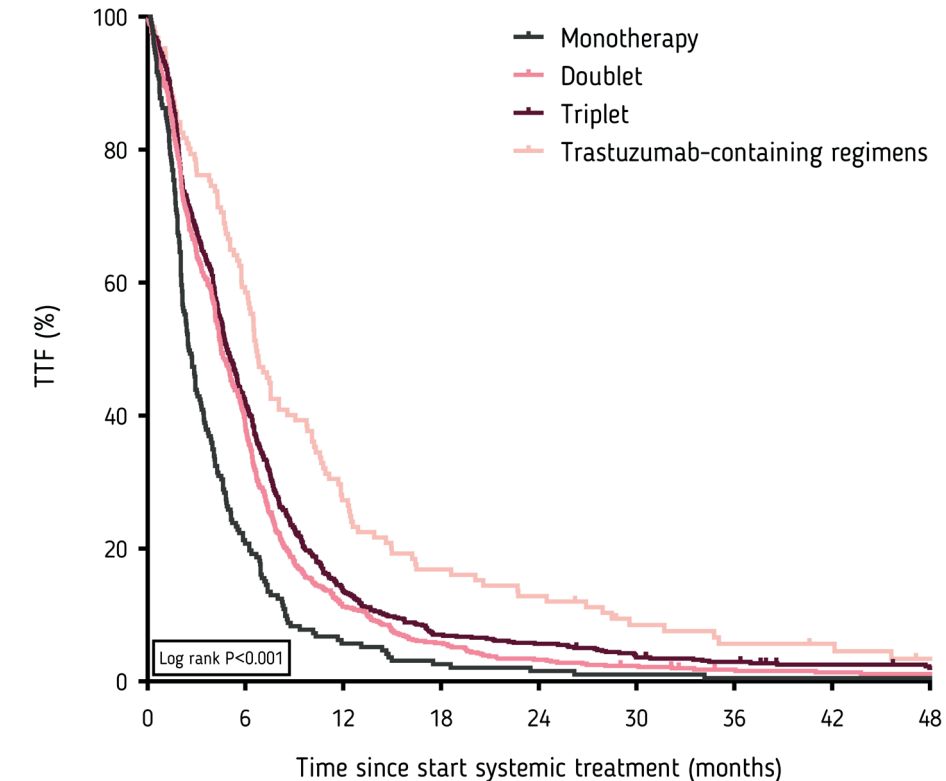
Kaplan−Meier curves displaying time to failure of first-line treatment in patients treated with one, two or three chemotherapeutic agents (monotherapy, doublet and triplet, respectively) and in patients treated with a trastuzumab-containing regimen, diagnosed between 2010 and 2015 (n = 1,680). Survival curve of patients treated with a regimen containing (nontrastuzumab) targeted therapy (n = 20) is not displayed.

Table 2a. Cox regression analyses for overall survival and time to failure of first-line treatment per systemic treatment strategy.

| | Overall survival (n = 2204) | | | | | | | | Time to failure of first-line treatment (n = 1700) | | | | | | | |
| | Patients No. | Median OS (months) | Univariable analyses | | | Multivariable analyses | | | Patients No. | Median TTF (months) | Univariable analyses | | | Multivariable analyses | | |
			HR	95% CI	P value	HR	95% CI	P value			HR	95% CI	P value	HR	95% CI	P value
Systemic treatment strategy																
Monotherapy	228	4.1	1.71	1.48-1.98	<0.001	1.67	1.43-1.96	<0.001	205	2.5	1.51	1.29-1.77	<0.001	1.65	1.39-1.96	<0.001
Doublet	980	7.4	Ref			Ref			683	4.5	Ref			Ref		
Triplet	758	7.7	0.94	0.85-1.03	0.188	0.92	0.83-1.02	0.110	666	4.8	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	6.7	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	9.2	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	4.8	Ref			Ref		
60-69	856	7.5	1.03	0.93-1.14	0.542	1.01	0.91-1.12	0.901	669	4.6	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	4.3	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	4.1	1.19	0.84-1.69	0.330	0.94	0.65-1.35	0.721
Sex																
Male	1670	7.5	Ref			Ref			1290	4.6	Ref			Ref		
Female	534	7.5	1.02	0.93-1.13	0.645	0.92	0.83-1.03	0.135	410	4.6	1.01	0.90-1.13	0.909	0.93	0.83-1.05	0.251
Performance status																
0 or 1	1220	8.3	Ref			Ref			902	4.8	Ref			Ref		
≥2	152	4.7	1.73	1.46-2.06	<0.001	1.61	1.36-1.92	<0.001	114	2.9	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	4.3	1.14	1.03-1.26	0.011	1.14	1.02-1.26	0.016
Comorbidities																
0	805	7.6	Ref			Ref			652	4.8	Ref			Ref		
1	621	7.0	0.94	0.84-1.04	0.233	0.94	0.84-1.05	0.272	475	4.1	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	4.7	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	6.2	0.77	0.55-1.09	0.140	0.74	0.52-1.05	0.088
Tumor location																
Esophagus	1014	7.8	Ref			Ref			772	4.6	Ref			Ref		
Gastro-esophageal junction or cardia	410	7.6	0.95	0.85-1.07	0.395	0.95	0.84-1.08	0.417	316	5.0	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	4.4	0.98	0.88-1.09	0.691	0.98	0.85-1.12	0.729
Histology																
Adenocarcinoma	2056	7.6	Ref			Ref			1580	3.7	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	4.7	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	3.1	1.27	0.77-2.07	0.347	1.03	0.73-2.00	0.452
Liver metastasis	1169	7.4	0.98	0.90-1.07	0.628	1.17	1.06-1.29	0.002	920	4.6	1.00	0.90-1.10	0.943	1.22	1.01-1.26	0.041
Distant lymph node metastasis	890	7.2	1.06	0.97-1.15	0.226	1.17	1.07-1.29	0.001	684	4.5	0.97	0.88-1.07	0.571	1.16	0.92-1.14	0.620
Peritoneal metastasis	524	6.9	1.22	1.11-1.35	<0.001	1.42	1.25-1.61	<0.001	385	4.1	1.11	0.99-1.24	0.079	1.31	1.05-1.41	0.009
Lung metastasis	430	7.0	1.09	0.98-1.21	0.122	1.16	1.04-1.29	0.010	327	4.1	1.14	1.01-1.29	0.032	1.13	1.02-1.32	0.021
Other metastases locations	499	6.6	1.25	1.13-1.39	<0.001	1.35	1.22-1.50	<0.001	379	4.1	1.23	1.09-1.38	<0.001		1.16-1.47	<0.001
Year of diagnosis			0.95	0.93-0.97	<0.001	0.97	0.95-0.99	0.009			1.00	0.97-1.02	0.724	1.02	0.99-1.05	0.230

Table 2b. Cox regression analyses for overall survival and time to failure of first-line treatment per systemic treatment regimen.

	Overall survival (n = 2204)		Univariable analyses			Multivariable analyses			Time to failure of first-line treatment (n = 1700)		Univariable analyses			Multivariable analyses		
	Patients No.	Median OS (months)	HR	95% CI	P value	HR	95% CI	P value	Patients No.	Median TTF (months)	HR	95% CI	P value	HR	95% CI	P value
Systemic treatment strategy																
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	0.80	0.52-1.24	0.313	20	4.2	1.05	0.67-1.65	0.833	0.86	0.52-1.41	0.541
G-doublet (GP, GC)	50	4.7	1.84	1.38-2.45	<0.001	1.67	1.24-2.26	<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	0.88	0.76-1.03	0.115	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	0.94	0.83-1.05	0.271	638	4.8	0.89	0.78-1.02	0.085	0.91	0.80-1.05	0.197
T-triplet (TCF, FOxT)	50	11.8	0.61	0.45-0.82	0.001	0.63	0.46-0.86	0.003	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	0.62	0.52-0.73	<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	0.66	0.43-1.02	0.059	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	1.01	0.91-1.12	0.842	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	1.00	0.89-1.13	0.991	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	0.99	0.71-1.38	0.933	33	4.1	1.19	0.84-1.69	0.330	0.92	0.64-1.32	0.646
Sex																
Male	1670	7.5	Ref			Ref			1290	4.6	Ref			Ref		
Female	534	7.5	1.02	0.93-1.13	0.645	0.91	0.82-1.02	0.093	410	4.6	1.01	0.90-1.13	0.909	0.93	0.83-1.05	0.270
Performance status																
0 or 1	1220	8.3	Ref			Ref			902	4.8	Ref			Ref		
≥2	152	4.7	1.73	1.46-2.06	<0.001	1.61	1.35-1.91	<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	1.17	1.06-1.28	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	0.94	0.84-1.04	0.227	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	0.96	0.86-1.07	0.442	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	0.68	0.53-0.88	0.003	35	6.2	0.77	0.55-1.09	0.140	0.74	0.52-1.05	0.091
Tumor location																
Esophagus	1014	7.8	Ref			Ref			772	4.6	Ref			Ref		
Gastro-esophageal junction or cardia	410	7.6	0.95	0.85-1.07	0.395	0.93	0.82-1.05	0.252	316	5.0	0.90	0.79-1.03	0.131	0.90	0.78-1.04	0.158
Stomach	780	6.9	1.08	0.98-1.18	0.132	1.00	0.89-1.13	0.995	612	4.4	0.98	0.88-1.09	0.691	0.94	0.82-1.08	0.410
Histology																
Adenocarcinoma	2056	7.6	Ref			Ref			1580	3.7	Ref			Ref		
Squamous cell carcinoma	128	6.5	1.24	1.03-1.48	0.021	1.24	1.02-1.51	0.032	104	4.7	1.40	1.15-1.71	0.001	1.35	1.08-1.69	0.009
Carcinoma NOS	20	4.6	1.54	0.99-2.40	0.054	1.59	0.99-2.53	0.053	16	3.1	1.27	0.77-2.07	0.347	1.30	0.76-2.20	0.337
Liver metastasis	1169	7.4	0.98	0.90-1.07	0.628	1.17	1.06-1.29	0.002	920	4.6	1.00	0.90-1.10	0.943	1.13	1.01-1.26	0.035
Distant lymph node metastasis	890	7.2	1.06	0.97-1.15	0.226	1.16	1.06-1.28	0.002	684	4.5	0.97	0.88-1.07	0.571	1.02	0.92-1.13	0.720
Peritoneal metastasis	524	6.9	1.22	1.11-1.35	<0.001	1.42	1.25-1.61	<0.001	385	4.1	1.11	0.99-1.24	0.079	1.23	1.06-1.42	0.006
Lung metastasis	430	7.0	1.09	0.98-1.21	0.122	1.15	1.03-1.29	0.015	327	4.1	1.14	1.01-1.29	0.032	1.16	1.02-1.31	0.024
Other metastases locations	499	6.6	1.25	1.13-1.39	<0.001	1.35	1.21-1.50	<0.001	379	4.1	1.23	1.09-1.38	<0.001	1.30	1.15-1.47	<0.001
Year of diagnosis			0.95	0.93-0.97	<0.001	0.98	0.96-1.00	0.058			1.00	0.97-1.02	0.724	1.02	0.99-1.05	0.136

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 dived 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.

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%).

Table 3. Grade 3–5 toxicity in patients treated with monotherapy, doublet chemotherapy and triplet chemotherapy and patients who received a trastuzumab-containing regimen between 2010 and 2014.

Grade 3-5 toxicity	All patients (n = 1221)	Monotherapy (n = 164)	Doublet (n = 455)	Triplet (n =511)	Trastuzumab-containing regimens (n = 71)	P value[1]
Patients without adverse events	801 (65.6%)	115 (70.1%)	327 (71.9%)	313 (61.3%)	36 (50.7%)	<0.001
Patients with adverse events	332 (27.2%)	28 (17.1%)	97 (21.3%)	166 (32.5%)	32 (45.1%)	
Grade 3-4	314	26	92	159	29	
Grade 5	18	2	5	7	3	
Unknown	88 (7.2%)	21 (12.8%)	31 (6.8%)	32 (6.3%)	3 (4.2%)	

[1]Chi-square test: adverse event rate monotherapy vs. doublet vs. triplet vs. trastuzumab -containing regimens. Toxicity of patients who received targeted (nontrastuzumab) therapy (n = 20) was not displayed separately.

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 treatment combinations, since second-line treatment options are often registered under the assumption that certain compounds have been administered in the first line. The use of an unusual treatment regimen may limit opportunities for second-line treatment and subsequent OS benefit. Analysis of beyond first-line treatments is currently ongoing.

Current national and international guidelines recommend a fluoropyrimidine and platinum doublet in metastatic esophagogastric cancer patients, with the addition of an anthracycline or taxane in selected patients.[8,10,12,13,22] Until 2016, Dutch esophageal and gastric cancer guidelines advised systemic therapy only in patients with good performance status, without specifying the type of regimen.[23,24] This could have contributed to the heterogeneity in administered systemic therapy regimens. Another explanation for the variation could be that palliative treatment of esophagogastric cancer is not centralized in specialized hospitals in the Netherlands, in contrast to curative treatment.[25,26]

Since the added value of the addition of an anthracycline to a platinum–fluoropyrimidine doublet remains uncertain,[15,27-29] doublet chemotherapy tends to be the favored choice of first-line palliative treatment because of its better tolerance.[4-6,14] In our study, we found less serious (grade 3–5) toxicity in patients receiving doublets (21%) compared to triplets (33%) as well as similar OS and TTF rates, which supports the shift toward doublet therapy as preferred strategy in these patients.

Taxane triplets showed superior OS and TTF compared to fluoropyrimidine doublets. From previous randomized studies, it is known that this increased effectiveness comes at the cost of more toxicity.[6] However, because of the limited number of patients who received a taxane triplet, definite conclusions from this real-world population cannot be drawn. In the curative setting, docetaxel, oxaliplatin and 5-FU/leucovorin (FLOT) showed longer survival in gastric cancer when used as a perioperative regimen as compared to anthracycline triplets.[30] The use of FLOT followed by resection with curative intent in patients with limited metastatic disease is currently being explored in the AIO-FLOT5 trial.[31] However, in the palliative setting, it remains inconclusive whether first-line taxane triplets or fluoropyrimidine doublets followed by second-line taxanes should be preferred in view of survival benefit and toxicity.[6,11] Monotherapy showed a significantly worse OS compared to doublets, which is in line with recently published reviews.[4-6] In addition, grade 3–5 toxicity rate was only marginally lower compared to doublets (18% vs. 21%, respectively). This could partly be caused by selection bias, since patients treated with monotherapy are more likely to have a poorer performance status.

However, reported HRs were adjusted for both performance status and number of comorbidities. The use of no systemic treatment instead of monotherapy should therefore be considered in patients who potentially do not tolerate doublet therapy, since the median OS is comparable to that of patients who receive best supportive care only.[4,5]

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.[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.[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.[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 supraclavicular lymph nodes, as well as patients who had long-term radiotherapy alongside systemic treatment, since radiotherapy could affect survival rates.[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.[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 undesirable since it may negatively affect outcomes in these patients.

SUPPLEMENTARY MATERIAL

Baseline characteristics of all and selected metastatic esophagogastric cancer patients treated with systemic therapy and diagnosed between 2010-2014.

Characteristics	All patients 2010-2014 (n = 2735)	Subset patients 2010-2014 (n = 1386)	P value
Male, No. (%)	2051 (75.0%)	1040 (75.0%)	0.975[a]
Age, years, median (IQR)	64 (56, 70)	63 (55, 70)	0.164[b]
Tumor location, No. (%)			0.397[a]
Esophagus	1309 (47.9%)	668 (48.2%)	
Gastroesophageal junction or cardia	465 (17.0%)	255 (18.4%)	
Stomach	961 (35.1%)	463 (33.4%)	
Histology, No. (%)			0.419[a]
Adenocarcinoma	2422 (88.6%)	1242 (89.6%)	
Squamous cell carcinoma	288 (10.5%)	129 (9.3%)	
Carcinoma NOS	25 (0.9%)	15 (1.1%)	
Type of hospital of treatment, No. (%)			0.044[a]
Academic	377 (13.8%)	160 (11.5%)	
Non-academic	2358 (68.2%)	1226 (88.5%)	

Baseline characteristics of all synchronous metastatic esophagogastric cancer patients treated with systemic therapy and diagnosed between 2010-2014, and the subset of patients treated in 43 hospitals selected as a representative sample of all hospitals in terms of annual number of patients, type of hospital, and location in the Netherlands. [a]= Chi square test, [b]= Mann-Whitney U test.

List of assumptions regarding definitions of first-line systemic treatment and time to failure of first-line treatment.

Assumptions regarding systemic treatment:
- If trastuzumab was added more than three days after the first-line systemic regimen had started, trastuzumab was considered to be part of the first-line treatment regimen, because there could have been a delay in the determination of HER2.
- If capecitabine was started more than three days before or after the other agents, in the absence of any other fluoropyrimidine, capecitabine was considered to belong to the regimen of the other agent(s) as well, because there is a possibility the prescription date instead of the actual start date was registered.
- If only the agents epirubicin and oxaliplatin were registered as a regimen, we added capecitabine because we found that some data managers interpreted EOX as epirubicin and oxaliplatin only.
- Second-line treatment was defined as the first systemic treatment after first-line treatment in which an agent of a drug group was not applied in first-line treatment.

Assumptions regarding time to failure of first-line treatment:
- Time to failure of first-line treatment was calculated in patients with complete follow-up, i.e., patients diagnosed between 2010 and 2015.
- Time to failure of first-line treatment was considered as a proxy for progression-free survival.
- Time to failure of first-line treatment was calculated until the first progression date that resulted in termination of first line or end of follow-up.
- If there was a progression date registered after which first-line treatment continued, we regarded this as continuation of first-line treatment.
- If there was no progression detected and the patient died within 90 days after the last hospital visit, the date of death was considered as an event for analyses on TTF as well.
- If a progression date was not registered, but the reason for discontinuation was progressive disease, the date of discontinuation of the regimen was considered the moment of failure of first-line treatment.

Supplementary Table 3. Most frequently administered systemic therapy regimens.

Combination regimen	All patients (n = 2204) No. (%)
Capecitabine and oxaliplatin (CapOx)	468 (21.2%)
Epirubicin, oxaliplatin, and capecitabine (EOX)	448 (20.3%)
Carboplatin and paclitaxel	293 (13.3%)
Epirubicin, cisplatin, and capecitabine (ECC)	214 (9.7%)
Capecitabine monotherapy	203 (9.2%)
5-FU, leucovorin, and oxaliplatin (FOLFOX)	138 (6.3%)
Capecitabine, oxaliplatin, and trastuzumab	73 (3.3%)
Capecitabine, cisplatin, and trastuzumab	65 (3.0%)
Other	302 (13.7%)

Frequency of systemic therapy regimens administered in at least 50 patients.

Supplementary Figure 1. Word cloud of all 45 systemic therapy regimens that were administered.

Font size of the word corresponds to the number of patients who received the regimen.

Supplementary Figure 2. Subdivision of systemic therapy regimens.
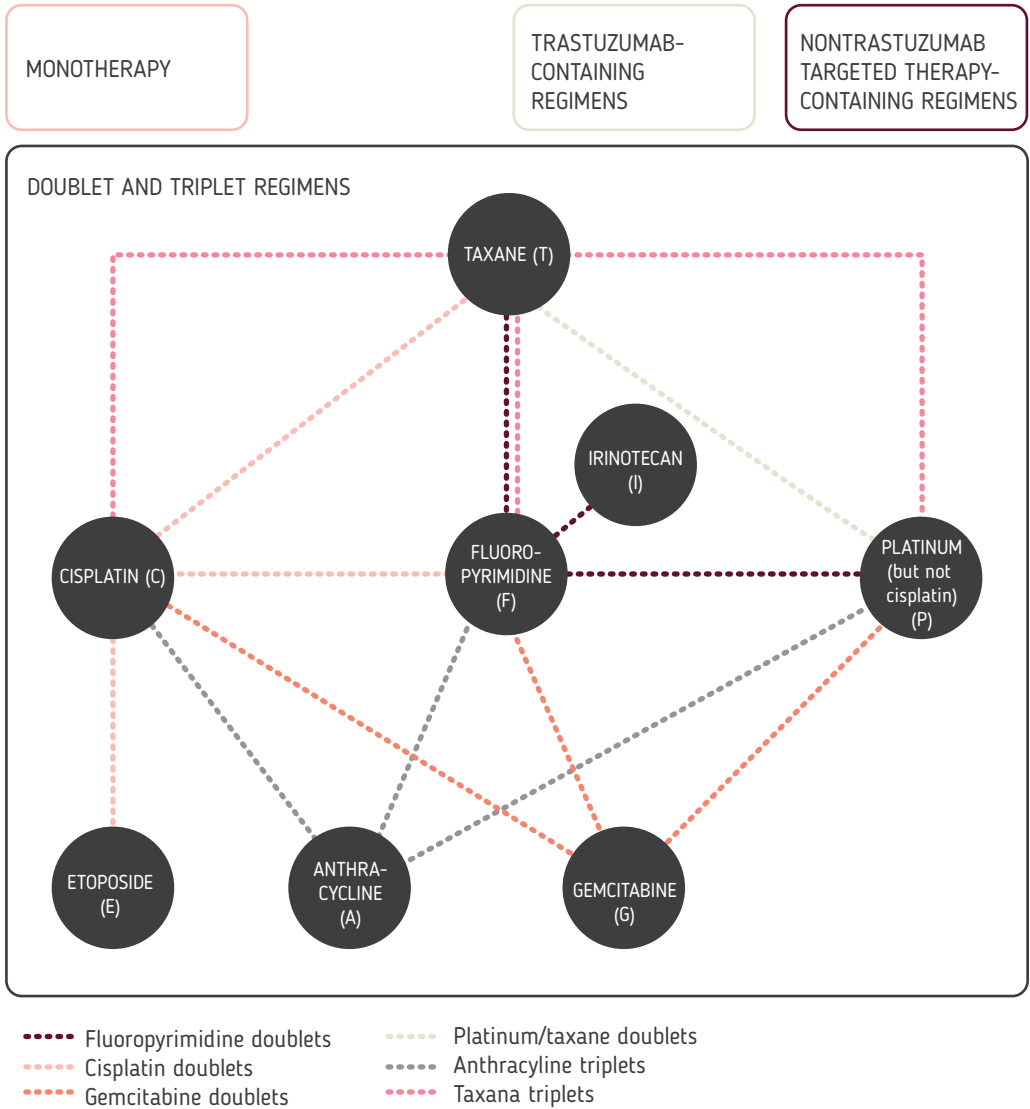
Systemic treatment regimens were dived as follows: monotherapy; fluoropyrimidine doublets (with a platinum [but not cisplatin], taxane, or irinotecan); cisplatin doublets (with a fluoropyrimidine, taxane, or etoposide); gemcitabine doublets (with a platinum/cisplatin); platinum (but not cisplatin)/taxane 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. The colors of the lines correspond with the different doublet regimens, e.g., fluoropyrimidine doublets consist of a fluoropyrimidine with either a platinum (but not cisplatin) or taxane, as shown by the blue interconnecting lines.

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03

Increased assessment of HER2 in metastatic gastroesophageal cancer patients: A nationwide population-based cohort study

Gastric Cancer, 2020.

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ABSTRACT

Background: Addition of trastuzumab to first-line palliative chemotherapy in gastroesophageal cancer patients with HER2 overexpression has shown to improve survival. Real-world data on HER2 assessment and administration of trastuzumab are lacking. The aim of this study was to assess HER2 testing, trastuzumab administration, and overall survival (OS) in a nationwide cohort of metastatic gastroesophageal cancer patients.

Methods: Data of patients with synchronous metastatic gastroesophageal adenocarcinoma diagnosed in 2010–2016 that received palliative systemic treatment (n = 2846) were collected from the Netherlands Cancer Registry and Dutch Pathology Registry. The ToGA trial criteria were used to determine HER2 overexpression. Proportions of HER2 tested patients were analyzed between hospital volume categories using Chi-square tests, and over time using trend analysis. OS was tested using the Kaplan Meier method with log rank test.

Results: HER2 assessment increased annually, from 18% in 2010 to 88% in 2016 (P < 0.01). Median OS increased from 6.9 (2010–2013) to 7.9 months (2014–2016; P < 0.05). Between the hospitals, the proportion of tested patients varied between 29–100%, and was higher in high-volume hospitals (P < 0.01). Overall, 77% of the HER2 positive patients received trastuzumab. Median OS was higher in patients with positive (8.8 months) and negative (7.4 months) HER2 status, compared to non-tested patients (5.6 months; P < 0.05).

Conclusion: Increased determination of HER2 and administration of trastuzumab have changed daily practice management of metastatic gastroesophageal cancer patients receiving palliative systemic therapy, and possibly contributed to their improved survival. Further increase in awareness of HER2 testing and trastuzumab administration may improve quality of care and patient outcomes.

INTRODUCTION

Palliation by systemic therapy may improve quality as well as quantity of life in patients with metastatic gastroesophageal cancer.[1-5] In clinical trials, the addition of the targeted agent trastuzumab to cytotoxic therapy in metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma patients with overexpression of the human epidermal growth factor receptor 2 (HER2) has resulted in a median overall survival (OS) benefit of 2.8 months,[6] and a positive impact on quality of life.[7] Trastuzumab has therefore become standard of care in HER2 positive tumors, and HER2 testing is strongly recommended in all patients with metastatic gastroesophageal adenocarcinoma eligible for HER2 targeted treatment.[8-13]

HER2 testing and the administration of trastuzumab in gastroesophageal cancer might be underexposed within individual centers, because gastroesophageal cancer has a relatively low incidence in Western countries, and only 15–25% of the adenocarcinomas show HER2 overexpression.[14-16] In recent years, several studies have been published showing that gastroesophageal cancer patients treated in high-volume hospitals have better outcomes.[17-25] Patient volume can therefore be regarded as a proxy for quality of care, possibly due to multimodal expertise and a well-developed organization of care in high-volume hospitals.[22, 26] Moreover, although HER2 testing is routinely performed in breast cancer, HER2 expression in gastroesophageal cancer is more heterogenous as a reflection of the distinct biology of these

tumors, and as a result, the interpretation of HER2 immunohistochemistry (IHC) patterns is more complicated.[6,27,28]

Currently, data on HER2 testing, and the administration of trastuzumab in clinical practice are lacking. In this real-world study covering a nationwide cohort of synchronous metastatic gastroesophageal adenocarcinoma patients treated with systemic therapy, our aim was to explore the rate of HER2 testing, the administration of trastuzumab, interhospital variation, and survival in these patients.

METHODS

Data collection

Patients with synchronous metastatic gastroesophageal adenocarcinoma (classified as C15 and C16 according to the International Classification of Diseases for Oncology[29]) treated with systemic therapy, and therefore eligible for HER2 targeted therapy, were selected from the nationwide Netherlands Cancer Registry (NCR). All patients diagnosed in 2010–2015 were identified, and a subset of patients diagnosed in 2016 because not all patients were registered in the NCR at the time of selection. Pathology reports of all confirmed cancer diagnoses in the Netherlands are archived in the nationwide network and registry of histo- and cytopathology (PALGA).[30] Every pathology laboratory in the Netherlands is part of the PALGA network, and excerpts of all pathological reports are automatically transferred from the laboratories to the central databank of PALGA. Also, modifications in the excerpts or results of additional pathological tests, e.g., HER2 testing, are added to the central database automatically. Of included patients, information of HER2 testing was extracted from PALGA reports concerning histologic material with gastroesophageal origin.

Data on patient and tumor characteristics were extracted from the hospital's medical records by trained data managers, and information on vital status from the Dutch population register (updated until 1 February 2019). OS was assessed from start of treatment until death or end of follow-up. Time to failure (TTF) was calculated from the start of treatment to the first progression that resulted in termination of first-line treatment, end of follow-up, or death within 90 days after the last hospital visit in case no progression was registered. Details on systemic treatment regimen and TTF were available in patients who were diagnosed in 2015 (n = 445) or in a subset of Dutch hospitals between 2010 and 2014 (n = 1107), due to logistic reasons. The subset of hospitals was selected as a representative sample of all Dutch hospitals in terms of patient volume, and hospital type and location, as described earlier.[31]

Patient selection

The NCR provided 3164 patients diagnosed with gastroesophageal adenocarcinoma and synchronous metastases diagnosed between 2010 and 2016 and treated with systemic therapy. The linkage of the NCR and the PALGA database identified 3139 patients, with a total of 7545 available pathology excerpts (Fig. 1).

Figure 1. Flow chart of patient selection.

Nationwide network and registry of histo– and cytopathology in the Netherlands (PALGA) *7.545 pathology reports**	**Netherlands Cancer Reigstry** Patients with synchronous metastatic esophagogastric adenocarcinoma treated with systemic theraoy, diagnosed between 2010 abd 2016 N=3.164

Excluded:
– Patients of whom no pathology reports were found (N=25)

Patients with available pathology reports
N=3.139

Included patients
N=2.846

Excluded (N=293):
– Patients with oesophageal, GEJ or cardia carcinoma and non-regional cervical lymph node metastases only (N=108)
– Patients treated with chemoradiotherapy (N=143)
– Patients that received chemotherapy abroad (N=27)
– Patients without follow-up data on vital satus (N=1)
– Patients that participated in a trial and possibly received a placebo (N=9)
– Patients that started with systemic therapy and in whom the primary tumor was then considered to be other than esophagogastric (N=6)

Patients with an esophageal or gastroesophageal junction or cardia carcinoma with solely non-regional head and neck lymph node metastases were excluded, because they could have received definitive chemoradiotherapy with potential curative intent in case of involvement of only the supraclavicular lymph nodes. *Of the majority of the patients (n = 1990), more than one report was included. GEJ gastroesophageal junction.

HER2 status

HER2 testing is usually initiated by the treating clinician in The Netherlands. A validated testing algorithm for HER2, based on the results of the ToGA trial,[28] is suggested in international and national guidelines.[8, 9, 10, 32, 33, 34] The Dutch gastric cancer guideline recommends the use of validated HER2 antibodies for IHC and validated ISH tests, and a scoring system for the interpretation of these tests as described by Rüschoff et al.[27, 34] A gastroesophageal tumor can be considered HER2 positive when the result of the IHC staining pattern is 3+ , and negative when it is 0 or 1+ . In case of a equivocal IHC result (2+), additional testing using in situ hybridization (ISH) is indicated. The definition of HER2 ISH positivity is a HER2:chromosome 17 ratio of ≥ 2.[27] Genomic testing techniques such as multiplex ligation-dependent probe amplification (MLPA) are used instead of ISH as well.[12]

HER2 status was regarded as unknown if type and/or results of testing were not reported, because we could not verify if the HER2 criteria of the ToGA trial were used. In case of an equivocal IHC with an unknown ISH or MLPA result, HER2 status was also assumed unknown. If HER2 was tested multiple times, the last test result that was performed prior to or within 31 days after start of first-line systemic treatment was considered the definitive result, because this was expected to be decisive for the choice of systemic treatment. If HER2 testing was not mentioned in the reports, we assumed that it had not been performed.

Hospital volume

Per hospital the volume of all gastroesophageal cancer patients (both adenocarcinoma and squamous cell carcinoma) that received systemic therapy in 2015–2016, regardless of tumor stage and the intent of treatment, was calculated. With the aim to reflect current practice, the volume of the two most recent years, was used. Hospitals were categorized into quartiles according to these volumes to compare the proportion of HER2 tested patients.

Statistical analyses

Baseline characteristics and details on HER2 testing were displayed with counts and percentages, or medians and interquartile ranges (IQRs). Differences in the proportions of HER2 tested patients between the hospital volume categories were analyzed using Chi-square tests, and over time using the Cochran-Armitage test for trend. Factors possibly associated with HER2 testing were identified using logistic regression. Differences in survival were tested univariably with the log rank test using Kaplan Meier curves and through multivariable proportional hazards regression analyzes with adjustment for relevant patient and tumor characteristics. For survival analyzes, patients in whom HER2 was tested > 31 days after first-line systemic treatment were excluded to reduce immortal time bias. P values below 0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

RESULTS

Patient characteristics

The majority of all 2846 included patients was male (76%), and median age was 64 (IQR, 56–71) years (Table 1). The primary tumor location was the esophagus in 41%, the non-cardia stomach in 40% and GEJ/cardia in 19%. More than half (54%) of the patients had an intestinal-type adenocarcinoma, followed by 27% with a diffuse, and 6% with an indeterminate type, based on the Lauren's criteria [35]. In 13%, histological type was not specified. The majority of the tumors had a poor differentiation (53%).

HER2 testing

HER2 status was determined in 54% of the patients (n = 1524; Table 1). The proportion of tested patients increased over time (P < 0.001), from 18% in 2010, to 88% in 2016 (Fig. 2). This trend was seen in esophageal (11–89%), GEJ (24–93%) and gastric tumors (22–83%; all P < 0.001). HER2 tested patients were significantly younger, more often female, and had more frequently GEJ/cardia or stomach compared to esophageal tumors, and diffuse type adenocarcinomas than non-tested patients (Table 1).

　　　　HER2 was positive in 19% of 1524 tested patients, and negative in 68% (Supplementary Table 1). In 204 (13%) patients, HER2 status was unknown because detailed HER2 test results were not described. The number of HER2 positive tumors increased from 14% in 2010–2012 to 20% in 2015–2016 (Fig. 2). Overall, HER2 positivity was found in 28% of esophageal, 16% of GEJ/cardia, and 12% of gastric adenocarcinomas (P < 0.001).

Table 1. Baseline characteristics of included patients (n = 2846).

	All patients (n = 2846) No. (%)	Non-tested (n = 1322) No. (%)	HER2 tested (n = 1524) No. (%)	P value
Male	2152 (75.6%)	1023 (77.4%)	1129 (74.1%)	0.041[a]
Age (years) - median (IQR)	64.0 (56.0, 71.0)	65.0 (58.0, 72.0)	63.0 (55.0, 69.0)	<0.001[b]
<50	963 (33.8%)	383 (29.0%)	580 (38.1%)	<0.001[a]
50-64	1079 (37.9%)	510 (38.6%)	569 (37.3%)	
65-79	735 (25.8%)	386 (29.2%)	349 (22.9%)	
≥80	69 (2.4%)	43 (3.3%)	26 (1.7%)	
Comorbidities				<0.001[a]
0	739 (26.0%)	285 (21.6%)	454 (29.8%)	
1	555 (19.5%)	245 (18.5%)	310 (20.3%)	
≥2	629 (22.1%)	278 (21.0%)	351 (23.0%)	
Unknown	923 (32.4%)	514 (38.9%)	409 (26.8%)	
Tumor location				<0.001[a]
Esophageal	1159 (40.7%)	589 (44.6%)	570 (37.4%)	
Gastroesophageal junction/cardia	545 (19.1%)	219 (16.6%)	326 (21.4%)	
Stomach (non-cardia)	1142 (40.1%)	514 (38.9%)	628 (41.2%)	
Tumor histology				0.012[a]
Adenocarcinoma NOS	362 (12.7%)	160 (12.1%)	202 (13.3%)	
Intestinal type adenocarcinoma	1540 (54.1%)	744 (56.3%)	796 (52.2%)	
Diffuse type adenocarcinoma	772 (27.1%)	327 (24.7%)	445 (29.2%)	
Indeterminate type adenocarcinoma	172 (6.0%)	91 (6.9%)	81 (5.3%)	
Tumor differentiation				<0.001[a]
Well differentiated	37 (1.3%)	15 (1.1%)	22 (1.4%)	
Moderately differentiated	495 (17.4%)	221 (16.7%)	274 (18.0%)	
Poorly differentiated	1496 (52.6%)	648 (49.0%)	848 (55.6%)	
Unknown	818 (28.7%)	438 (33.1%)	380 (24.9%)	
Metastatic sites				<0.001[a]
1	1571 (55.2%)	757 (57.3%)	814 (53.4%)	
≥2	1275 (44.8%)	565 (42.7%)	710 (46.6%)	
Year of diagnosis				<0.001[a]
2010	414 (14.5%)	341 (25.8%)	73 (4.8%)	
2011	386 (13.6%)	265 (20.0%)	121 (7.9%)	
2012	423 (14.9%)	240 (18.2%)	183 (12.0%)	
2013	410 (14.4%)	172 (13.0%)	238 (15.6%)	
2014	451 (15.8%)	156 (11.8%)	295 (19.4%)	
2015	445 (15.6%)	109 (8.2%)	336 (22.0%)	
2016	317 (11.1%)	39 (3.0%)	278 (18.2%)	

Tumor histology and differentiation are based on the primary tumor. Diffuse type tumors were classified as poorly differentiated. [a]Chi square test, [b]Mann-Whitney U test.
IQR, interquartile range; NOS, not otherwise specified.

HER2 testing methods

Supplementary Table 2 displays which diagnostic methods were used for the HER2 assessment, and all test results of all performed tests. IHC, ISH and MLPA were used in 88%, 49%, and 3% of the 1524 tested patients, respectively, while testing methods were unknown in 13%. Of the patients in whom IHC was performed (n = 1328), scores of 0, 1+ , 2+ , 3+ were found in 38%, 23%, 24%, and 14%, respectively.

HER2 testing was performed more than once in 225 patients: in 194 patients, it was

Figure 2. HER2 testing and overexpression stratified for primary tumor location.
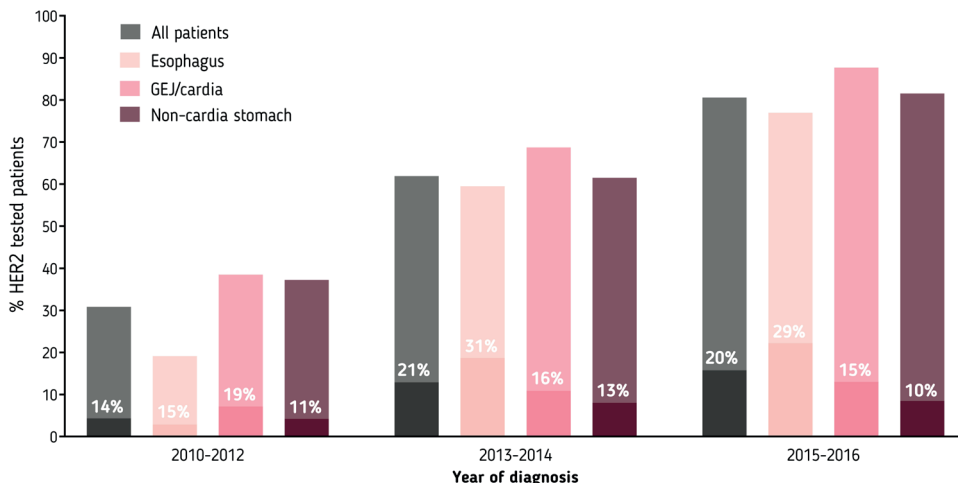
Proportion of HER2 tested patients over time. The percentages within the bars reflect the proportion of patients of whom the tumor showed HER2 overexpression. GEJ gastroesophageal junction.

Table 2. HER2 testing by hospital volume of systemic treatment in 2015–2016.

Hospital volume	Hospitals No.	Patients No.	HER2 tested patients No. (%)	P value
<13 patients	17	72	49 (68.1%)	<0.001
13-31 patients	19	157	119 (75.8%)	
32-76 patients	19	231	179 (77.5%)	
>76 patients	19	302	267 (88.4%)	

Hospital volume-based differences in proportion of HER2-tested patients with metastatic gastroesophageal cancer diagnosed in 2015 and 2016. Hospitals are categorized in quartiles based on the hospital volume of all gastroesophageal cancer patients treated with systemic therapy in 2015 and 2016.

tested twice, in 30 patients three times, and in one patient four times. In 87% of the tested patients, HER2 was determined on solely the primary tumor, followed by metastasis only in 7%, and on both the primary tumor and metastasis in 6% of the patients. Testing methods were known in 1537/1764 tests, and in 398/1537 (26%) of these tests, ISH was used despite an IHC test result that would not necessarily require further testing (0, 1+ or 3+ ; Supplementary Table 2).

Hospital variation
The subdivision of hospitals resulted in volume categories of < 13, 13−31, 32−76 and > 76 patients treated with systemic therapy in 2015 and 2016. The proportion of HER2 tested patients differed between these volumes in patients diagnosed in 2015−2016 (P < 0.001), with the highest proportions of tested patients being found in the high-volume centers (88%; Table 2). Interhospital variation in HER2 tested was 29−100% (Fig. 3).

Figure 3. Hospital variation in HER2 testing in The Netherlands.
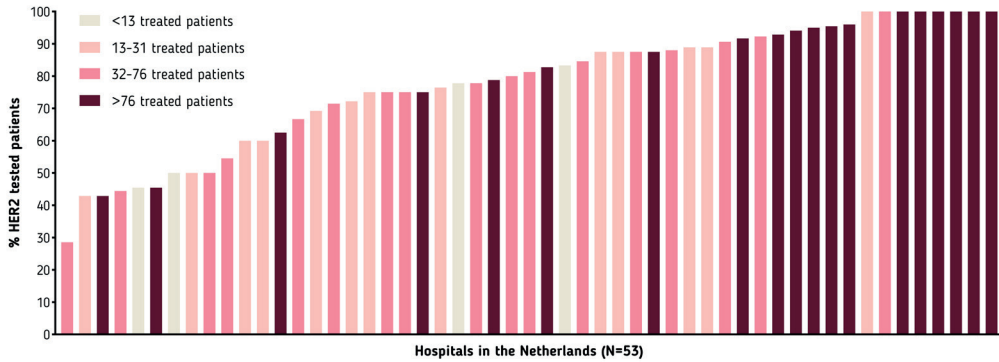
Proportion of patients treated with systemic therapy for whom HER2 was assessed in 53 Dutch hospitals in 2015 and 2016. Each bar represents a hospital. Hospitals that treated less than six metastatic gastroesophageal adenocarcinoma patients with palliative systemic therapy in 2015 and 2016 were not displayed (n = 24).

Table 3. Multivariable logistic regression analyses for chance of HER2 assessment for patients with metastatic gastroesophageal cancer treated with systemic therapy and diagnosed in 2015 and 2016 (n = 762).

	Patients No.	Univariable			Multivariable		
		OR	95% CI OR	P value	OR	95% CI OR	P value
Sex							
Female	166	Ref			Ref		
Male	596	0.41	0.24-0.69	0.001	0.43	0.24-0.77	0.005
Age (years)							
<50	235	Ref			Ref		
50-64	292	0.67	0.42-1.06	0.087	0.84	0.51-1.40	0.510
65-79	216	0.58	0.36-0.94	0.026	0.65	0.38-1.11	0.113
≥80	19	0.37	0.13-1.03	0.057	0.37	0.12-1.14	0.084
Performance status							
0 or 1	490	Ref			Ref		
≥2	49	0.78	0.42-1.48	0.453	0.99	0.50-1.97	0.981
Unknown	223	0.66	0.45-0.98	0.040	0.73	0.47-1.12	0.144
Number of comorbidities							
0	236	Ref			Ref		
1	208	0.61	0.37-1.00	0.048	0.62	0.36-1.06	0.081
≥2	256	0.54	0.34-0.87	0.011	0.66	0.39-1.11	0.119
Unknown	62	0.68	0.33-1.41	0.295	0.50	0.23-1.10	0.087
Primary tumor location							
Esophagus	356	0.76	0.51-1.13	0.170	0.80	0.51-1.24	0.315
Gastroesophageal junction/cardia	146	1.61	0.90-2.89	0.110	2.09	1.12-3.90	0.020
Stomach	260	Ref			Ref		
Year of diagnosis							
2015	445	Ref			Ref		
2016	317	2.31	1.55-.3.45	<0.001	2.54	1.67-3.88	<0.001
Hospital volume*							
<13 patients	72	0.28	0.15-0.51	<0.001	0.26	0.14-0.51	<0.001
13-31 patients	157	0.41	0.25-0.68	<0.001	0.37	0.22-0.64	<0.001
32-76 patients	231	0.45	0.28-0.72	<0.001	0.46	0.28-0.75	0.002
>76 patients	302	Ref			Ref		
Deceased within 90 days after start systemic therapy	166	0.56	0.38-0.84	0.005	0.61	0.38-0.95	0.029

Multivariable logistic regression analyses for HER2 testing in patients diagnosed in 2015 and 2016. OR, odds ratio, CI, confidence interval, GEJ, gastroesophageal junction.

Factors contributing to probability of HER2 testing

Male sex, all but the highest hospital volumes, and death within 90 days after start of treatment were independently associated with lower probability of being tested for HER2 in patients diagnosed in 2015–2016, and GEJ/cardia tumors with a higher chance of testing to non-cardia gastric tumors (Table 3).

Survival

OS was 7.3 (IQR, 3.5, 12.6) months in all 2846 patients, and increased from 6.9 (IQR, 3.5, 12.0) months in patients diagnosed in 2010–2013 (n = 1633) to 7.9 (IQR, 3.6, 13.6) months in 2014–2016 (n = 1213). OS was 6.2 (IQR, 2.9, 10.7) months in non-tested patients (n = 1322) versus 8.3 (IQR, 4.2, 14.4) months in HER2 tested patients (n = 1524).

Figure 4. Kaplan Meier curve for overall survival in HER2 tested and non-tested patients.

Number at risk								
HER2 positive	256	171	95	66	46	30	16	11
HER2 unknown	186	111	49	28	18	13	8	5
HER2 negative	913	538	247	135	77	44	26	15
HER2 not tested	1322	688	281	134	76	52	41	32
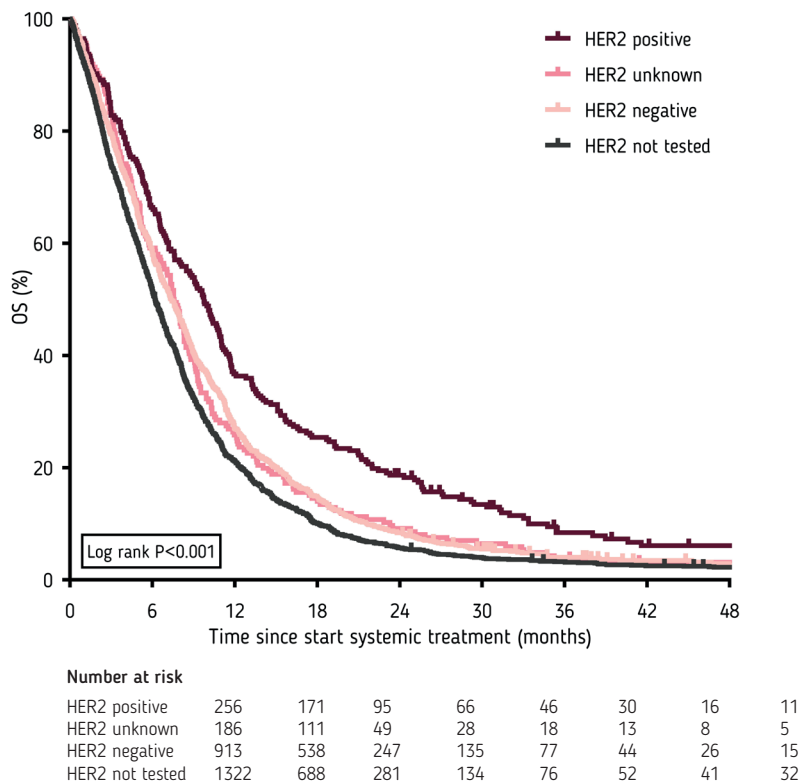
Overall survival in patients in whom HER2 overexpression was not determined (N = 1322), and in patients in whom HER2 was determined before or within a month after start of systemic treatment (N = 1355) categorized in negative (N = 913), positive (N = 256) and unknown (patients in whom test results were not specified; N = 186) HER2 status. Survival of patients in whom HER2 was determined after 31 days of start of systemic treatment (N = 169) is not displayed to prevent an immortal time bias. OS overall survival.

In 1355 patients that were tested within 1 month after start of systemic treatment, median OS in patients with unknown, negative and positive HER2 status was 7.6, 7.4, and 9.8 months, respectively (Fig. 4). OS was significantly higher in HER2 positive and negative patients, compared to non-tested patients (HER2 negative: adjusted hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.65–0.99; HER2 positive: HR 0.65, 95% CI 0.50–0.86; Table 4). Diffuse type tumors, ≥ 2 metastatic locations, and performance status ≥ 2 were independently associated with worse survival. Hospital volume categorized into 4 quartiles was not independently associated with OS, while HRs in the two lowest quartiles were 1.26 and 1.19, respectively. When hospital volumes were subdivided in low (below median) versus high (above median), patients treated in low-volume hospitals had a significantly worse survival (HR 1.19, 95% CI 1.00–1.41; P = 0.044).

Treatment with trastuzumab

Details of systemic treatment and TTF were known in 1552 patients diagnosed in 2010–2015. HER2 was determined in 53% of these patients, of whom 17% were HER2 positive and 69% negative, and in 14% HER2 was unknown. Of the 141 HER2 positive patients, 77% (n = 108) received a trastuzumab-containing regimen, which increased from 60% (n = 35) in 2010–2013 to 88% (n = 73) in 2014–2015. OS increased in this period from 6.9 (IQR, 3.2–11.7) to 7.2 (IQR, 3.4–12.8) months (P = 0.079). Ninety-seven of trastuzumab-treated patients received it in first-line, and 11 patients beyond first-line treatment. In trastuzumab-containing regimens, chemotherapy backbones were doublets in 59%, triplets in 20%, and monotherapy in 11%. Most frequently used backbones were capecitabine/5-FU with oxaliplatin (n = 33) or with cisplatin (n = 31).

In HER2 positive patients, median TTF of first-line trastuzumab-containing therapy was 6.5 (IQR, 3.0, 11.7) and OS 11.6 (IQR, 5.3, 21.6) months, while TTF of nontrastuzumab-containing first-line treatment was 5.4 (IQR, 3.1, 7.4) and OS 6.6 (IQR, 5.1, 11.0) months (n = 33). In HER2 negative patients, median TTF of first-line treatment was 5.2 (IQR, 2.2, 9.0) and OS 7.5 (IQR, 3.9, 13.1) months.

DISCUSSION

Adequate HER2 testing is crucial for optimal decision-making on systemic treatment in metastatic gastroesophageal adenocarcinoma patients. In international guidelines it is therefore recommended to perform HER2 testing in all of these patients.[8, 9, 10, 33] In this nationwide cohort of 2846 patients with synchronous metastases and treated with palliative systemic therapy, HER2 testing increased over the study period from one in five to almost all patients. We found a large variety in the percentage of HER2 tested patients between the hospitals, and the volume of treated patients in a hospital independently associated with the probability of being tested for HER2.

Table 4. Multivariable Cox regression analyses overall survival in patients diagnosed between 2015 and 2016 (n = 735)[a].

	Patients No.	Median OS (months)	Univariable HR	95% CI HR	P value	Multivariable HR	95% CI HR	P value
Sex								
Female	161	6.1	Ref			Ref		
Male	574	7.6	0.94	0.79-1.13	0.520	0.98	0.80-1.19	0.804
Age (years)								
<50	228	7.6	Ref			Ref		
50-64	282	7.3	1.02	0.85-1.22	0.833	1.05	0.87-1.27	0.641
65-79	207	6.5	1.00	0.82-1.22	0.988	1.04	0.84-1.28	0.754
≥80	18	5.8	1.33	0.82-2.16	0.245	1.20	0.72-1.99	0.477
Performance status								
0 or 1	459	7.8	Ref			Ref		
≥2	65	3.4	1.78	1.37-2.32	<0.001	1.75	1.34-2.30	<0.001
Unknown	211	6.0	1.20	1.02-1.42	0.033	1.19	1.00-1.42	0.047
Number of comorbidities								
0	225	7.6	Ref			Ref		
1	205	7.2	0.93	0.76-1.13	0.474	0.91	0.74-1.11	0.351
≥2	246	6.2	1.18	0.98-1.42	0.088	1.15	0.94-1.41	0.165
Unknown	59	8.9	0.89	0.66-1.19	0.427	0.83	0.61-1.13	0.231
Primary tumor location								
Esophagus	344	7.3	0.94	0.79-1.11	0.431	1.05	0.85-1.29	0.659
Gastroesophageal junction/cardia	143	7.8	0.85	0.69-1.05	0.138	0.96	0.76-1.21	0.703
Stomach	248	6.5	Ref			Ref		
Tumor histology								
Adenocarcinoma NOS	178	7.3	Ref			Ref		
Intestinal type adenocarcinoma	350	8.0	1.00	0.83-1.21	0.992	0.95	0.77-1.19	0.671
Diffuse type adenocarcinoma	169	6.0	1.31	1.05-1.64	0.015	1.33	1.01-1.74	0.040
Indeterminate type adenocarcinoma	38	5.9	1.36	0.95-1.94	0.096	1.26	0.86-1.84	0.243
Number of metastatic locations								
1	389	7.7	Ref			Ref		
≥2	346	6.6	1.22	1.05-1.42	0.010	1.25	1.07-1.46	0.005
Year of diagnosis								
2015	429	6.7	Ref			Ref		
2016	306	7.7	0.88	0.76-1.03	0.107	0.95	0.79-1.14	0.580
Hospital volume*								
<13 patients	70	5.2	1.28	0.97-1.67	0.081	1.26	0.95-1.67	0.104
13-31 patients	151	6.4	1.26	1.03-1.54	0.026	1.19	0.96-1.47	0.135
32-76 patients	220	7.0	1.11	0.93-1.33	0.247	1.04	0.86-1.25	0.669
>76 patients	294	7.9	Ref			Ref		
HER2 status								
HER2 not tested	148	5.6	Ref			Ref		
HER2 tested, HER2 negative	392	7.4	0.77	0.64-0.94	0.010	0.81	0.66-1.00	0.040
HER2 tested, HER2 positive	118	8.8	0.62	0.48-0.80	<0.001	0.66	0.49-0.85	0.002
HER2 tested, HER2 unknown	77	7.9	0.81	0.61-1.07	0.136	0.81	0.60-1.06	0.165

Multivariable Cox regression analyses for overall survival in patients diagnosed in 2015 and 2016. [a]Patients in whom HER2 was determined after 31 days of start of systemic treatment (N=27) were excluded to prevent an immortal time bias. [b]Hospitals are categorized in quartiles based on the hospital volume of all gastroesophageal cancer patients treated with systemic therapy in 2015 and 2016. OS, overall survival, HR, hazard ratio, CI, confidence interval, GEJ, gastroesophageal junction, NOS, not otherwise specified.

Noteworthy, even in patients for whom the decision to be treated with systemic therapy had already been taken as is the case in our cohort still more than 10% of patients were not tested for HER2 in 2016. Even when we restrict our analysis to patients included in the ToGA study, i.e., with gastric or GEJ tumors, we still observed that 17% of gastric and 7% of GEJ adenocarcinoma patients diagnosed in 2016 were not tested. Male sex and treatment in lower hospital volumes were associated with a lower probability of HER2 assessment. Possible reasons for not testing could include contraindications for treatment with trastuzumab, and unawareness among physicians.

The HER2 overexpression rate of 19% is comparable with other studies.[14, 15, 16] In our study, this rate increased over time, probably because of the rise in tested esophageal adenocarcinomas, with a higher HER2 positivity rate compared to GEJ/cardia and stomach tumors. Overall, 23% of HER2 positive patients did not receive trastuzumab despite treatment with systemic therapy, which is remarkable as the additive side effects of trastuzumab are mild, while survival benefit is significant.[6] It cannot be excluded that financial reasons played a role.[36] For example, the reimbursement of trastuzumab could have been an issue if patients were not eligible for treatment with cisplatin, capecitabine or 5-FU, since the costs of trastuzumab are only covered when combined with this chemotherapy.[37]

Furthermore, we found an interhospital variation in the proportion of HER2 tested patients of 29–100%, with a lower probability of undergoing HER2 assessment in low-volume compared to high-volume hospitals. A similar association with hospital volume was recently found in the probability of undergoing surgical treatment for gastric cancer.[20] Although we did not find a statistically significant association between hospital volume quartiles and, this was possibly a result of the limited number of patients in the lower hospital volumes. We did find this association when hospitals were categorized in two volume categories, which is in line with earlier published nationwide results.[22] This suggests HER2 assessment could increase if physicians of high-volume centers are involved in treatment decision-making, e.g., through regional multidisciplinary tumor boards.

Importantly, we found that in 26% of the HER2 assessments performed, ISH or MLPA was used despite a non-equivocal IHC result.28 Reasons for additional ISH testing could include inadequate assessment of IHC staining due to HER2 heterogeneity or discordance between the primary tumor and metastasis.[28, 38, 39, 40] HER2 should therefore ideally be assessed on multiple specimens of the primary tumor, as well as on metastases, since HER2 targeted therapy is indicated if in one of the tumor specimens HER2 overexpression is observed.[13]

HER2 positive patients treated with a trastuzumab-containing regimen had a longer survival compared to chemotherapy alone (11.6 and 6.6 months, respectively). However, survival in both groups was remarkably lower than in the ToGA trial (13.8 and 11.0 months, respectively),[6] probably due to restrictions in trial inclusion (e.g., performance status > 2), and because median age of our cohort was higher (64 versus 59 years in the ToGA trial). Nevertheless, the rise in trastuzumab administration over time could have contributed to the increased survival in our cohort from 6.9 (2010–2013) to 7.9 months (2014–2016).

Both HER2 positive and negative patients showed prolonged survival compared to non-tested patients. This supports the assumption of a selection of prognostically favorable patients that are tested for HER2, also endorsed by the higher number of tested patients

without comorbidities compared to non-tested patients. Another explanation could be that non-tested patients are treated more frequently in low-volume hospitals. Moreover, the non-tested, but HER2 positive patients that did not receive trastuzumab could also have contributed to the lower survival in this group, since HER2 overexpression without targeted treatment is regarded a negative prognostic factor, although this is still subject of debate.[41, 42,43] This is the first study in which real-world HER2 testing and outcomes of a nationwide gastroesophageal cancer cohort are described. However, the assumption that HER2 was not tested if it was not disclosed in pathology reports could have resulted in an underestimation of HER2 tested patients. Another limitation is the lack of information on reasons why HER2 testing was not performed or why trastuzumab was not administered. Lastly, as in any retrospective study, there were some missing data, which possibly hampered correction for confounding in multivariable analyses.

Our finding that still more than 10% of the patients treated with systemic therapy were not tested for HER2 is worrisome, not only because trastuzumab is currently the only targeted therapy in first-line palliative systemic treatment that has shown to improve survival rates, but also because other promising targets and biomarkers are on their way,[44] such as programmed death-ligand 1 (PD-L1)[45,46], Epstein-Barr Virus (EBV)[47,48] and microsatellite instability (MSI)[49,50] as biomarkers for checkpoint inhibition and selection in case of promising targeted therapies. Increased uptake of biomarker testing is therefore highly warranted in clinical practice.

In conclusion, daily practice management of metastatic gastroesophageal cancer has changed due to increased determination of HER2 status and administration of trastuzumab, which may have contributed to the improved survival in these patients over time. Advances in clinical practice could include a further increase in awareness of HER2 testing, especially in low-volume hospitals, and in trastuzumab administration.

SUPPLEMENTARY MATERIAL

Baseline characteristics of patients in whom HER2 was tested (n=1524).

	HER2 negative (n = 1035) No. (%)	HER2 positive (n = 285) No. (%)	HER2 unknown (n = 204) No. (%)
Male	748 (72.3%)	225 (78.9%)	156 (76.5%)
Age (years) - median (IQR)	63.0 (55.0, 69.0)	63.0 (55.0, 69.0)	63.0 (55.5, 70.0)
<50	398 (38.5%)	107 (37.5%)	75 (36.8%)
50-64	381 (36.8%)	113 (39.6%)	75 (36.8%)
65-79	238 (23.0%)	61 (21.4%)	50 (24.5%)
≥80	18 (1.7%)	4 (1.4%)	4 (2.0%)
Comorbidities			
0	301 (29.1%)	77 (27.0%)	76 (37.3%)
1	209 (20.2%)	67 (23.5%)	34 (16.7%)
≥2	238 (23.0%)	76 (26.7%)	37 (18.1%)
Unknown	287 (27.7%)	65 (22.8%)	57 (27.9%)
Tumor location			
Esophageal	339 (32.8%)	159 (55.8%)	72 (35.3%)
Gastroesophageal junction/cardia	228 (22.0%)	53 (18.6%)	45 (22.1%)
Stomach (non-cardia)	468 (45.2%)	73 (25.6%)	87 (42.6%)
Tumor histology			
Adenocarcinoma NOS	131 (12.7%)	43 (15.1%)	28 (13.7%)
Intestinal type adenocarcinoma	493 (47.6%)	194 (68.1%)	109 (53.4%)
Diffuse type adenocarcinoma	351 (33.9%)	35 (12.3%)	59 (28.9%)
Indeterminate type adenocarcinoma	60 (5.8%)	13 (4.6%)	8 (3.9%)
Tumor differentiation			
Well differentiated	12 (1.2%)	6 (2.1%)	4 (2.0%)
Moderately differentiated	169 (16.3%)	73 (25.6%)	32 (15.7%)
Poorly differentiated	629 (60.8%)	108 (37.9%)	111 (54.4%)
Unknown	225 (21.7%)	98 (34.4%)	57 (27.9%)
Metastatic sites			
1	589 (56.9%)	132 (46.3%)	93 (45.6%)
≥2	446 (43.1%)	153 (53.7%)	111 (54.4%)
Year of diagnosis			
2010	51 (4.9%)	7 (2.5%)	15 (7.4%)
2011	90 (8.7%)	15 (5.3%)	16 (7.8%)
2012	123 (11.9%)	31 (10.9%)	29 (14.2%)
2013	158 (15.3%)	44 (15.4%)	36 (17.6%)
2014	199 (19.2%)	67 (23.5%)	29 (14.2%)
2015	242 (23.4%)	47 (16.5%)	47 (23.0%)
2016	172 (16.6%)	74 (26.0%)	32 (15.7%)

Tumor histology and differentiation are based on the primary tumor. Diffuse type tumors were classified as poorly differentiated. Abbreviations: IQR, interquartile range; NOS, not otherwise specified.

Supplementary Table 2. HER2 testing methods and results.

Reported IHC result	ISH/MLPA performed	Reported HER2 result	HER2 tests[1] (n = 1764) No. (%)	Clinically unnecessary ISH/MLPA	Interpreted HER2 result	HER2 tested patients[2] (n = 1524) No. (%)
0	No	Negative	451 (25.6%)		Negative	498 (32.7%)
	Yes	Negative	141 (8.0%)	X		
1+	No	Negative	214 (12.1%)		Negative	299 (19.6%)
	Yes	Negative	128 (7.3%)	X		
	Yes	Positive	2 (0.1%)	X		
2+	Yes	Negative	269 (15.2%)		Negative	238 (15.6%)
	Yes	Positive	80 (4.5%)		Positive	73 (4.8%)
	Yes	Unknown	6 (0.2%)		Unknown	3 (0.2%)
	No	Negative	1 (0.1%)		Unknown	5 (0.3%)
	No	Positive	2 (0.1%)			
	No	Unknown	8 (0.3%)			
3+	No	Negative	1 (0.1%)		Positive	212 (13.9%)
	No	Positive	107 (6.1%)			
	Yes	Negative	2 (0.1%)	X		
	Yes	Positive	125 (7.1%)	X		
Unknown	No	Negative	107 (6.1%)		Unknown	196 (12.9%)
	No	Positive	23 (1.3%)			
	Yes	Negative	74 (4.2%)			
	Yes	Positive	23 (1.3%)			

IHC results that were reported to be 0-1+ or 1+ were scored as 1+, and 0-2+, 1-2+, 2+, or 2-3+ as 2+.
[a] All HER2 tests that were performed. HER2 assessments that were performed as part of a study were not included, since these often include both IHC and ISH, regardless of the IHC result.
[b] If HER2 was tested multiple times, the last test result that was performed with a maximum of 31 days after start of systemic treatment is displayed. Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization; MLPA, multiplex ligation-dependent probe amplification.

Conflict of interest

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Hospital volume and beyond first-line palliative systemic treatment in metastatic oesophagogastric adenocarcinoma:
A population-bat study

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ABSTRACT

Background: Beyond first-line palliative systemic treatment can be beneficial to selected oesophagogastric cancer patients, but experience with its administration may be limited and vary among hospitals. In a population-based study, we analysed the association between hospital systemic treatment volume and administration of beyond first-line treatment in oesophagogastric adenocarcinoma, as well as the effect on overall survival (OS).

Methods: Synchronous metastatic oesophagogastric adenocarcinoma patients (2010–2017) were selected from the Netherlands Cancer Registry. Hospitals were categorised in volumes quartiles. The association between hospital systemic treatment volume and the use of beyond first-line treatment was assessed using trend and multivariable logistic regression analyses. OS was compared between hospitals with high and low beyond first-line treatment administration and treatment strategies using Kaplan–Meier curves with log-rank test and multivariable Cox proportional hazard regression.

Results: Beyond first-line treatment was administered in 606 of 2,466 patients who received first-line treatment, and increased from 20% to 31% between 2010 and 2017 (P < 0.001). The lowest hospital volumes were independently associated with lower beyond first-line treatment administration compared to the highest volume (odds ratio 0.62, 95% confidence interval 0.39–0.99; odds ratio 0.67, 95% confidence interval 0.48–0.95). Median OS was higher in all patients treated in hospitals with a high versus low beyond first-line treatment administration (7.9 versus 6.2 months, P < 0.001). Second-line paclitaxel/ramucirumab was administered most frequently and independently associated with longer OS compared to taxane monotherapy (HR 0.74, 95% CI 0.59–0.92).

Conclusion: Higher hospital volume was associated with increased beyond first-line treatment administration in oesophagogastric adenocarcinoma. Second-line paclitaxel/ramucirumab resulted in longer survival compared to taxane monotherapy.

INTRODUCTION

Life expectancy of patients with metastatic oesophagogastric cancer is poor.[1] Palliative systemic therapy aims to prolong survival while maintaining quality of life.[2-5] Median time from start of first-line systemic treatment to failure was only 4.6 months in a real-world patient cohort.[6] Therefore, beyond first-line, i.e. second and third-line, treatment options are needed.

Single-agent chemotherapy such as irinotecan[7] or a taxane[8, 9] have demonstrated activity in second line. A second-line regimen containing the VEGF inhibitor ramucirumab with or without a taxane has shown to have an additional survival benefit when administered for oesophagogastric adenocarcinoma.[10, 11] Although trials on third-line treatment are still scarce, increasing evidence confirms this could be beneficial in highly selected patients.[12]

Since oesophagogastric cancer has a relatively low incidence, and only a part of patients who receive palliative systemic therapy are eligible for beyond first-line treatment, the experience in its administration of might be limited within individual centers. Therefore, the beyond first-line treatment administration could vary between hospitals. If so, it could be related to the number of patients treated in a hospital, i.e. hospital volume, as this has

been observed in the administration of first-line systemic treatment[13] and the probability of undergoing curative treatment[14, 15] of oesophagogastric cancer as well.

The effect of hospital volume on the use of beyond first-line treatment has not been described yet. Moreover, the proportion of patients that receives beyond first-line treatment, the type of treatment that is administered, and the outcomes of these patients in clinical practice are unknown. Nationwide real-world data on the use and benefit of beyond first-line treatment in oesophagogastric adenocarcinoma patients could provide valuable information on outcomes of patients who have received these treatments. In this population-based study, we analysed the association between hospital volume and the use of beyond first-line treatment, and the effects of beyond first-line palliative systemic treatment strategies on overall survival (OS) and time to failure of treatment (TTF).

MATERIALS AND METHODS

Data collection
Patients of ≥18 years with an adenocarcinoma of the oesophagus, gastro-oesophageal junction, or stomach ((International Classification of Diseases for Oncology (ICD-O), ICD-O-3: C15 and C16[16]) with synchronous metastases who received palliative systemic treatment, 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 nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA)[17] that comprises all histologically confirmed cancer diagnoses. Patients were included if diagnosed during 2015–2017, or in a subset of Dutch hospitals during 2010–2014. This subset was selected because of logistic limitations, and regarded as a representative sample of all Dutch hospitals.[6] Two hospitals were excluded, because of missing details on treatment.

Patient, tumour and treatment characteristics were extracted from medical records by specially trained registrars. Human epidermal growth factor receptor 2 (HER2) data were retrieved from PALGA.[18] Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020.

Systemic treatment
Assumptions regarding systemic treatment are listed in Supplementary Table 1. A systemic treatment line was defined as systemic therapy agents that started within 3 days of each other and were given until suspension, as described earlier.[6] A sequential treatment line was specified as treatment in which an agent of a drug group was administered that was not used in the preceding line, with the exception of trastuzumab and ramucirumab.

The proportion of patients that received beyond first-line treatment was described in all patients, and in those considered eligible for this treatment, i.e. if they survived >90 days after stop of first-line treatment. This time frame was chosen because systemic treatment administration in the last months before death is generally considered undesirable.[19, 20]

Hospital volume

Per hospital, the volume of all oesophagogastric adenocarcinoma patients who received systemic treatment in curative setting, or palliative setting for synchronous metastatic disease was calculated. With the aim to reflect current practice, the volume of recent years (2015–2017) was used. Hospitals were categorised into quartiles according to these volumes to compare the proportion of patients that received beyond first-line treatment. Furthermore, hospitals were divided above and below the median proportion of patients that received beyond first-line treatment per hospital, and OS of all patients was compared between these categories.

Overall survival and time to failure

OS was assessed from start of a treatment line until death or end of follow-up. To take into account all reasons for treatment discontinuation besides progressive disease, we used TTF as a proxy for progression-free survival (Supplementary Table 1). OS and TTF of second-line treatment strategies that were applied in at least 10% of the patients were compared.

Statistical analysis

Patient and tumour characteristics are displayed with counts and percentages, or medians and interquartile ranges (IQRs). Differences between groups were analysed using chi-squared tests, Fisher's exact tests or Mann–Whitney U tests, whichever was appropriate. The association between beyond first-line treatment administration with hospital volume and over time were analysed using the Chi-square and Cochran-Armitage trend test. The association between first-line hospital volume and the probability of receiving beyond first-line treatment was tested using multivariable logistic regression, with adjustment for factors that could be associated with treatment administration. OS/TTF of second-line treatment were analysed with Kaplan–Meier curves and log-rank tests. The association between hospital volume, second-line treatment strategies and OS/TTF were tested using multivariable Cox proportional hazard regression analyses by adjusting for relevant patient and tumour characteristics. P values < 0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

RESULTS

Beyond first-line treatment administration

Of all 2,466 patients who received first-line systemic treatment, second-, third-, fourth- and fifth-line treatment were administered in 25% (n = 606), 4% (n = 107), 1% (n = 19) and 0.1% (n = 3), respectively. Three patients had not finished first-line treatment at end of follow-up. We observed a gradual increase in the administration of beyond first-line treatment between 2010 and 2017 (from 20% to 31%; P < 0.001). First-line mono and triplet chemotherapy administration decreased in 2015–2018 compared to 2010–2014 (14% to 6% and 44% to 21%, respectively), while the use of first-line doublet and trastuzumab therapy increased (34% to 57%, and 6% to 16%, respectively). Nevertheless, still most patients were treated with doublets or triplets (79% in 2010–2014 and 77% in 2015–2018).

Of the patients who did not die within 90 days and therefore were considered eligible

to receive beyond first-line treatment, 41% received beyond first-line treatment, compared to 5% of non-eligible patients (Fig. 1). Over time, this proportion increased in eligible patients from 31% to 48% between 2010 and 2017 (P < 0.001). Eligible patients had a better performance status, less comorbidities, less affected and different metastatic sites, more frequently a oesophageal/GEJ tumour and HER2 overexpression compared to non-eligible patients (Supplementary Table 2). Moreover, they received less often first-line monotherapy, and more often a doublet or trastuzumab-containing regimen.

Figure 1. Patient selection.

Subset of patients with metastatic esophagogastric adenocarcinoma ($T_{1-4b}N_{all}M_1$) treated with first-line systemic therapy diagnosed in 2010-2014 N=1,217

All patients with metastatic esophagogastric adenocarcinoma ($T_{1-4b}N_{all}M_1$) treated with first-line systemic therapy diagnosed in 2015-2017 N= 1,521

Patients with metastatic esophagogastric cancer treated with first-line systemic therapy N= 2,738

Excluded (N=272):
- Patients with oesophageal, gastro-esophageal junction or cardia carcinoma and non-reional head and neck lymph node metastases only (N=95)
- Patients treated with chemoradiotherapy (N=96)
- Patients that received firs- or second-line systemic tratment abroad (N=45)
- Patients in whom first- or second-line sustemic therapy regimens were not specified (N=14)
- Patients without follow-up data on vital satus (N=8)
- Patients that participated in a first-line trial and possibly received a placebo (N=9)
- Patients that started with first-line systemic therapy and in which the primary tumor was then considered to be other than esophagogastric (N=6)

Patients treated with first-line systemic treatment N=2,466

Patients who died <90 days after stop of first-line treatment N=1,133

Patients who did not died <90 days after stop of first-line treatment N=1,133

Patients treated with beyond-first line systemic treatment N=56 (5%)

Patients treated with beyond-first line systemic treatment N=550 (41%)

Patients treated with beyond-first line systemic treatment N=606

Second-line treatment

Median age before start of second-line treatment was 64 years (n = 606, Table 1). Performance status was 0−1 in 49% of the patients, ≥2 in 7%, and unknown in 44%. Half of the patients (n = 303) received first-line doublets. Patients treated with first-line trastuzumab-containing regimens received most often second-line treatment (32%), followed by first-line doublet (26%) and triplet (24%) chemotherapy, non-trastuzumab targeted therapy-containing treatment (15%) and monotherapy (11%; P < 0.001; Fig. 2).

Table 1. Patient characteristics before start of second-line systemic treatment and details of first-line treatment in patients who received second-line therapy (n=606).

Characteristics	Patients who received second-line therapy (n = 606) No. (%)
Female	139 (23%)
Age, years, median (IQR)	64 (57, 70)
<60	214 (35%)
60-69	234 (39%)
70-79	146 (24%)
≥80	12 (2%)
Performance status	
0 or 1	300 (49%)
≥2	42 (7%)
Unknown	264 (44%)
Number of comorbidities	
0	381 (63%)
1	155 (26%)
≥2	51 (8%)
Unknown	19 (3%)
Tumor location	
Esophagus	272 (45%)
Gastro-esophageal junction or cardia	134 (22%)
Stomach	200 (33%)
Lauren classification	
Intestinal	288 (48%)
Diffuse	123 (20%)
Mixed	19 (3%)
Indeterminate	20 (3%)
Unknown	156 (26%)
HER2 overexpression	
Positive	119 (20%)
Negative	355 (59%)
Unknown	3 (0%)
Not tested	129 (21%)
Metastatic sites	
1	230 (38%)
≥2	376 (62%)
Distant lymph node metastases	280 (46%)
Liver metastases	369 (61%)
Peritoneal metastases	188 (31%)
Lung metastases	151 (25%)
Bone metastases	99 (16%)
Other metastatic sites	108 (18%)
First-line treatment characteristics	
First-line systemic treatment strategy	
Monotherapy	26 (4%)
Doublet chemotherapy	303 (50%)
Triplet chemotherapy	183 (30%)
Trastuzumab-containing regimen	90 (15%)
Non-trastuzumab targeted therapy-containing regimen	4 (1%)
Duration first-line treatment (months), median (IQR)	3.7 (2.3, 6.2)
Unknown	7 (1%)
Reasons discontinuation first-line treatment	
Progressive disease	568 (94%)
Toxicity	18 (3%)
Patient's request	0 (0%)
Other	4 (1%)
Unknown	16 (3%)

Figure 2. First- and second-line systemic treatment strategies in all patients (n=2,466) and second-line treatment regimens (n=606).

FIRST – AND SECOND-LINE TREATMENT STRATEGIES
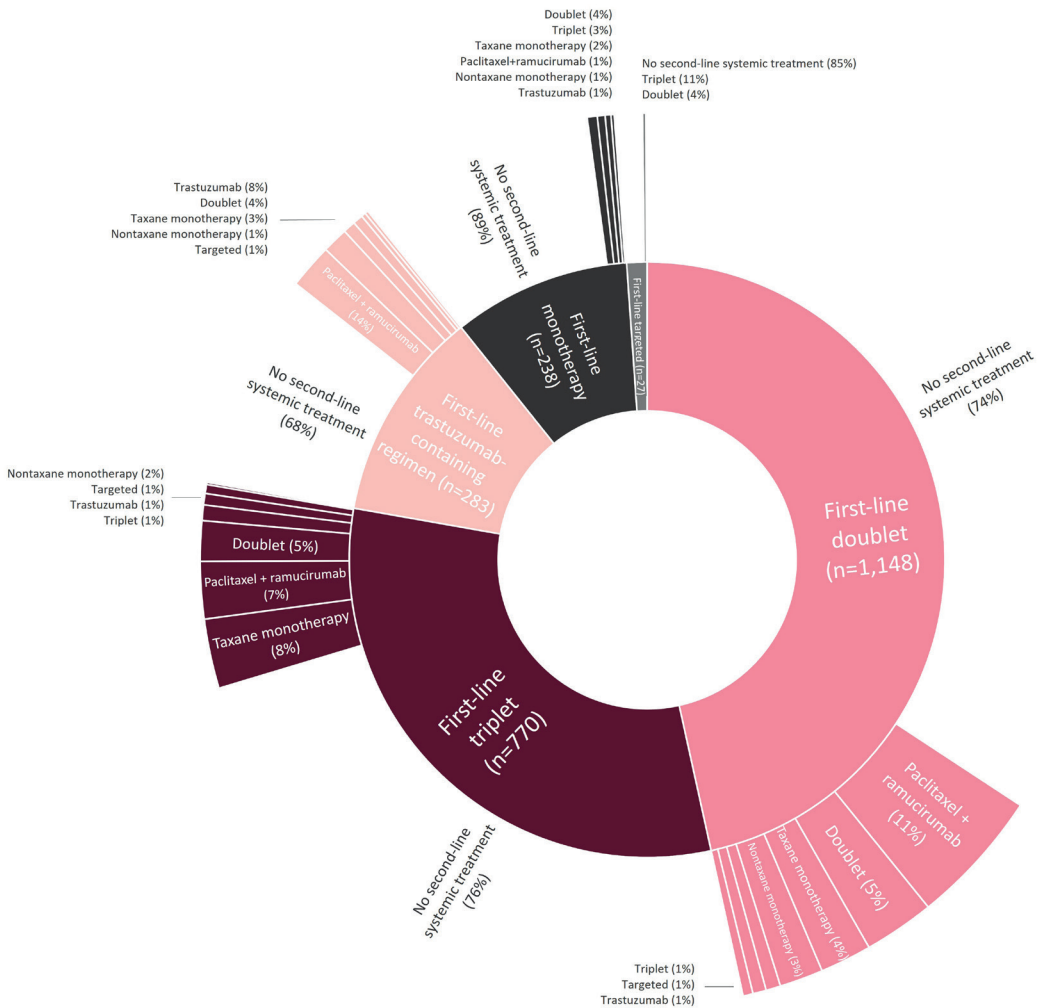
First-line systemic treatment strategies were subdivided in chemotherapy regimens (monotherapy, doublet and triplet), trastuzumab-containing regimens and non-trastuzumab targeted therapy-containing regimens. Second-line treatment strategies were administered in 606 patients, and subdivided in chemotherapy regimens (taxane monotherapy, non-taxane monotherapy, doublet and triplet), paclitaxel and ramucirumab, trastuzumab-containing regimens, and non-trastuzumab targeted therapy-containing regimens.

SECOND-LINE TREATMENT REGIMENS

CapOx

Capecitabine+cisplatin+trastuzumab
FOLFOX
Capecitabine+docetaxel
Paclitaxel+regorafenib
Docetaxel+pazopanib
FLOT
EOX
FOLFOX+trastuzumab

Erlotinib
FOLFIRI
FOLFIRI+ramucirumab
Epirubicine
Docetaxel

ECF
CapOx+trastuzumab
Capecitabine+trastuzumab+bevacizumab
Ramucirumab

Capecitabine+irinotecan
Docetaxel+trastuzumab
Paclitaxel+trastuzumab
5-FU+cisplatin

Paclitaxel+ramucirumab

DOC+trastuzumab
Carboplatin+paclitaxel+trastuzumab

Pembrolizumab
Everolimus
ECC
Irinotecan
Carboplatin

Paclitaxel
Gemcitabine+carboplatin

ECarboX
FOLFIRI+trastuzumab
Nivolumab

Carboplatin+paclitaxel
DOC

Doxorubicine
Gemcitabine+carboplatin+trastuzumab
ECC+trastuzumab
Carboplatin+olaparib

Capecitabine

Capecitabine+trastuzumab
5-FU+paclitaxel

The word cloud shows all 44 second-line systemic therapy regimens that were administered. Font size of the word corresponds to the number of patients that received the regimen

Forty-four different second-line regimens were administered (Fig. 2). Paclitaxel and ramucirumab was used most frequently (35%), followed by taxane monotherapy (20%) and doublet chemotherapy (20%; Supplementary Table 3). Of the 44 patients who received trastuzumab-containing treatment, 23 also received firstline trastuzumab with a different chemotherapy backbone.

In 2011, 38% of the patients received taxane monotherapy, which decreased to 8% in 2017. The administration of paclitaxel and ramucirumab increased from 22% in 2015, i.e. the first year that ramucirumab was available apart from clinical studies in the Netherlands, to 58% in 2017.

Table 2. Probability of receiving beyond first-line systemic treatment per hospital volume quartile in patients who received palliative systemic treatment (n=2,466).

Hospital volume	Hospitals No.	Patients No.	Beyond first-line treatment No. (%)	P value	Multivariable logistic regression		
					OR[b]	95% CI	P value
Q1 - <18 patients	17	233	40 (17%)	<0.001[a]	0.62	0.39-0.99	0.045
Q2 - 18-41 patients	19	451	88 (20%)		0.67	0.48-0.95	0.024
Q3 - 42-82 patients	19	749	184 (25%)		0.99	0.76-1.30	0.945
Q4 - ≥83 patients	19	1033	294 (28%)		Ref		

OR, odds ratio, CI, confidence interval, Q1-Q4, quartiles 1-4.
Hospitals in which patients received first-line systemic treatment were categorized in quartiles based on the hospital volume of esophagogastric adenocarcinoma patients treated with systemic therapy with either curative or palliative intent, and who were diagnosed between 2015 and 2017.
[a] Cochran-Armitage trend test.
[b] Odds ratios were adjusted for sex, age, number of comorbidities, primary tumor location, Lauren classification, year of diagnosis and death within 90 days after stop of systemic treatment.

Beyond second-line treatment

Twenty-seven different third-line regimens were administered (n=107), consisting of combination (doublet or triplet) chemotherapy (30%), non-trastuzumab targeted therapy-containing regimens (18%), irinotecan (16%) and non-irinotecan monotherapy (16%), paclitaxel and ramucirumab (10%) and trastuzumab-containing regimens (10%). Fourth-line systemic treatment was applied in 19 patients, consisting of irinotecan (n=8) and nonirinotecan monotherapy (n=3), trastuzumabcontaining regimens (n=3), paclitaxel and ramucirumab (n=2), combination chemotherapy (n=2), and non-trastuzumab targeted therapy-containing regimens (n=1). Fifth-line treatment was applied in three patients, of whom one received a trastuzumab-containing regimen, and two monotherapy. 3.4. Hospital volume Hospital volumes were categorised in < 0.001). Q1 and Q2 were associated with a lower probability of beyond first-line treatment administration compared to Q4 (adjusted odds ratio [OR] 0.62, 95% confidence interval [CI] 0.39e0.99 and OR 0.67, 95% CI 0.48e0.95; Table 2).

The interhospital variation in the proportion of patients that received beyond first-line treatment was 0–71%, with a median of 21% (IQR 13%, 32%). When categorised in either high (≥21%) or low (<21%) proportions of beyond first-line treatment administration, median OS of all patients who received first-line treatment in hospitals that treated a high proportion of their patients with beyond first-line treatment was longer (7.9 months) compared to hospitals with a low proportion (6.2 months; P < 0.001; Fig. 3).

Figure 3. Kaplan Meier curves for overall survival in patients who received palliative systemic treatment stratified for hospitals with a high and low proportion of beyond first-line treatment administration.
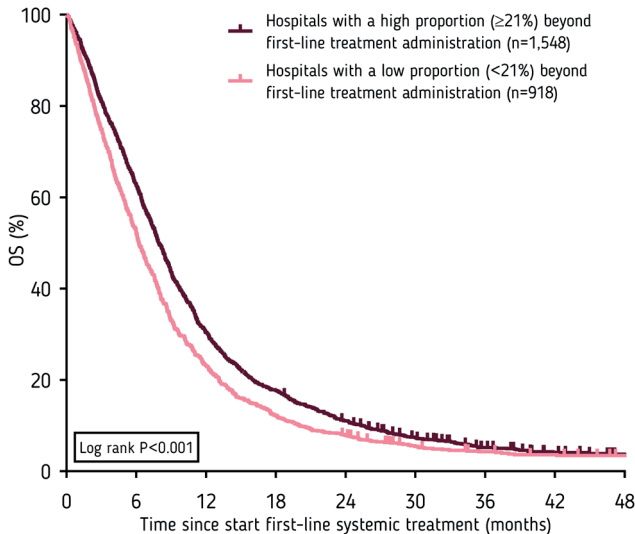
Overall survival in all patients who received at least first-line systemic treatment (n = 2,466), stratified for hospitals with a high and low proportion (above and below the median 21%) of patients treated with beyond first-line systemic treatment.

Overall survival and time to failure

Overall, median OS since start of second-line treatment was 5.4 (IQR 2.8, 9.0) and TTF 3.4 (IQR 1.8, 5.6) months (n = 606). Median OS since start of third-line treatment was 5.4 (IQR 3.0, 9.1) months, and TTF 3.1 (IQR 1.8, 6.2) months (n = 107). Survival of fourth- and fifth-line treatment was not calculated because of the limited number of patients.

Median OS of second-line paclitaxel and ramucirumab, doublet chemotherapy and taxane monotherapy was 6.1, 5.5 and 4.1 months, respectively (Fig. 4). Paclitaxel and ramucirumab resulted in longer OS and TTF in univariable (P = 0.008 and P = 0.002, respectively) and multivariable analyses (adjusted hazard ratio [HR] 0.71, 95% CI 0.52–0.95) and TTF (HR 0.61, 95% CI 0.44–0.83) compared to taxane monotherapy (Table 3). Doublets resulted neither in better OS (HR 0.76, 95% CI 0.57–1.01) nor TTF (HR 0.75, 95% CI 0.56–1.01) than taxane monotherapy. Compared to doublets, paclitaxel and ramucirumab resulted in similar OS (HR 0.93, 95% CI 0.70–1.24) and TTF (HR 0.81, 95% CI 0.60–1.10).

Figure 4. Kaplan-Meier curves displaying overall survival in patients who received second-line systemic treatment.

Number at risk									
Paclitaxel+ramucirumab	215	170	108	60	31	16	10	6	4
Doublet chemotherapy	120	85	54	26	15	7	3	2	1
Taxane monotherapy	122	76	39	21	16	8	6	3	3
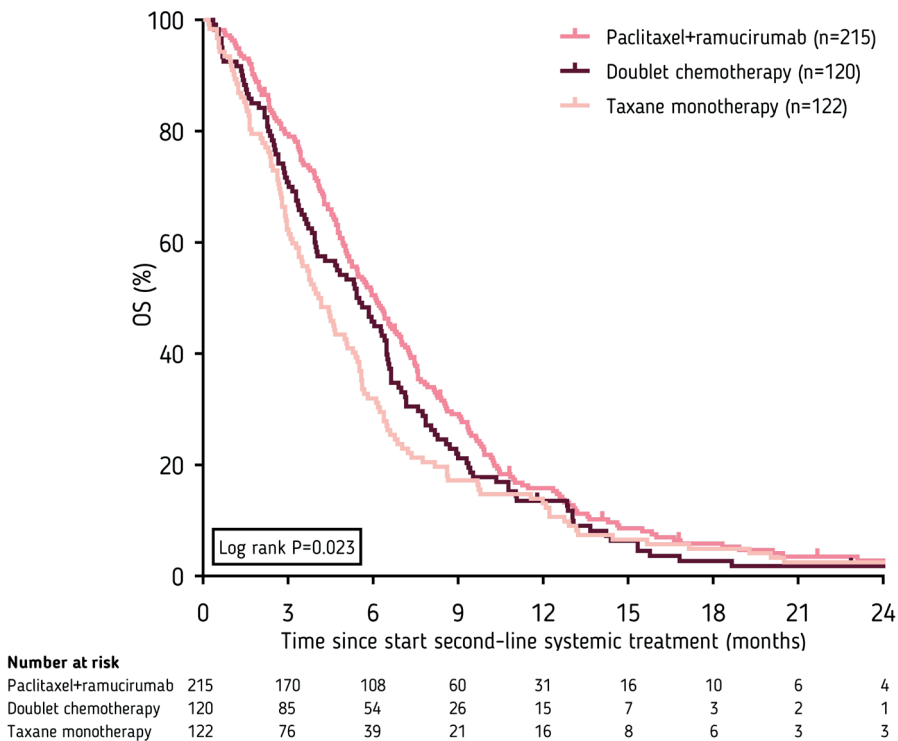
Overall survival in 457 patients receiving second-line systemic treatment. Second-line systemic treatment strategies that were administered in at least 10% of the patients are displayed.

Table 3. Cox regression analyses for OS and TTF of second-line systemic treatment strategies.

	Overall survival (n = 457)								Time to failure of second-line treatment (n = 457)						
			Univariable analyses			Multivariable analyses				Univariable analyses			Multivariable analyses		
	Patients No.	Median OS (months)	HR	95% CI	P value	HR	95% CI	P value	Median TTF (months)	HR	95% CI	P value	HR	95% CI	P value
Second-line systemic treatment strategy															
Taxane monotherapy	122	4.1	Ref			Ref			2.5	Ref			Ref		
Doublet chemotherapy	120	5.5	0.86	0.67 1.11	0.246	0.76	0.57 1.01	0.057	3.9	0.83	0.64 1.09	0.185	0.75	0.56 1.01	0.056
Paclitaxel + ramucirumab	215	6.1	0.73	0.59 0.92	0.007	0.71	0.52 0.95	0.021	4.1	0.69	0.55 0.88	0.002	0.61	0.44 0.83	0.002
Sex															
Male	350	5.5	Ref			Ref			3.6	Ref			Ref		
Female	107	5.0	0.90	0.72 1.12	0.346	0.89	0.70 1.14	0.358	3.4	0.99	0.79 1.25	0.925	1.01	0.78 1.30	0.953
Age	-	-	0.99	0.98 1.00	0.149	1.00	0.99 1.01	0.443	-	0.99	0.98 1.00	0.073	0.99	0.98 1.00	0.145
Performance status															
0 or 1	224	5.9	Ref			Ref			3.6	Ref			Ref		
≥2	35	4.7	0.98	0.68 1.42	0.908	0.99	0.68 1.44	0.936	2.7	0.84	0.58 1.23	0.377	0.82	0.55 1.21	0.315
Unknown	198	4.9	1.21	1.00 1.47	0.057	1.11	0.91 1.37	0.304	3.5	1.06	0.86 1.30	0.587	0.96	0.78 1.18	0.689
Number of comorbidities															
0	296	5.3	Ref			Ref			3.4	Ref			Ref		
1	113	5.1	1.07	0.85 1.33	0.576	1.07	0.85 1.36	0.568	3.4	1.01	0.80 1.26	0.954	1.07	0.84 1.36	0.602
≥2	36	6.9	0.78	0.55 1.11	0.171	0.72	0.50 1.05	0.086	5.1	0.64	0.43 0.95	0.028	0.62	0.41 0.93	0.022
Unknown	12	5.6	0.98	0.55 1.75	0.984	1.04	0.57 1.88	0.909	4.7	0.90	0.48 1.70	0.753	1.09	0.57 2.09	0.796
Tumor location															
Esophagus	185	5.5	Ref			Ref			3.5	Ref			Ref		
Gastro-esophageal junction or cardia	110	5.7	0.91	0.71 1.16	0.436	1.01	0.78 1.31	0.935	4.2	0.86	0.67 1.11	0.251	0.95	0.73 1.24	0.728
Stomach	162	5.0	1.10	0.89 1.36	0.399	1.13	0.85 1.50	0.405	3.4	1.06	0.85 1.33	0.603	1.11	0.83 1.47	0.486
Lauren classification															
Intestinal	211	5.6	Ref			Ref			3.4	Ref			Ref		
Diffuse	104	4.6	1.35	1.06 1.72	0.014	1.21	0.92 1.58	0.177	3.1	1.16	0.90 1.48	0.248	1.01	0.76 1.34	0.950
Mixed	11	4.7	1.03	0.56 1.89	0.923	0.78	0.41 1.48	0.443	4.7	0.80	0.39 1.62	0.533	0.65	0.31 1.36	0.253
Indeterminate	15	4.8	1.81	1.07 3.08	0.028	1.75	1.02 3.01	0.042	2.7	1.52	0.86 2.67	0.150	1.40	0.79 2.49	0.250
Unknown	116	6.1	1.12	0.89 1.41	0.335	1.25	0.98 1.60	0.077	4.7	0.87	0.69 1.11	0.267	0.93	0.72 1.20	0.565
Distant lymph node metastasis	213	5.1	1.16	0.96 1.40	0.121	1.28	1.04 1.58	0.023	3.3	1.25	1.03 1.52	0.025	1.41	1.14 1.75	0.002
Liver metastasis	270	5.5	0.96	0.79 1.16	0.673	1.28	1.01 1.61	0.041	3.4	1.05	0.86 1.28	0.646	1.41	1.10 1.81	0.008
Peritoneal metastasis	160	4.8	1.25	1.03 1.53	0.024	1.33	1.03 1.71	0.027	3.1	1.24	1.02 1.52	0.035	1.41	1.09 1.83	0.009
Lung metastasis	115	5.1	1.25	1.01 1.56	0.040	1.28	1.02 1.61	0.037	3.5	1.19	0.95 1.48	0.134	1.12	0.88 1.42	0.368
Bone metastasis	68	3.6	1.70	1.30 2.21	<0.001	1.86	1.39 2.50	<0.001	2.5	1.63	1.25 2.13	<0.001	1.81	1.35 2.43	<0.001
Other metastases locations	90	4.8	1.20	0.91 1.51	0.126	1.07	0.82 1.38	0.622	3.4	1.20	0.94 1.53	0.140	1.15	0.88 1.50	0.316
Year of diagnosis	-	-	0.96	0.92 1.00	0.071	0.98	0.93 1.04	0.592	-	0.95	0.91 0.99	0.027	1.00	0.94 1.06	0.983

Lastly, the impact of hospital volume of second-line treatment on OS was assessed. Adjusted HRs of patients treated with second-line treatment in lower treatment volume hospitals (Q1, Q2 and Q3) compared to the highest volume (Q4) were 1.41, 1.56 and 1.15, respectively, although this was only statistically significant in Q2 hospitals (Table 4).

Table 4. Cox regression analyses for the association between hospital volume and overall survival in patients who received beyond first-line treatment (n=606).

Hospital volume	Patients (n = 606) No. (%)	HR[a]	95% CI	P value
Q1 - <18 patients	34 (6%)	1.41	0.92-2.17	0.111
Q2 - 18-41 patients	82 (14%)	1.56	1.15-2.13	0.005
Q3 - 42-82 patients	188 (31%)	1.16	0.93-1.44	0.193
Q4 - ≥83 patients	302 (50%)	Ref		

Hospitals in which patients received second-line systemic treatment were categorised in quartiles based on the hospital volume of oesophagogastric adenocarcinoma patients treated with (neo)adjuvant systemic therapy and synchronous metastatic oesophagogastric cancer patients treated with palliative systemic therapy between 2015 and 2017.
[a]Hazard ratios were adjusted for sex, age, performance status, number of comorbidities, primary tumour location, Lauren classification, metastatic sites, and year of diagnosis.
HR, hazard ratio, CI, confidence interval, Q1-Q4, quartiles 1–4.

DISCUSSION

In this nationwide cohort of 2,466 patients with synchronous metastatic oesophagogastric adenocarcinoma who received first-line palliative systemic treatment, we observed an association between hospital volume and the probability of receiving beyond first-line treatment, and overall survival. In recent years, studies in the curative setting showed that oesophagogastric cancer patients treated in high-volume hospitals have a higher chance of receiving treatment, and better outcomes.[14, 15, 21-25] Our study adds to the increasing body of evidence that this finding also applies in the metastatic setting.[13,18] Clearly, the simple fact that a patient received treatment could explain the improved survival in high-volume centers, as beyond first-line treatment has been shown to improve survival compared to best supportive care.[9,10] However, importantly, we observed that OS of all patients who were treated with palliative systemic treatment (with or without beyond first-line treatment) in a hospital with a high use of beyond first-line treatment was longer compared to hospitals with a low use of beyond first-line treatment. In addition, we showed in multivariable analysis that HRs for death decreased when the hospital treatment volume increased, which suggests that not only patient, tumour and treatment characteristics are related to better patient outcomes, but also factors which may be specific to high-volume centers, such as well-developed structures and adequate resources for a multidisciplinary treatment approach.[13,26]

The heterogeneity of 44 different second-line regimens is in line with the variety of 46 first-line regimens that we observed earlier.[6] The former Dutch gastric cancer guideline that was used until 2016[27] and the current oesophageal cancer guideline[28] do not specify recommendations on systemic treatment regimens. This probably contributed to this heterogeneity, and to the limited number of patients who received beyond first-line

treatment at all. The publication of the results of the landmark RAINBOW trial in 2014[11] and the subsequent recommendation of its administration in the national gastric cancer guideline in 2016[29] probably boosted the observed increase in the administration of paclitaxel and ramucirumab in 2017, and the overall rise in the use of beyond first-line treatment from 31% in 2010 to 48% of the eligible patients in 2017, i.e. the patients who survived >90 days after stop of first-line treatment, and will hopefully result in further uptake of beyond first-line treatment recommendations of (inter)national guidelines. The rise of beyond first-line treatment use could also be a result of a better performance status in patients after first-line treatment as a result of increased efficacy, e.g. due to the rise in the administration of trastuzumab-containing regimens and decrease in monotherapy use,[18] or less toxicity in first line, e.g. due to the increase in doublet and decrease in triplet chemotherapy administration.[6] Overall, beyond first-line treatment was administered in 41% of eligible patients, which is similar to a recent real-world study,[30] and in 5% of non-eligible patients. These results suggest that patient selection for this treatment and assessment of life expectancy is performed adequately in most cases.[19,20]

The paclitaxel and ramucirumab regimen was administered in 58% of the patients who received second-line treatment in 2017, and independently associated with a longer OS and TTF compared to taxane monotherapy, which confirms the result of the RAINBOW trial.[11] Although the median OS in both groups was lower than in this trial, the median OS difference of 2.2 months was comparable to our study (RAINBOW: 9.6 versus 7.4 months; our study: 6.1 versus 4.1 months), as well as the hazard ratios (RAINBOW: HR 0.80, 95% CI 0.68−0.96; our study: HR 0.71, 95% CI 0.52−0.95). Inferior survival rates in population-based studies compared to trials have been identified frequently.[31] Although we could not analyze treatment-related toxicity because of missing data, paclitaxel and ramucirumab have been considered well-tolerated in both the RAINBOW trial and real world.[11,32] Because the introduction of ramucirumab changed the landscape of second-line treatment from 2015 onwards, we adjusted for year of diagnosis in the Cox regression analyses. When we restrict our analyses to patients diagnosed in 2015−2017, the survival benefit of paclitaxel and ramucirumab compared to taxane monotherapy is even larger (OS: HR 0.61, 95% CI 0.42−0.88; TTF: HR 0.53, 95% CI 0.36−0.79).

There was no survival benefit of doublet chemotherapy over taxane monotherapy, which supports the findings of an earlier meta-analysis[8], while doublet chemotherapy probably induces more toxicity.[6, 8] Other population-based studies on beyond first-line treatment in oesophagogastric cancer did not compare outcomes or toxicity between these two strategies.[30, 33] More real-world data on the actual benefit and harms of second-line doublet chemotherapy are needed to justify its administration.

Beyond second-line treatment was used in only a few patients, probably because evidence of its efficacy was scarce until 2017, and still is. Recent results showing that trifluridine/tipiracil and nivolumab are third-line treatment options[34,35] will probably result in increased third-line treatment administration in the coming years.

A limitation of this study is that we missed data on performance status in a considerable number of patients. We therefore not only adjusted for performance status, but also for the number of comorbidities, age, and death within 90 days after stop of systemic treatment, as a proxy for performance status, in order to achieve the most optimal adjustment

for confounders that could be associated with a patient's condition and subsequently, beyond first-line treatment administration. Unfortunately, toxicity data were unknown no in 76% of the patients. Furthermore, the heterogeneity in second-line regimens and the subsequent small group size per regimen resulted in lack of statistical power to compare regimens. Moreover, although we included a nationwide oesophagogastric cancer population, our data are restricted to The Netherlands, and therefore comparable studies in other countries are needed to confirm our results in different populations. Lastly, consensus about the definition of systemic treatment lines in real-world data is currently lacking, although some suggestions have been made.[36] This hindered us from optimally comparing this with other population-based studies.[30, 33] An international agreement on the definition of treatment lines and the best approach to analyze these data should be considered in order to enable fair comparisons between outcomes of population-based studies.

Improving patient selection for beyond first-line immunotherapy using molecular tumour analysis could further improve patient outcomes. Results of studies comparing treatment with the checkpoint inhibitor pembrolizumab with chemotherapy in patients who have a tumour with high levels of microsatellite instability and PD-L1 expression are promising.[37 38] In first-line treatment, we observed that still not all patients are tested for the only target that is currently available, i.e. HER2.[18] In the light of upcoming targeted therapies, uptake for biomarker testing must be improved in order to enhance personalised treatment. The rise of beyond first-line targeted treatment options should ideally result in increased administration of it in clinical practice and improved outcomes in oesophagogastric cancer patients.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Assumptions regarding systemic treatment.

Assumptions regarding systemic treatment regimens and strategies:
- Systemic treatment includes both chemotherapy and targeted therapy.
- A combination regimen is defined as all systemic agents starting within three days after the start of the first systemic agent.
- If trastuzumab is added more than three days after start, but before stop of the other agent(s), trastuzumab is considered to be part of the treatment regimen, because there could have been a delay in the determination of HER2.
- If ramucirumab is added more than three days after start, but before stop of the other agent(s), ramucirumab is considered to be part of the treatment regimen, because this delay is possibly due to logistical reasons.
- If capecitabine is added more than three days after start, but before stop of the other agent(s), in the absence of any other fluoropyrimidine, capecitabine is considered to belong to the regimen of the other agent(s) as well. We assume this is due to a registration error, in which the prescription date instead of the actual start date is registered.
- If oxaliplatin only is registered, we assume this was part of a capecitabine and oxaliplatin (CapOx) regimen of which capecitabine was not registered, so we add capecitabine. We regard this as a registration error, in which the administration of capecitabine has not been noticed by the data manager.

Assumptions regarding systemic treatment lines:
- A treatment line is defined as systemic therapy (monotherapy or combination regimen) administered at the same time until suspension, regardless of reason for discontinuation.
- If one of the agents of the initially started regimen was discontinued and the other agent(s) continued, e.g. capecitabine monotherapy after CapOx, this is considered to be continuation of a treatment line.
- If the same or an equivalent systemic treatment regimen is (re)started after registered progression, this is considered continuation of the treatment line, e.g., CapOx to 5-FU/oxaliplatin (FOLFOX), or EOX to CapOx.
- Treatment is considered as next line if an agent of a new drug group is started that is not applied in the previous systemic treatment regimen.
- Both adding a drug to a regimen (with the exception of trastuzumab and ramucirumab), e.g. CapOx to epirubicin, oxaliplatin and capecitabine (EOX), as well as switching to a regimen containing an agent of a new drug group, e.g. carboplatin and paclitaxel to paclitaxel and ramucirumab, are considered as next-line treatment, regardless of the reasons for addition or switch.

- Reasons of discontinuation of a treatment line are classified as follows:
  o Progression;
  o Toxicity;
  o Patient's request;
  o Other reasons;
  o Unknown reasons.
- First-line treatment strategies are categorized as follows:
  o Chemotherapy regimens (without targeted therapy) subdivided in: monotherapy (1 chemotherapy agent), doublets (2 chemotherapy agents) and triplets (3 chemotherapy agents);
  o Targeted therapy-containing regimens with or without chemotherapy, subdivided in: trastuzumab-containing regimens, and non-trastuzumab targeted therapy-containing regimens.
- Second-line treatment strategies are categorized as follows:
  o Taxane monotherapy;
  o Non-taxane monotherapy;
  o Doublet chemotherapy;
  o Triplet chemotherapy;
  o Paclitaxel and ramucirumab;
  o Trastuzumab-containing regimens;
  o Non-trastuzumab targeted therapy-containing regimens.
- Beyond second-line systemic therapy regimens are categorized as follows:
  o Irinotecan monotherapy;
  o Non-irinotecan monotherapy;
  o Combination (doublet or triplet) chemotherapy;
  o Paclitaxel and ramucirumab;
  o Trastuzumab-containing regimens;
  o Non-trastuzumab targeted therapy-containing regimens.

Assumptions regarding time to failure of a treatment line:
- Time to failure (TTF) of a treatment line is considered as a proxy for progression-free survival.
- TTF was calculated to take into account all reasons for treatment discontinuation besides progressive disease, and because in the NCR progression is not registered according to formal RECIST criteria.
- Time to failure of a systemic treatment line is calculated from start of a treatment line until the first registered progression date that results in failure/termination of this line, or end of follow-up.
- If a treatment line continues despite of progression, e.g., in case of reintroduction of the same or an equivalent regimen after a therapy break and detected progression, we regard this as continuation of the treatment line, and this progression is not considered as an event for analyses on TTF.
- If a progression date is registered during a treatment line, this progression is considered as an event for TTF in case it happens within 14 days before discontinuation of the regimen, because treatment evaluations can take place during treatment.
- If a progression date is not registered, but the reason for discontinuation of the systemic treatment line is recorded as progressive disease, the date of discontinuation of the regimen is considered the moment of failure of the treatment line.
- If progression is not registered and no systemic treatment is administered after this treatment line, and the patient dies within 90 days after the last hospital visit, the date of death is considered as an event for analyses on TTF.
- If progression is not registered, and no systemic treatment is administered after a treatment line, and the patient dies more than 90 days after the last hospital visit, the patient is censored on the date of the last hospital visit for analyses on TTF.
- If progression is not registered but a new systemic treatment line is started, the patient is censored on the moment of failure of the treatment line for analyses on TTF.

Supplementary Table 2. Patient and treatment characteristics of patients who did and did not die within 90 days after stop of first-line systemic treatment.

Characteristics	Patients who died ≤90 days after stop of first-line treatment (n = 1,133) No. (%)	Patients who did not die ≤90 days after stop of first-line treatment (n = 1,333) No. (%)	P value
Female	256 (23%)	326 (24%)	0.278 [a]
Age, years, median (IQR)	65 (57, 71)	64 (57, 71)	0.495 [b]
<60	363 (32%)	448 (34%)	0.729 [a]
60-69	434 (38%)	504 (38%)	
70-79	316 (28%)	353 (26%)	
≥80	20 (2%)	28 (2%)	
Performance status			<0.001[a]
0 or 1	592 (52%)	833 (62%)	
≥2	130 (11%)	69 (5%)	
Unknown	411 (36%)	431 (32%)	
Number of comorbidities*			0.012 [a]
0	637 (56%)	785 (59%)	
1	351 (31%)	362 (27%)	
≥2	119 (11%)	130 (10%)	
Unknown	26 (2%)	56 (4%)	
Tumor location			0.037 [a]
Esophagus	488 (43%)	595 (45%)	
Gastro-esophageal junction or cardia	200 (18%)	275 (21%)	
Stomach	445 (39%)	463 (35%)	
Lauren classification			0.055 [a]
Intestinal	503 (44%)	653 (49%)	
Diffuse	275 (24%)	285 (21%)	
Mixed	49 (4%)	37 (3%)	
Indeterminate	35 (3%)	42 (3%)	
Unknown	271 (24%)	316 (24%)	
HER2 overexpression			0.006[a]
Positive	144 (13%)	213 (16%)	
Negative	564 (50%)	702 (53%)	
Unknown	6 (1%)	7 (1%)	
Not tested	419 (37%)	411 (31%)	
Metastatic sites			<0.001[a]
1	546 (48%)	783 (59%)	
≥2	587 (52%)	550 (41%)	
Distant lymph node metastases	493 (44%)	490 (37%)	<0.001[a]
Liver metastases	597 (53%)	696 (52%)	0.812[a]
Peritoneal metastases	306 (27%)	313 (23%)	0.044 [a]
Lung metastases	232 (20%)	224 (17%)	0.019 [a]
Bone metastases	192 (17%)	139 (10%)	<0.001[a]
Other metastatic sites	157 (14%)	153 (11%)	0.076[a]
Systemic treatment characteristics			
First-line systemic treatment strategy			<0.001[a]
Monotherapy	160 (14%)	78 (6%)	
Doublet chemotherapy	504 (44%)	644 (48%)	
Triplet chemotherapy	341 (30%)	429 (32%)	
Trastuzumab-containing regimen	113 (10%)	170 (13%)	
Non-trastuzumab targeted therapy-containing regimen	15 (1%)	12 (1%)	
Duration first-line treatment (days), median (IQR)	52 (21, 113)	110 (63, 162)	<0.001[b]
Unknown	5 (0%)	35 (3%)	
Reasons discontinuation first-line treatment			<0.001[a]
Progressive disease	656 (58%)	1052 (79%)	
Toxicity	161 (14%)	74 (6%)	
Patient's request	121 (11%)	29 (2%)	
Other	20 (2%)	8 (1%)	
Unknown	175 (15%)	170 (13%)	
Beyond first-line treatment	56 (5%)	550 (41%)	<0.001[a]

[a] *Chi square test,* [b] *Mann-Whitney U test.*

Supplementary Table 3. Second-line systemic therapy regimens with OS and TTF.

Second-line systemic treatment regimen	Patients (n = 606) No. (%)	Median OS (months), IQR	Median TTF (months), IQR
Paclitaxel and ramucirumab	215 (35%)	6.1 (3.4, 9.6)	4.1 (2.4, 6.5)
Taxane monotherapy	122 (20%)	4.1 (2.4, 6.8)	2.5 (1.5, 4.7)
Doublet chemotherapy	120 (20%)	5.5 (2.7, 8.3)	3.9 (1.8, 5.6)
Platinum and taxane	43		
Fluoropyrimidine and irinotecan	35		
Fluoropyrimidine and platinum	31		
Gemcitabine and platinum	9		
Fluoropyrimidine and taxane	2		
Non-taxane monotherapy	58 (10%)	3.6 (2.2, 6.6)	2.2 (1.5, 4.1)
Irinotecan	34		
Fluoropyrimidine	21		
Anthracycline	2		
Platinum	1		
Trastuzumab-containing regimen	44 (7%)	9.0 (4.8, 13.7)	4.5 (2.3, 8.2)
Mono chemotherapy and trastuzumab*	25		
Doublet chemotherapy and trastuzumab	16		
Triplet chemotherapy and trastuzumab	3		
Triplet chemotherapy	25 (4%)	3.8 (2.9, 7.4)	2.5 (2.0, 4.3)
Anthracycline, platinum and fluoropyrimidine	21		
Taxane, platinum and fluoropyrimidine	4		
Non-trastuzumab targeted therapy-containing regimen[a]	22 (4%)	6.9 (4.8, 8.1)	3.5 (2.3, 5.5)
Tyrosine kinase inhibitor	11		
Pembrolizumab	4		
Nivolumab	3		
Everolimus	2		
FOLFIRI and ramucirumab	1		
Ramucirumab	1		

*OS and TTF were calculated from start of second-line therapy. *One patient received a regimen containing capecitabine, trastuzumab and bevacizumab.*

Ethical approval

According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper GI Cancer Group. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[39]

Conflict of interest statement

Rob Verhoeven reports grants from BMS and Roche. Judith de Vos-Geelen reports non-financial support from BTG, a consult/advisory role for Shire, and grants and non-financial support (consultancy) from Servier. Nadia Haj Mohammad reports a consult/advisory role for BMS, MSD Servier, Eli Lilly, research grant from Servier. Theo van Voorthuizen reports non-financial support from Astellas, Ipsen, Roche, and Bayer. Martijn van Oijen reports grants from Amgen, BMS, Eli Lilly, Nordic, Merck, Roche and Servier. Valery Lemmens received educational grants and unrestricted research grants from Roche. Hanneke van Laarhoven reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Eli Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

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05.

Management and outcomes of gastric cancer patients with interval distant metastases in clinical practice

Submitted.

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ABSTRACT

Background: In patients with gastric or gastroesophageal junction (GEJ) cancer treated with curative intent, distant interval metastases may be detected between start of neoadjuvant chemotherapy and surgery. The aim of this study was to explore the characteristics, allocated treatment and OS in gastric/GEJ cancer patients with interval metastases, and to compare OS with synchronous metastatic gastric/GEJ cancer patients who started palliative chemotherapy.
Methods: Patients with interval metastases were selected from the Netherlands Cancer Registry by including patients with potentially curable gastric/GEJ adenocarcinoma (2010-2018) who started chemotherapy without concurrent radiotherapy. OS since start of neoadjuvant treatment of patients with interval metastases was compared with a propensity score-matched cohort of patients with synchronous metastases who received palliative systemic treatment.
Results: 164 patients with interval metastases diagnosed in 2010-2018 were included. Metastases were most frequently detected during surgery (83%) and most frequently located in the peritoneum (77%). Peritoneal interval metastases were observed in 63% and 80% of the patients who did and did not have a diagnostic laparoscopy prior to neoadjuvant treatment, respectively (P=0.041). Median OS was 8.9 months (IQR 5.5-13.4), compared to 8.0 months (IQR 4.1-14.1) in matched synchronous metastatic patients calculated from start of neoadjuvant and palliative systemic treatment, respectively (P=0.848).
Conclusion: This population-based study shows that gastric/GEJ cancer patients who started neoadjuvant treatment and were diagnosed with interval metastases most frequently suffered from peritoneal metastases detected during (exploratory) surgery, even when a diagnostic laparoscopy was performed before start of treatment. OS was comparable to patients with synchronous metastatic gastric/GEJ cancer.

INTRODUCTION

Patients with gastric cancer without distant metastases or tumor invasion in surrounding organs at initial diagnosis (i.e. cT1-4aN0-3M0) are eligible for treatment with curative intent.[1-3] Currently, in most western countries a surgical resection with perioperative chemotherapy is the preferred treatment strategy.[1-4]

Unfortunately, data show that recurrence of disease is found in nearly 30% of the gastric cancer patients within a year after gastrectomy[5], mostly consisting of distant metastases.[5,6] Although several studies describe the rate of recurrence in patients after a gastrectomy[5-7], distant metastases can also be detected during, or even before surgery in patients who started neoadjuvant treatment, so-called interval metastases.

The exact number of patients that develop interval metastases, as well as their characteristics, management of these patients and their overall survival (OS) in daily clinical practice is unknown. The primary aim of this population-based study was to explore the characteristics, the use of palliative treatment and OS of a nationwide cohort of gastric or gastroesophageal junction (GEJ) cancer patients who started with preoperative chemotherapy and developed interval distant metastases. The secondary aim was to compare OS of the patients with interval metastases with gastric or GEJ cancer patients who had distant

metastases at initial diagnosis, i.e. synchronous metastases, and received palliative systemic treatment.

MATERIALS AND METHODS

Data collection
Patients of ≥18 years with a histologically confirmed adenocarcinoma of the GEJ or stomach (C16 according to the ICD-O-3[8]) diagnosed in 2010-2018 with a potentially curable tumor at initial diagnosis (cT1-4a,X N0-3 M0) who started systemic treatment without concurrent radiotherapy 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 nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA)[9] that comprises all histologically confirmed cancer diagnoses. Data were extracted from the hospital's electronical health record system or medical records by trained registrars. Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020.

Patients diagnosed in 2015-2018 were included, as well as patients diagnosed in a subset of Dutch hospitals between 2010-2014. This subset was selected because of logistic limitations, and can be regarded as a representative sample of all Dutch hospitals.10 Because the number of patients with an adenocarcinoma of the gastroesophageal junction or stomach who started neoadjuvant systemic treatment was available for 2015-2018 only, we were able to calculate the proportion of patients with interval metastases in these years.

Staging
Clinical and pathological staging was performed according to the TNM 7th (2010-2016) and 8th edition (2017-2018). Dutch guidelines recommend initial staging with gastroscopy with biopsies, endoscopic ultrasonography (EUS) on indication and CT scan in all patients, and from 2016 onwards fluorodeoxyglucose positron emission tomography (FDG-PET)/CT and diagnostic laparoscopy in patients with locally advanced gastric and GEJ tumors, i.e. cT3-4a or cN1-3.[1, 2] Before 2016, a diagnostic laparoscopy was recommended in patients with cT3-4a tumors.[11]

Interval metastases
Interval metastases were defined as distant metastases detected within five days after start of neoadjuvant chemotherapy and the day of the surgery (regardless of whether surgical resection of the primary tumor took place). In case no surgery was performed, distant metastases detected >120 days after stop of neoadjuvant chemotherapy were not considered interval metastases because this time interval is considered too long, as surgical resection is generally scheduled within 42 days after the last neoadjuvant treatment cycle.[4,12] Distant metastases detected <5 days after start of systemic treatment were considered synchronous metastases, as described earlier.[10]

Metastases locations were categorized in peritoneal, liver, distant lymph nodes, lungs, bones, other, and unknown. Metastatic dissemination was categorized in distant lymph nodes only, peritoneum only, and hematogenous if other sites were affected. Information on metastases detection using imaging or during surgery was available in all patients.

Neoadjuvant systemic treatment
The first cycle of systemic treatment after the diagnosis of the primary tumor was considered neoadjuvant treatment. Patients were excluded if they did not receive a regimen that consisted of at least a platinum compound (oxaliplatin, cisplatin or carboplatin) and a fluoropyrimidine (5-FU or capecitabine), because these regimens are generally used for neoadjuvant treatment. Neoadjuvant treatment was categorized in anthracycline triplets (anthracycline, fluoropyrimidine and platinum compound, e.g. epirubicine, oxaliplatin and capecitabine [EOX]), taxane triplets (taxane, fluoropyrimidine and platinum compound, e.g. 5-fluoropyrimidine (5-FU), leucovorin, oxaliplatin and docetaxel [FLOT]) or fluoropyrimidine-platinum doublets (e.g. capecitabine and oxaliplatin [CapOx]).[13]

Palliative treatment
Treatment that was initiated at the day of or after the detection of metastases was considered palliative treatment, and categorized in surgical resection (with or without metastasectomy or hyperthermic intraperitoneal chemotherapy [HIPEC]), systemic treatment, radiotherapy on the primary tumor, and radiotherapy on metastases. Palliative systemic treatment strategies were categorized in anthracycline triplets, fluoropyrimidine-platinum doublets, paclitaxel and ramucirumab, taxane monotherapy and other strategies. Systemic treatment regimens in which an agent of a drug group was included that was not used as neoadjuvant treatment were regarded second line, e.g. CapOx to paclitaxel.[14]

Statistical analysis
Patient and tumor characteristics were displayed with counts and percentages for categorical variables, and means and standard deviations or medians and interquartile ranges (IQRs) for continuous variables. Differences between groups were analyzed using chi-squared tests, Fisher's exact tests or Mann-Whitney U tests, whichever was appropriate.

OS was analyzed using the Kaplan Meier method with log-rank test. OS of patients with interval distant metastases was compared with gastric or GEJ adenocarcinoma patients with synchronous metastases who received palliative first-line systemic treatment by performing a propensity score matching using NCR data. Matching was performed at a one-to-one ratio according to the nearest neighbor method without replacement, i.e. striving for the best possible matches. The within-pair difference was minimized by setting a caliper of 0.25 of the standard deviation of the logit of the propensity score. After matching the balance per item between patients with interval and synchronous metastases was assessed by the standardized mean difference and displayed in Supplementary table 2. The following matching variables were included: sex, age, performance status, number of comorbidities, primary tumor location (GEJ/ vs. non-cardia stomach), clinical tumor stage, clinical nodal stage, Lauren classification, number of metastatic locations and period of diagnosis. P values <0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 164 patients with interval metastases were included over the period 2010-2018 (Figure 1). Of all patients diagnosed in 2015-2018 who had started neoadjuvant systemic treatment for gastric cancer (n=1,316), 114 (9%) were diagnosed with interval metastases. Patients with interval metastases more frequently had a cT4a or a cN2-3 stage, a diffuse histology type and a poor or unknown differentiation grade compared to patients in whom no interval metastases were detected (Supplementary Table 1).

Figure 1. Patients with interval metastases receiving neoadjuvant therapy for gastric cancer.

Patients diagnosed with potentially curable gastric or gastroesophageal junction adenocarcinoma (2015-2018) who started (neoadjuvant) systemic treatment N= 1,316

Patients with potentially curable gastric or gastro-esophageal junction adenocarcinoma (2010-2014) diagnosed with metastases after start (neaodjuvant) systemic treatment N=50

Patients diagnosed with metastases after start (neaodjuvant) systemic treatment (2015-2018) N=116

Exclusion of patients who did not receive at least a fluoropyrimidine and platinum compound (N=2)

Included patients with interval metastases (2010-2018) N=164

Flowchart of patient selection. Patients who did not receive at least a fluoropyrimidine and platinum compound received a regimen containing capecitabine in combination with docetaxel, or 5-FU monotherapy.

Of all 164 included patients with interval metastases, 40% were women and median age was 66 years (IQR 58-72; Table 1). Before start of neoadjuvant treatment, most patients had a WHO performance status of 0-1 (70%), whereas 5% had a performance status of 2 and performance status was unknown in 26%. The majority had a non-cardia stomach tumor (71%). Most patients received a neoadjuvant anthracycline triplet (84%); others received a taxane triplet (13%) or a fluoropyrimidine-platinum doublet (3%).

Staging

Staging information was available in patients diagnosed in 2015-2018 (n=114). Initial staging with a CT scan and gastroscopy was reported in 111 patients (missing: n=3). A diagnostic laparoscopy before start of treatment was performed in 36% and an FDG-PET/CT scan in 48% of 114 patients, and in 41% and 55% of patients with a cT3-4a or cN1-3 tumor (n=83), i.e. patients in whom this was indicated since 2016, respectively. Peritoneal interval metastases were observed in 58 of 73 patients (80%) who did not have a diagnostic laparoscopy prior to neoadjuvant treatment, compared to 26 of 41 patients (63%) who received a diagnostic laparoscopy (P=0.041).

Table 1. Patient characteristics before start of neoadjuvant treatment in patients with interval metastases (n=164).

Characteristics	Patients (n = 164) No. (%)
Female	66 (40%)
Age, years, median (IQR)	66 (58, 72)
<60	48 (29%)
60-69	61 (37%)
70-79	51 (31%)
≥80	4 (2%)
Performance status	
0 or 1	114 (69%)
2	8 (5%)
Unknown	42 (26%)
Number of comorbidities	
0	93 (57%)
1	45 (27%)
≥2	17 (10%)
Unknown	9 (5%)
Tumor location	
Gastro-esophageal junction or cardia	47 (29%)
Stomach	117 (71%)
Clinical tumor stage	
1-2	50 (30%)
3	74 (45%)
4a	15 (9%)
X	25 (15%)
Clinical nodal stage	
0	66 (40%)
1	48 (29%)
2-3	41 (25%)
X	9 (5%)
Lauren classification	
Intestinal	46 (28%)
Diffuse	75 (46%)
Mixed	7 (4%)
Indeterminate	4 (2%)
Unknown	32 (20%)
Signet ring cell histology	32 (20%)
Differentiation grade	
Good	4 (2%)
Moderate	16 (10%)
Poor	114 (70%)
Unknown	30 (18%)
Period of diagnosis	
2010-2014	50 (30%)
2015-2018	114 (70%)
Neoadjuvant treatment	
Anthracycline triplet (ECC, ECF, EOX, EOF)	138 (84%)
Taxane triplet (FLOT, DOC)[a]	21 (13%)
Fluoropyrimidine-platinum doublet (CapOx, FOLFOX, SOX, CapCis)	5 (3%)

[a] One patient received neoadjuvant DOC with trastuzumab.
IQR, interquartile range; ECC, epirubicin, cisplatin and capecitabine; ECF, epirubicin, cisplatin and 5-FU; EOX, epirubicin, oxaliplatin and capecitabine; EOF, epirubicin, oxaliplatin and 5-FU; FLOT, 5-FU, leucovorin, oxaliplatin and docetaxel; DOC, capecitabine, oxaliplatin and docetaxel; CapOx, capecitabine and oxaliplatin; SOX, S1 and oxaliplatin; CapCis, capecitabine and cisplatin.
FOLFOX, 5-FU and oxaliplatin; SOX, S1 and oxaliplatin; CapCis, capecitabine and cisplatin.

Table 2. Neoadjuvant treatment, interval metastases and palliative treatment characteristics in all patients (n=164).

	Patients (n = 164) No. (%)
Days between start of neoadjuvant treatment and metastasis detection, median (IQR)	90 (77, 109)
Days between stop of neoadjuvant treatment and metastasis detection, median (IQR)	47 (36, 62)
Number of metastatic sites	
1	150 (91%)
≥2	14 (9%)
Location of metastases[a]	
Peritoneal metastases	126 (77%)
Liver metastases	19 (12%)
Distant lymph node metastases	16 (10%)
Bone metastases	3 (2%)
Lung metastases	2 (1%)
Other metastatic sites	10 (6%)
Unknown location of metastases	5 (3%)
Dissemination of metastases	
Distant lymph nodes only	12 (7%)
Peritoneal only	114 (70%)
Hematogenous	33 (20%)
Unknown	5 (3%)
Detection of metastases[b]	
During (exploratory) surgery	136 (83%)
Restaging using (PET-)CT scan	11 (7%)
Unknown	17 (10%)
Surgical resection	53 (32%)
Resection primary tumor only	45
Resection primary tumor and metastasectomy	7
Resection primary tumor and HIPEC	1
Palliative systemic treatment	59 (36%)
Anthracycline triplet (ECC, ECF, EOX, EOF)	17
Fluoropyrimidine-platinum doublet (CapOx, FOLFOX, SOX, CapCis)	15
Paclitaxel and ramucirumab	12
Taxane monotherapy	8
Other	7
Palliative radiotherapy primary tumor	22 (13%)
Palliative radiotherapy metastases	4 (2%)
Best supportive care only	61 (37%)

[a] As patients can have metastases at multiple locations, the sum of all percentages is greater than 100%. IQR, interquartile range; PET, positron emission tomography; CT, computed tomography; HIPEC, hyperthermic intraperitoneal chemotherapy; ECC, epirubicin, cisplatin and capecitabine; ECF, epirubicin, cisplatin and 5-FU; EOX, epirubicin, oxaliplatin and capecitabine; EOF, epirubicin, oxaliplatin and 5-FU; FLOT, 5-FU, leucovorin, oxaliplatin and docetaxel; CapOx, capecitabine and oxaliplatin; FOLFOX, 5-FU and oxaliplatin; SOX, S1 and oxaliplatin; CapCis, capecitabine and cisplatin.

CH 05.

Location of metastases

In 83% of patients, distant metastases were detected during (exploratory) surgery. In the majority of the patients (77%), peritoneal metastases were found, followed by liver metastases (12%) and distant lymph node metastases (10%). In 70% of all patients, the peritoneum was the only metastasis location, whereas metastatic dissemination was limited to the distant lymph nodes in 8% of the patients. A total of 20% had hematogenous metastases, and the metastasis location was unknown in 3%.
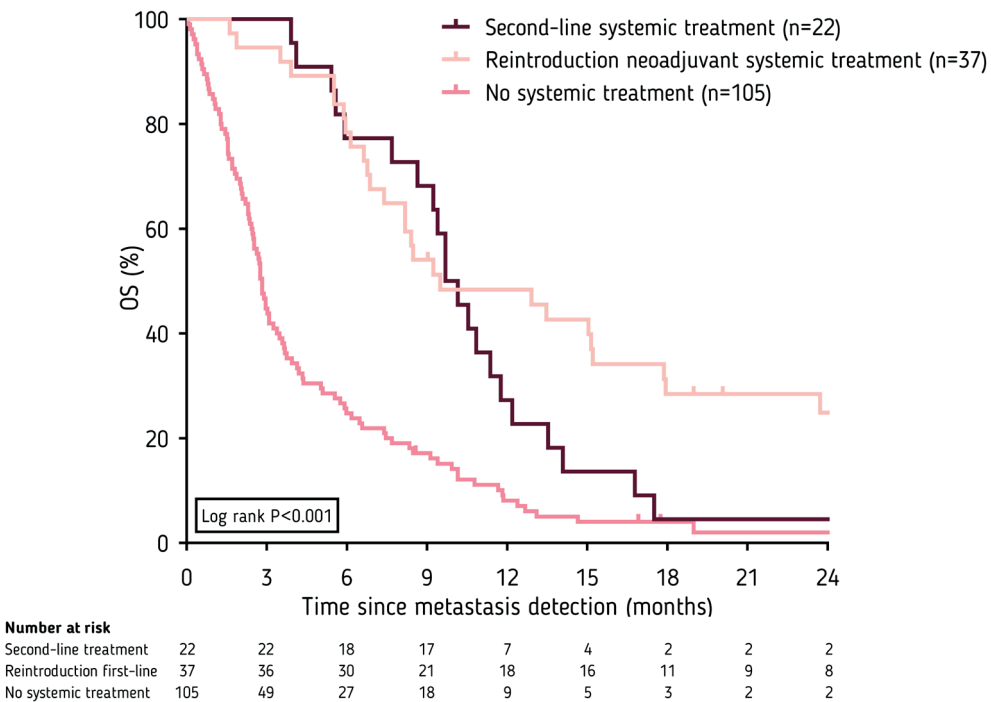
Palliative treatment

Fifty-three (32%) of 164 patients underwent a complete surgical resection of the primary tumor (Table 2). A total of 59 (36%) patients received palliative systemic treatment after

detection of interval metastasis. In 20 (34%) of these 59 patients, this was the same regimen which was administered as neoadjuvant treatment and in 17 (29%), a fluoropyrimidine with or without a platinum was administered (i.e. systemic agents that were administered as neoadjuvant treatment as well). In 22 (37%) of 59 patients, an agent of a drug group that was not used as neoadjuvant treatment was administered, which was regarded second-line treatment. Of these 22 patients, 12 received paclitaxel in combination with ramucirumab, 8 taxane monotherapy, 1 5-FU in combination with irinotecan (FOLFIRI), and one paclitaxel in combination with regorafenib. Radiotherapy to the primary tumor was applied in 13% of the patients, and to metastases in 2%. In 61 patients (37%) no treatment was allocated.

OS since detection of metastases
Median OS for all patients was 5.5 months (IQR 2.3-10.2) since detection of interval metastases. Both continuation of the systemic treatment regimen that was administered in the neoadjuvant setting (median OS since detection of metastases 9.5 months), and switch to second-line systemic treatment (median OS 9.9 months) were independently associated with improved OS compared to no systemic treatment (median OS 2.8 months; Figure 2).

Figure 2. Kaplan Meier curves showing OS for interval metastases patients stratified for type of treatment after detection of metastasis.

Number at risk								
Second-line treatment	22	22	18	17	7	4	2	2	2
Reintroduction first-line	37	36	30	21	18	16	11	9	8
No systemic treatment	105	49	27	18	9	5	3	2	2

Primary tumor resection includes both resection of primary tumor only and resection of the primary tumor with HIPEC or metastasectomy, not followed by systemic treatment. OS, overall survival.
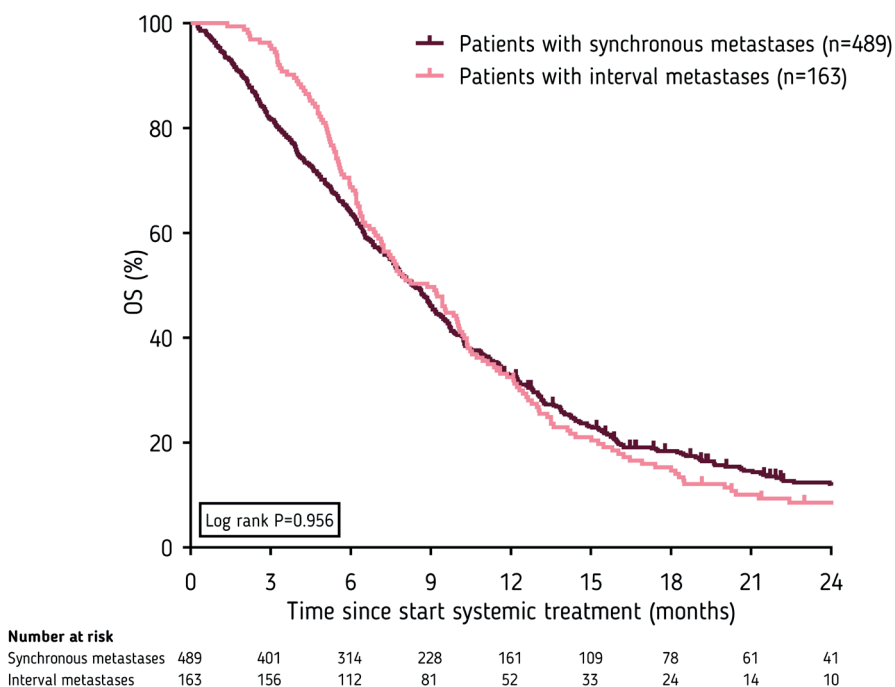
OS since start of treatment in patients with interval versus synchronous metastases

For the secondary aim, OS was compared with a propensity score matched cohort of patients with gastric or GEJ adenocarcinoma and synchronous metastases who received palliative systemic treatment. First, 163 patients with interval metastases (regardless of treatment) were matched to 489 synchronous metastatic patients (one interval metastases patient was excluded because less than three matches were found; Supplementary Table 2). Median OS since start of neoadjuvant treatment was 8.9 months (IQR 5.5, 13.4), compared to 8.3 months (IQR 4.0, 14.3) since start of first-line treatment in synchronous metastatic patients (P=0.956; Figure 3).

DISCUSSION

In our population-based study, interval metastases were observed in nearly one in ten gastric cancer patients who started with neoadjuvant treatment. Metastases were most frequently detected during surgery, and located in the peritoneum. Longer OS was observed in patients who received systemic treatment after interval metastasis detection compared to no

Figure 3. Kaplan Meier curves for overall survival in patients with interval metastases versus a matched cohort of patients with synchronous metastases who received palliative systemic treatment.

Overall survival was calculated since start of neoadjuvant treatment in patients with interval metastases, and first-line palliative systemic treatment in the matched cohort of patients with synchronous metastases. OS, overall survival.

treatment. OS of patients with interval metastases who received palliative systemic treatment - irrespective of subsequent treatment -, calculated since start of neoadjuvant treatment, did not differ from OS of patients with synchronous metastatic gastric cancer since start of palliative systemic treatment.

We observed that 9% of all patients who started neoadjuvant chemotherapy between 2015 and 2018 developed interval metastases. In the pivotal MAGIC-trial, 12% of 237 patients who started neoadjuvant chemotherapy did not undergo surgery for unknown reasons, but presumably interval metastases played an important role.[12] In the recent FLOT4-trial, 8% of the 705 patients who started neoadjuvant treatment did not have a surgical resection.[4] In a recent population-based study metastases were observed peroperatively in 4% of patients who received neoadjuvant FLOT.[15] Thus, our population-based results add to earlier findings that in a considerable number of gastric cancer patients metastases are detected soon after start of treatment with curative intent.

Initial staging in gastric cancer is routinely performed using gastroscopy and CT. However, sensitivity of CT to detect peritoneal and distant metastasis is low.[16, 17] In our study, the proportion of patients with interval metastases that were located in the peritoneum was 77%. This rate was higher in patients who did not have a diagnostic laparoscopy before neoadjuvant treatment compared to patients who did have a diagnostic laparoscopy, albeit a limited difference (80% versus 63%). This implies that although diagnostic laparoscopy can be helpful to exclude radiologically occult (peritoneal) metastases18 and is recommended in (inter)national guidelines, in particular in patients with a cT3-4a tumor,[1, 2] it cannot sufficiently rule out early peritoneal involvement. Improved staging techniques at initial diagnosis may enhance detection of metastases in an early stage and decrease the rate of interval metastases. Currently, the added value of FDG-PET/CT and diagnostic laparoscopy as initial staging in patients with cT3-T4 tumors is investigated in the PLASTIC study.[19] However, it is unlikely that FDG-PET/CT will aid in the detection of peritoneal metastases specifically.[16, 20] The implementation of novel methods such as the detection of mRNA in peritoneal lavage fluid[21, 22] could contribute to peritoneal metastases detection.

The median survival time calculated from start of neoadjuvant treatment of 8.9 months was comparable with OS of patients with synchronous metastases who received first-line palliative systemic treatment. These results implicate that interval metastases can be regarded as synchronous metastases in terms of OS, and suggest a similar response to systemic treatment. Importantly, patients diagnosed with synchronous peritoneal metastases are known to have a poor prognosis.[23] These are detected with imaging rather than laparoscopy and may therefore have a higher tumor load than in patients with interval peritoneal metastases detected at a later stage. These interval metastases patients with most likely limited peritoneal dissemination may have a more favorable tumor biology and may be particularly suitable for local peritoneal treatment with HIPEC.[24]

Improving the diagnosis of metastatic disease at initial staging could improve decision-making on systemic treatment strategies, and thereby improve patient outcomes. This has several reasons. First, although components of the neoadjuvant treatment are similar to first-line palliative systemic treatment, in contrast to the curative setting, doublet chemotherapy is preferred over triplet chemotherapy in the palliative setting because of similar survival rates, while doublets are less toxic. Furthermore, in neoadjuvant treatment,

HER2 is not taken into consideration, whereas the use of trastuzumab in first-line palliative treatment can improve patient outcomes in HER2 positive patients.[25, 26] Finally, the use of a taxane triplet as initial treatment (such as FLOT) could impair the use of a taxane in second line, which is currently recommended as second-line monotherapy or in combination with ramucirumab.[2]

Patients who received systemic treatment after detection of metastases showed better survival rates compared to no systemic treatment. Although these results clearly suggest that interval metastases patients may benefit from systemic treatment, the question remains what the optimal treatment strategy after detection of metastases is. Our results indicate that both continuing neoadjuvant treatment and switching to second-line systemic treatment seem beneficial, suggesting any of these systemic treatment strategies may improve outcomes in these patients. Interestingly, a remarkable number of patients (63%) did not receive systemic treatment after detection of metastases, despite they were considered eligible to undergo surgery at initial diagnosis. Future studies should focus on reasons for refraining from sequential treatment in these patients, which most probably will include patients' request or performance status, as these were most frequently reasons to refrain from gastrectomy.[27]

A limitation of this study includes missing data in the patients diagnosed in 2010-2014, e.g. on staging. Moreover, we could only analyze the proportion of patients with interval metastases in patients who were diagnosed in 2015-2018. In addition, data on performance status after neoadjuvant treatment or surgery was missing in all patients, and therefore we could not rule out a selection bias. Another limitation is that the study design was retrospective. Our analysis is strengthened by the inclusion of a large nationwide cohort.

In conclusion, interval metastases were observed in 9% of gastric cancer patients after start of neoadjuvant treatment in daily clinical practice, of which the majority was located in the peritoneum and detected during (exploratory) surgery. OS did not differ from synchronous metastatic gastric cancer patients treated with systemic therapy. Use of palliative systemic treatment after detection of metastases could be beneficial for these patients in terms of OS. Novel initial staging methods to detect metastases may improve decision-making on palliative treatment and survival outcomes in these patients.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Patient characteristics before start of neoadjuvant treatment in patients diagnosed in 2015-2018 who started neoadjuvant systemic treatment stratified for the presence of interval metastases.

	Patients without interval metastases (n = 1,202) No. (%)	Patients with interval metastases (n = 114) No. (%)	P value
Female	404 (34%)	47 (41%)	0.102[a]
Age, years, median (IQR)	67 (59, 73)	67 (58, 73)	0.944[b]
<60	321 (27%)	30 (26%)	0.819[a]
60-69	400 (33%)	42 (37%)	
70-79	446 (37%)	38 (33%)	
≥80	35 (3%)	4 (4%)	

Performance status			0.187[a]
0 or 1	881 (73%)	83 (73%)	
2	44 (4%)	8 (7%)	
Unknown	277 (23%)	23 (20%)	
Number of comorbidities			0.642[a]
0	354 (29%)	33 (29%)	
1	175 (15%)	13 (11%)	
≥2	115 (10%)	9 (8%)	
Unknown	354 (29%)	33 (29%)	
Tumor location			0.238[a]
Gastro-esophageal junction or cardia	308 (26%)	35 (31%)	
Stomach	894 (74%)	79 (69%)	
Clinical tumor stage			0.018[a]
1-2	429 (36%)	39 (34%)	
3	522 (43%)	50 (44%)	
4a	59 (5%)	13 (11%)	
X	192 (16%)	12 (11%)	
Clinical nodal stage			0.011[a]
0	653 (54%)	47 (41%)	
1	325 (27%)	32 (28%)	
2-3	195 (16%)	30 (26%)	
X	29 (2%)	5 (4%)	
Lauren classification			0.010[a]
Intestinal	542 (45%)	32 (28%)	
Diffuse	410 (34%)	49 (43%)	
Mixed	52 (4%)	6 (5%)	
Indeterminate	14 (1%)	1 (1%)	
Unknown	184 (15%)	26 (23%)	
Signet ring cell histology	184 (15%)	18 (16%)	0.892[a]
Differentiation grade			0.017[a]
Good	23 (2%)	4 (4%)	
Moderate	302 (25%)	15 (13%)	
Poor	738 (61%)	76 (67%)	
Unknown	139 (12%)	19 (17%)	

[a] *Chi square test,* [b] *Mann-Whitney U test. IQR, interquartile range.*

Supplementary Table 2. Matching variables in patients with synchronous metastases who received first-line palliative systemic treatment and patients with interval metastases.

	Patients with synchronous metastases (n = 489) No. (%)	Patients with interval metastases (n = 163) No. (%)	SMD
Female	188 (38%)	65 (40%)	0.029
Age, years, median (IQR)	66 (58, 72)	66 (58, 72)	-0.009
Performance status			0.000
0 or 1	338 (69%)	113 (69%)	
≥2	25 (5%)	8 (5%)	
Unknown	126 (26%)	42 (26%)	
Number of comorbidities			0.108
0	282 (58%)	93 (57%)	
1	133 (27%)	45 (28%)	
≥2	41 (8%)	16 (10%)	
Unknown	33 (7%)	9 (6%)	
Tumor location			0.031
Gastro-esophageal junction or cardia	148 (30%)	47 (29%)	
Stomach	341 (70%)	116 (71%)	
cT stage			0.023
1-2	147 (30%)	50 (31%)	
3-4	271 (55%)	88 (54%)	
X	71 (15%)	25 (15%)	

cN stage			0.069
0-1	323 (66%)	113 (69%)	
2-3	135 (28%)	41 (25%)	
X	31 (9%)	9 (6%)	
Lauren classification			0.124
Intestinal	142 (29%)	46 (28%)	
Diffuse	224 (46%)	74 (45%)	
Mixed	26 (5%)	7 (4%)	
Indeterminate	16 (3%)	4 (2%)	
Unknown	81 (20%)	32 (20%)	
Number of metastatic locations			0.038
1	452 (92%)	149 (91%)	
≥2	37 (8%)	14 (9%)	
Period of diagnosis			0.038
2010-2014	145 (30%)	50 (31%)	
2015-2018	344 (70%)	113 (69%)	

Patients were matched for the following variables: sex, age, performance status, number of comorbidities, primary tumor location, cT stage, cN stage, Lauren classification, number of metastatic locations, and year of diagnosis.
IQR, interquartile range; SMD, standardized mean difference.

Ethical approval

According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper GI Cancer Group. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[28]

Conflicts of interest

Rob Verhoeven reports grants from BMS and Roche. Nadia Haj Mohammad reports a consult/advisory role for BMS, MSD Servier, Eli Lilly, reserach grant from Servier. Suzanne Gisbertz reports a research grant from Olympus and consulting fees from Medtronic. Martijn van Oijen reports grants from Amgen, BMS, Lilly, Nordic, Merck, Roche and Servier. Hanneke van Laarhoven reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

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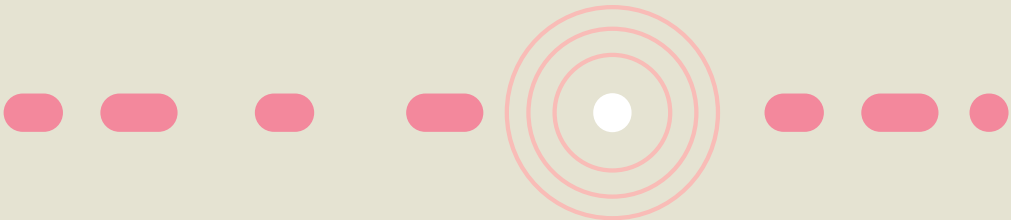
Management and outcomes of gastric cancer patients with interval distant metastases in clinical practice

Annals of Thoracic Surgery, 2021.

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ABSTRACT

Background: Esophageal cancer patients develop distant metastases between start of neoadjuvant chemoradiotherapy (nCRT) and planned surgery, so-called interval metastases. The primary aim was to assess management, overall survival (OS), and prognostic factors for OS in these patients. A secondary aim was to compare OS with synchronous metastatic patients.

Methods: Esophageal cancer patients with interval distant metastases were identified from the Netherlands Cancer Registry (2010-2017). Management was categorized into metastasis-directed therapy (MDT), primary tumor resection or best supportive care (BSC). The OS was calculated from the diagnosis of the primary tumor. Prognostic factors affecting OS were studied using Cox proportional hazard models. Propensity score-matching (1:3) generated matched cases with synchronous distant metastases.

Results: 208 patients with interval metastases were identified of whom in 87 patients (42%) MDT was initiated, in 10% primary tumor resection only, in 7% primary tumor resection plus MDT and 41% BSC. Median OS was 10.0 months (IQR 8.6-11.1). Compared to BSC, superior OS was independently associated with MDT (hazard ratio 0.36, 95% confidence interval 0.26-0.49), primary tumor resection (hazard ratio 0.55, 95% confidence interval 0.33-0.94) and primary tumor resection plus MDT (hazard ratio 0.20, 95% confidence interval 0.10-0.38). Worse OS was independently associated with signet ring cell carcinoma (hazard ratio 1.92, 95% confidence interval 1.12-3.28) and poor differentiation grade (hazard ratio 1.96, 95% CI: 1.35-2.83). The OS was comparable between matched patients with interval and synchronous distant metastases (10.2 versus 9.4 months, P=0.760).

Conclusion: In esophageal cancer patients treated with nCRT with interval distant metastases the OS was poor and comparable to synchronous metastatic patients.

INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is currently considered an important multimodality treatment option in patients with locally advanced esophageal or gastroesophageal junction cancer.[1-5] Perioperative chemotherapy is an alternative multimodality treatment option in locally-advanced gastroesophageal junction adenocarcinoma.[1,5–8] The overall survival (OS) of patients with locally-advanced esophageal or gastroesophageal junction cancer treated with nCRT followed by surgery remains relatively poor with an estimated 5-year OS rate of 40-50%, predominantly due to distant recurrences.[4,9]

Distant metastases may also appear at initial presentation (i.e. synchronous metastases) or between start of nCRT and planned surgery, so-called interval metastases.[10] These distant metastases are labeled as interval distant metastases because they were not recognized during initial staging and were detected before completion of treatment with curative intent.[10,11] Restaging with ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computerized tomography (^{18}F-FDG PET/CT) imaging after nCRT – before surgery – detects interval distant metastases in approximately 8% of esophageal cancer patients.[10,12–14] Since evidence is scarce, the efficacy of different treatment strategies and prognostic factors

for OS in patients with interval distant metastases are unknown. In addition, specific knowledge of the OS in comparison to patients with synchronous distant metastases is lacking. Therefore, the primary aims of this population-based cohort study was to assess management, OS, and prognostic factors for OS of patients with interval distant metastases. A secondary aim was to compare the OS with a matched group of patients with synchronous distant metastases.

METHODS

Study design and population
This population-based cohort study included patients with interval distant metastases registered in the Netherlands Cancer Registry (NCR) between 2015-2017. The NCR captures new cancer incidences among all 17.4 million residents in the Netherlands. In addition, because the NCR did not routinely record interval distant metastases between 2010-2014, for this specific research question additional data were collected by the NCR from a subset of 43 (of 80) Dutch hospitals. This subset can be considered a representative sample 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.[15] Vital status is obtained through annual linkage with the municipal population registers, and was last updated on the first of February 2019. This study did not need approval by an institutional review board in the Netherlands according to the Central Committee on Research involving Human Subjects. This study was reported in accordance with the STROBE statement.[16]

Patient inclusion
Patients with newly diagnosed, locally-advanced (i.e. according to TNM 7th edition[17] cT1-4a, cN0-3, cM0) cancer of the thoracic esophagus or gastroesophageal junction (i.e. according to ICD-O version 3[18] C15.3-15.5, C15.9 and C16.0) who received nCRT prior to an planned esophagectomy or gastrectomy were eligible for inclusion. Interval distant metastases were defined as distant metastases detected between 3 days after start of nCRT and 120 days after completion of nCRT or detected during planned surgery. Distant metastases detected >120 days after completion of nCRT were not considered interval metastases because this was considered an unusually long waiting time between completion of nCRT and elective surgery (median 56 days in the Netherlands).[19] Patients who received nCRT other than the CROSS protocol[3] or who had received prior systemic therapy for the same tumor were excluded. Finally, patients with a clinical complete response after CRT with an intentional wait-and-see strategy were excluded (because distant metastases in this group were considered as recurrent disease rather than interval metastases).

Staging
The Dutch national esophageal cancer guideline recommended routine baseline staging with ^{18}F-FDG PET/CT since 2014.[20] Before 2014, guidelines recommended baseline staging with CT only. Although restaging after nCRT has not been part of the Dutch guideline, many

institutions performed restaging as standard of care with either CT or ^{18}F-FDG PET/CT.

Variables

Data extracted from the NCR were patient characteristics including age, sex, year of diagnosis of the primary tumor, baseline WHO performance score, and number of comorbidities. Disease characteristics including histology, location, clinical stage and differentiation grade. Characteristics on interval metastases including the location and number of locations affected, the method of confirmation of distant metastases, as well as the time interval between start of nCRT and the detection of distant metastases. The pattern of dissemination was categorized into hematogenous to a single organ or location only (e.g. lung or bone), peritoneum, extra-regional lymph node, non-specified single location, or multiple locations.

Management and outcomes

Management was categorized into metastasis-directed therapy (MDT, including systemic therapy, radiation therapy directed at metastasis, or metastasectomy), primary tumor resection, primary tumor resection plus MDT or best supportive care (BSC). The OS was defined as the time interval between moment of the detection of the primary tumor and death or last follow-up.

Statistical analysis

Uni- and multivariable Cox proportional hazard models were used to identify prognostic factors (independently) associated with OS and were expressed using hazard ratios (HRs) with 95% confidence intervals (CIs). For multivariable analysis, prognostic factors with a p-value <0.25 in univariable analysis were entered in a model, and subsequent backward stepwise elimination based on the Akaike Information Criterion was performed.[21] Kaplan-Meier curves were constructed of statistically significant prognostic factors in multivariable analysis.

For the secondary aim, patients with synchronous distant metastases from esophageal or gastroesophageal junction cancer were identified from the NCR (2010-2017) and nearest neighbor (1:3) propensity score-matching was performed to generate matched cases of the interval distant metastases cohort. A propensity score was generated using logistic regression, based on the covariates age, gender, year of diagnosis, location of primary tumor, histology, differentiation grade, clinical T- and N-stage, and number of locations with distant metastases. Propensity score-matching was stratified for patients who received BSC and MDT. The within-pair difference was minimized by setting a caliper of 0.1 of the standard deviation of the logit of the propensity score. Fisher's exact test and Kaplan-Meier curves with log-rank tests were used to compare management and OS differences among the two groups. All statistical analyses were performed using R version 3.5.1 using packages 'survival' and 'ggplot2'. A p-value of <0.05 was considered statically significant.

RESULTS

Patient inclusion

A total of 235 patients were eligible for inclusion (Figure 1). Subsequently, 19 patients were excluded because nCRT other than the CROSS-regimen was used, 7 because distant

metastases were detected during an intentional wait-and-see strategy, and 1 patient had received prior systemic therapy for the same tumor. Consequently, 208 patients with interval distant metastases were included (7% of all patients who underwent nCRT).

Patient characteristics
Patients had a median age of 66 years (interquartile range [IQR] 59-71), 82% were male, and 82% had a baseline WHO performance score of 0-1 (Table 1). The primary tumor was predominantly an adenocarcinoma (86%), located in the lower third of the thoracic esophagus (77%). The majority of patients were initially staged with cT3 (70%) and cN1 (39%) disease. Staging modalities included besides a baseline PET/CT in 100% an endoscopy, in 59.4% an endoscopic ultrasound (EUS), and in 7.5% a diagnostic laparoscopy. A total of 31 patients did not complete the entire CROSS protocol (patients prematurely stopped with chemotherapy (19), radiotherapy (4), or both (8)).

Figure 1. Patient selection.
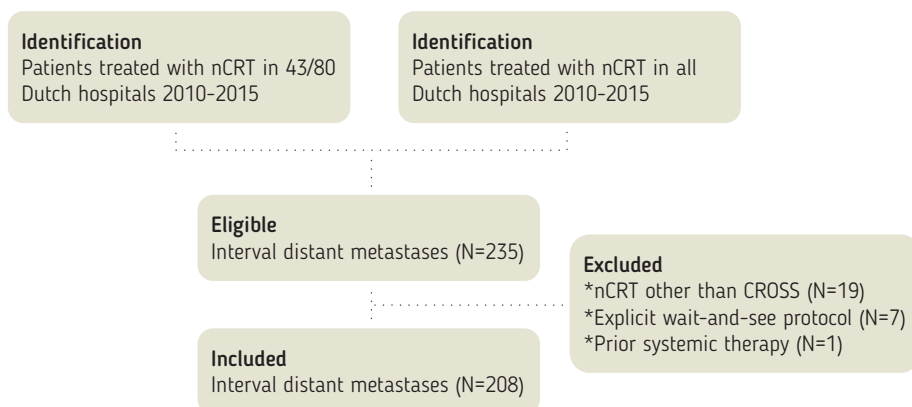
Table 1. Baseline characteristics of patients with interval distant metastases.

Characteristics	Patients (n = 208)
Median age [IQR]	66 [59-71]
Sex, No. (%)	
Male	171 (82.2)
Female	37 (17.8)
Baseline performance score, No. (%)	
WHO 0	87 (41.8)
WHO 1	85 (40.9)
WHO 2	6 (2.9)
Missing	30 (14.4)
Year of diagnosis primary tumor, No. (%)	
2010-2014	48 (23.1)
2015	43 (20.7)
2016	58 (27.9)
2017	59 (28.4)
Location of primary tumor, No. (%)	
Superior or mid third thoracic esophagus	16 (7.7)
Lower third thoracic esophagus	161 (77.4)

Gastroesophageal junction	25 (12.0)
Thoracic esophagus not specified	6 (2.9)
Clinical tumor stage, No. (%)	
cT1	1 (0.5)
cT2	49 (23.6)
cT3	146 (70.2)
cT4	7 (3.4)
Not specified	5 (2.4)
Clinical nodal stage, No. (%)	
cN0	53 (25.5)
cN1	82 (39.4)
cN2	57 (27.4)
cN3	16 (7.7)
Histology, No. (%)	
Adenocarcinoma	178 (85.6)
Squamous cell carcinoma	30 (14.4)
Signet ring cell carcinoma, No. (%)	
No	191 (91.8)
Yes	17 (8.2)
Differentiation grade, No. (%)	
Well/moderate	63 (30.3)
Poor	80 (38.5)
Not specified	65 (31.2)

IQR = interquartile range; WHO = World Health Organization.

Characteristics of interval distant metastases

The median time interval between detection of the primary tumor and detection of the first distant metastasis was 18 weeks (IQR 16-21) and the time interval between start of nCRT and the detection of the first interval distant metastasis was 12 weeks (IQR 10-14). In 98% metastases were detected after nCRT. The method of 13 confirmation of metastases was pathology (i.e. histology or cytology) in 63% of cases. Dissemination was 38% hematogenous to one organ or location, 22% peritoneal, 12% extra-regional lymph node, or 5% to a single non-specified location, and 24% to multiple locations (Table 2).

Table 2. Characteristics of interval distant metastases.

| Characteristics	n = 208
Detection of interval distant metastases	
Median number of weeks after diagnosis of the primary tumor [IQR]	18 [16-21]
Median number of weeks after start of nCRT [IQR]	12 [10-14]
During surgery, No. (%)	80 (38.4)
Pattern of dissemination, No. (%)	
Single hematogenous location only	79 (38.0)
Liver	39 (18.8)
Bone	17 (8.2)
Lung	8 (3.9)
Soft tissue	5 (2.4)
Brain	3 (1.4)
Other hematogenous location	7 (3.3)
Peritoneum only	45 (21.6)
Extra-regional lymph node only	25 (12.0)
Head and neck only	10 (4.8)

Intra-abdominal only	9 (4.3)
Other extra-regional lymph node	6 (2.9)
Single non-specified location	10 (4.8)
Multiple locations	49 (23.6)
Method of confirmation, No. (%)	
Pathology	132 (63.5)
Histology	113 (54.3)
Cytology	19 (9.1)
No pathology	76 (36.5)
Intraoperatively detected without pathology	3 (1.4)
Clinical diagnostic studies	52 (25.0)
Not specified	21 (10.1)

nCRT, neoadjuvant chemoradiotherapy; IQR, interquartile range.

Management of interval distant metastases

In 87 patients (42%) MDT was initiated, 10% primary tumor resection only, 7% primary tumor resection plus MDT and in 41% BSC (Table 3). The 'MDT' group consisted of patients who underwent systemic therapy (30%), radiation therapy (7%), chemoradiation therapy (4%), metastasectomy (1%), and metastasectomy plus radiation therapy (1%). In 38% (80/208) metastases were detected during surgery of whom in 44% (35/80) surgeons proceeded with resection of the primary tumor of whom after surgery in 43% (15/35) MDT was applied (i.e. 'primary tumor resection plus MDT') and in 57% (20/35) after surgery BSC was applied (i.e. 'primary tumor resection only'). The 'primary tumor resection plus MDT' group consisted of patients who underwent primary tumor resection plus metastasectomy (2%), systemic therapy (1%), metastasectomy and radiation therapy (1%), radiation therapy (1%), or chemoradiation therapy (1%). Supplementary Table 1 demonstrates the baseline characteristics stratified on the type of management, showing significant differences between the groups with regard to age, performance status, cT-stage and location of metastases.

Figure 2. Management of patients with interval and synchronous distant metastases.

CH 06.
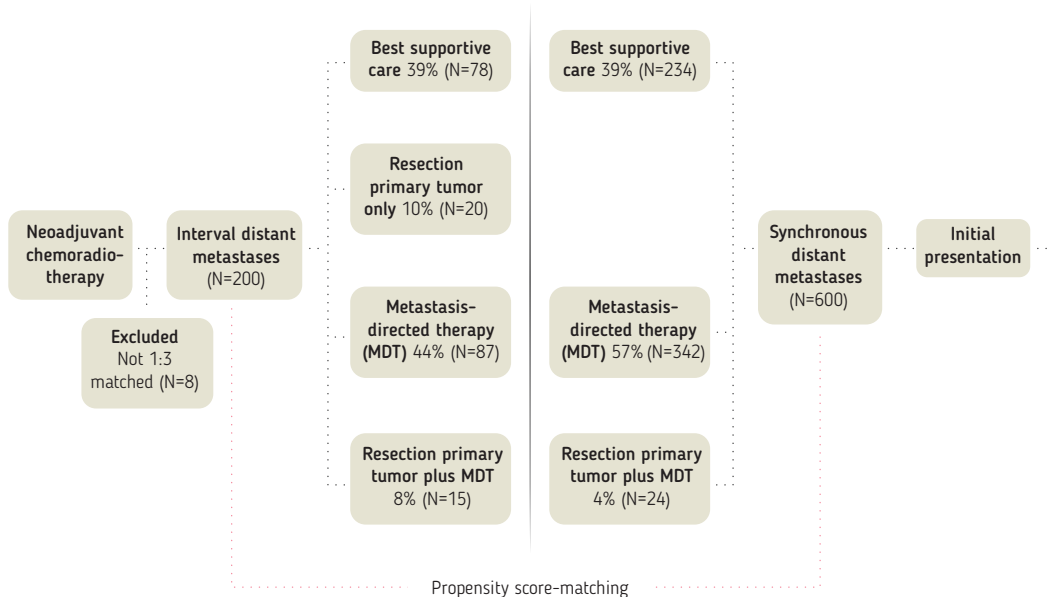
OS and prognostic factors for OS of interval distant metastases

The median follow-up time was 10.1 months (range 1-50). Median follow-up time for survivors was 17.7 months (IQR 15.8-22.6). Median OS after the diagnosis of the primary tumor in patients with interval distant metastasis was 10.0 months (IQR 14 8.6-11.1). In comparison to BSC superior OS was independently associated with either MDT (HR 0.36, 95% CI: 0.26-0.49), primary tumor resection (HR 0.55, 95% CI: 0.33- 0.94) and primary tumor resection plus MDT (HR 0.20, 95% CI: 0.10-0.38; Figure 3A). Worse OS was independently associated with a signet ring cell carcinoma (HR 1.92, 95% CI: 1.12-3.28, Figure 3B; p<0.001) and poor differentiation grade (HR 1.96, 95% CI:1.35-2.83, Figure 3C; p=0.002; Table 4). Sensitivity analysis demonstrated no difference in OS in 176 patients who completed the entire nCRT treatment as compared with 31 patients who did not complete the entire nCRT treatment (p=0.400). The OS after the moment of detection of interval distant metastases was 5.3 months (IQR: 2.4-10.5).

Table 3. Management of patients with interval distant metastases.

Management category	n = 208
Metastasis-directed therapy (MDT), No. (%)	87 (41.8)
Systemic therapy	62 (29.8)
Radiation therapy	15 (7.2)
Chemoradiation therapy	8 (3.8)
Metastasectomy	2 (1.0)
Metastasectomy and radiation therapy	1 (0.5)
Primary tumor resection only	20 (9.6)
Primary tumor resection plus MDT, No. (%)	15 (7.2)
Resection plus metastasectomy	5 (2.4)
Resection plus systemic therapy	3 (1.4)
Resection plus metastasectomy and radiation therapy	3 (1.4)
Resection plus radiation therapy	2 (1.0)
Resection plus chemoradiation therapy	2 (1.0)
Best supportive care, No. (%)	86 (41.3)

Management and OS in comparison to patients with synchronous distant metastases

Propensity score-matching among 200 patients with interval distant metastases resulted in a matched cohort of 600 patients with synchronous distant metastases (Figure 2 and Supplementary Table 2). Median OS after the diagnosis of the primary tumor in 200 patients with interval distant metastases was comparable with 600 patients with synchronous distant metastases (10.2 versus 9.4 months, Figure 4; p=0.760).

Table 4. Results Cox proportional hazard model analysis for overall survival in patients with interval distant metastases.

Characteristics	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age*	1.00 (0.98-1.02)	0.734		
Sex				
Male	Ref			
Female	1.21 (0.82-1.75)	0.332		
Baseline performance score				
WHO 0	Ref			
WHO 1-2	1.06 (0.78-1.44)	0.669		
Missing	1.20 (0.77-1.86)	0.418		
Number of comorbidities*	1.01 (0.89-1.13)	0.880		
Clinical tumor stage				
cT1-cT2	Ref			
cT3-cT4	1.10 (0.78-1.54)	0.583		
Missing	1.54 (0.60-3.89)	0.363		
Clinical nodal stage				
cN0	Ref		Ref	
cN1	1.09 (0.76-1.57)	0.632	1.06 (0.72-1.57)	0.772
cN2-cN3	1.37 (0.94-1.98)	0.092	1.49 (0.99-2.22)	0.053
Year of diagnosis primary tumor*	1.02 (0.94-1.10)	0.589		
Location primary tumor				
Superior or mid third esophagus	Ref			
Lower third esophagus	0.69 (0.41-1.16)	0.160		
Gastroesophageal junction	0.53 (0.28-1.01)	0.057		
Esophagus not specified	0.59 (0.21-1.61)	0.303		
Signet ring cell carcinoma				
No	Ref		Ref	
Yes	2.37 (1.41-4.00)	<.001	1.92 (1.12-3.28)	**0.017**
Histology				
Adenocarcinoma	Ref			
Squamous cell carcinoma	1.15 (0.78-1.74)	0.456		
Differentiation grade				
Well/moderate	Ref		Ref	
Poor	1.84 (1.30-2.61)	0.001	1.96 (1.35-2.83)	**<0.001**
Not specified	1.35 (0.92-1.95)	0.115	1.29 (0.88-1.91)	0.194
Type of dissemination				
Single hematogenous location	Ref			
Peritoneum only	1.10 (0.75-1.62)	0.611		
Extra-regional lymph node only	1.02 (0.64-1.64)	0.916		
Non-specified single location	0.92 (0.48-1.79)	0.813		
Multiple locations	1.03 (0.71-1.50)	0.869		
Management				
Best supportive care	Ref		Ref	
Metastasis-directed therapy (MDT)	0.37 (0.27-0.50)	<0.001	0.36 (0.26-0.49)	**<0.001**
Resection of the primary tumor only	0.51 (0.32-0.85)	0.009	0.55 (0.33-0.94)	**0.027**
Resection primary tumor plus MDT	0.22 (0.11-0.45)	<0.001	0.20 (0.10-0.38)	**<0.001**
Method of confirmation				
No pathology	Ref			
Pathology (i.e. histology or cytology)	0.80 (0.57-1.10)	0.169		
Not specified	1.04 (0.63-1.73)	0.872		

*HR, hazard ratio; CI, confidence interval; * analyzed as a continuous variable.*

Figure 3. (A) Overall survival stratified by management: best supportive care (BSC [red line]) ; primary tumor resection (green line); metastasisdirected therapy (MDT [blue line]); or primary tumor resection plus MDT (purple line).
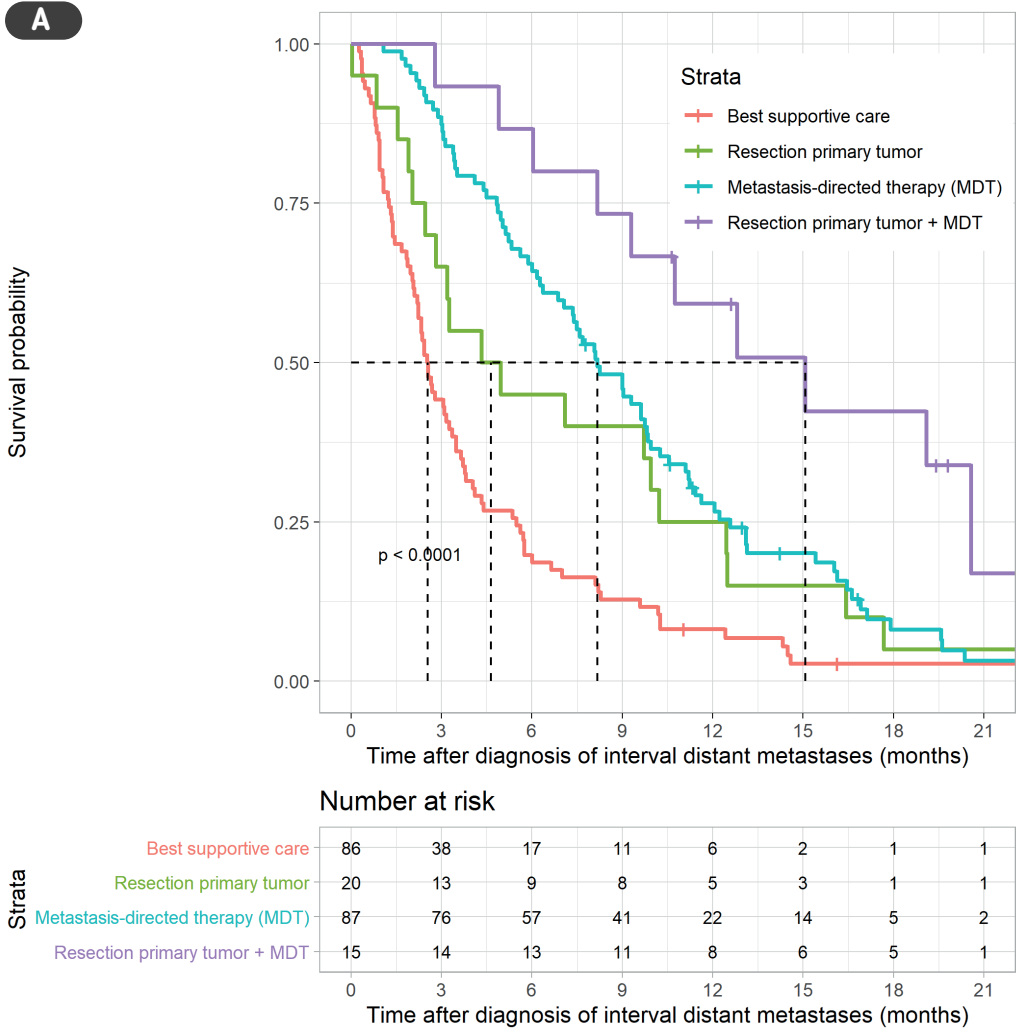
(B) Overall survival stratified by signet ring cell carcinoma (blue line) or no signet ring cell carcinoma (orange line).
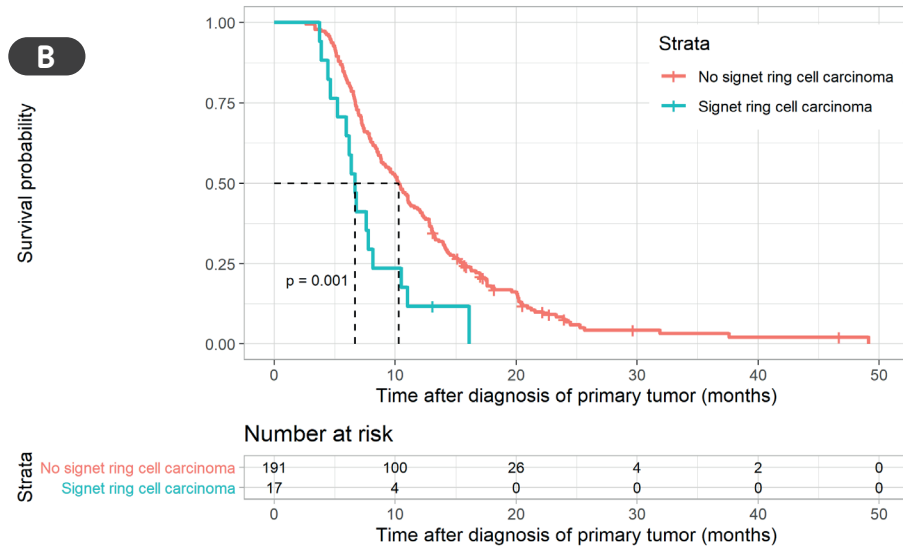
(C) Overall survival stratified on differentiation grade: well/moderate (orange line); poor (green line); or missing (blue line).
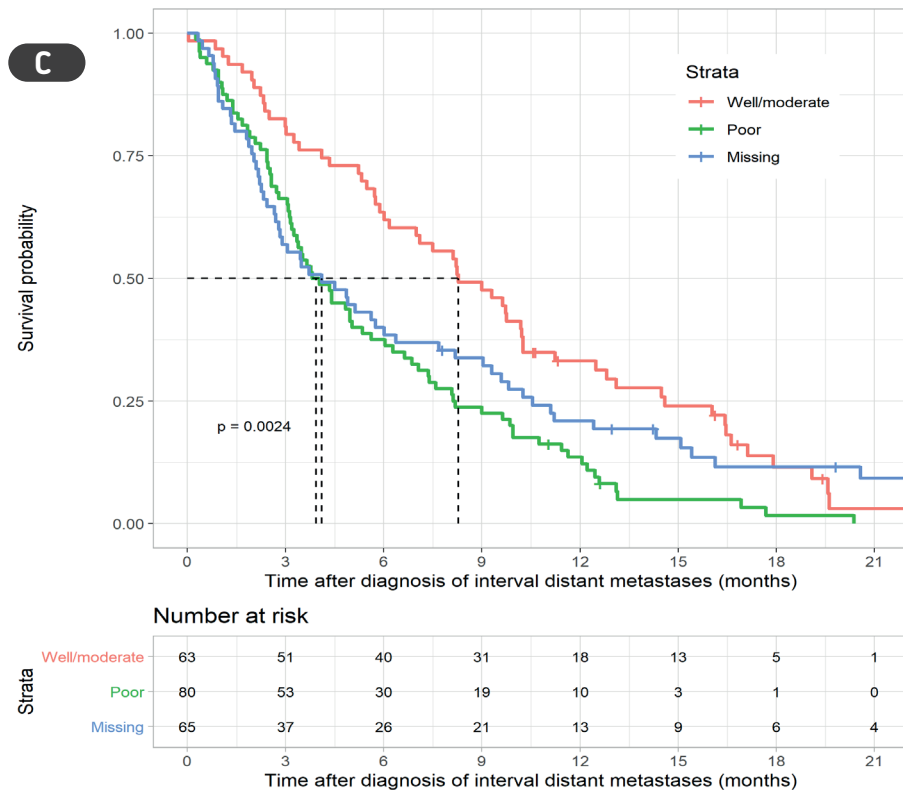
Figure 4. Overall survival after interval metastases (interval M1 [orange line]) and synchronous distant metastases (synchronous M1 [green line]).
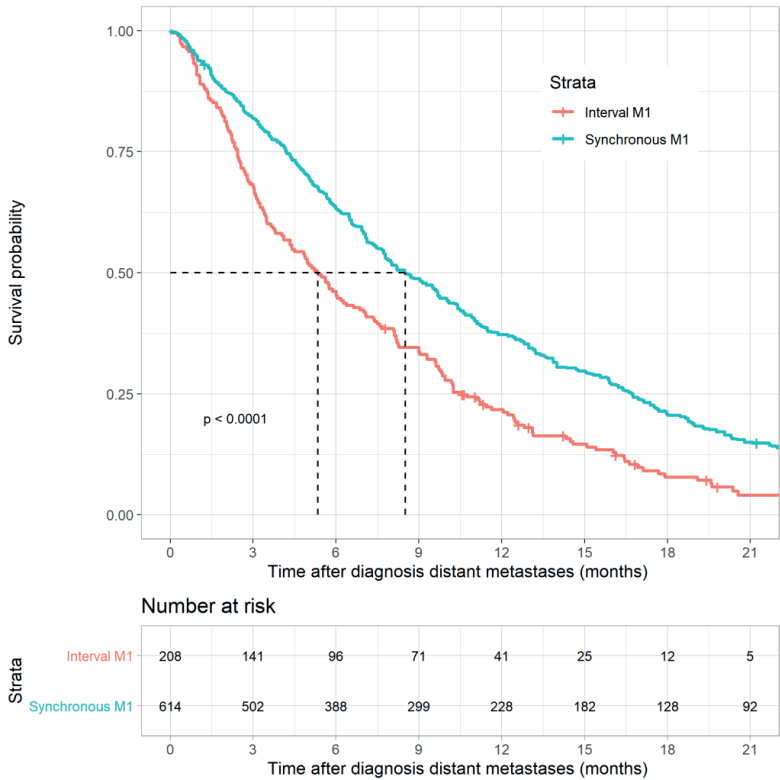
DISCUSSION

This study shows that 7% of esophageal or gastroesophageal junction cancer patients who underwent nCRT according to the CROSS protocol develop interval distant metastases. The OS after the diagnosis of the primary tumor was 10.0 months. Independent prognostic factors for worse OS were signet ring cell carcinoma, poor differentiation grade, and lack of management in which metastases were treated. Median OS after the diagnosis of the primary tumor in patients with interval distant metastases was comparable with matched patients with synchronous distant metastases (p=0.760).

The median OS of 200 interval metastatic patients (10.2 months) was comparable to 600 matched synchronous metastatic patients (9.4 months) and with previously reported OS rates of synchronous metastatic patients in either real world populations (6-8 months[15,22]) or clinical trials populations (11 months).[23] This comparable OS suggest that in patients with interval distant metastases, microscopic progression (undetectable with baseline staging) may already have occurred at the time of diagnosis of the primary tumor. Because all patients with interval distant metastases underwent baseline PET/CT imaging and in 8% diagnostic

laparoscopy, we think this does not reflect inaccurate baseline staging but rather microscopic tumor progression (undetectable with baseline staging). In addition, the incidence of interval distant metastases after nCRT in this study (7%) was comparable with a meta-analysis on the detection of interval distant metastases in esophageal cancer patients who underwent neoadjuvant therapy and baseline and restaging PET/CT (8%).[12]

This study shows great heterogeneity in the type of management of patients with interval distant metastases. Up to 12 different types of management were initiated. Generally, OS was poor and physicians should reserve radical treatment for very carefully selected patients. In selective cases, primary tumor resection plus MDT was associated with an improved OS, possibly explained by an oligometastatic disease state.[24] Finally, restaging might be able to impact on treatment decision-making and OS by earlier detection of distant metastases and thus earlier application of systemic treatment.[13]

Strengths of this study include the generalizability of the study cohort. In this study, patients were included who underwent nCRT according to the CROSS protocol only. Other strengths include data registration by specifically trained personnel and the prospectively maintained vital status due to annual linkage with the municipal population registers. Finally, to the best of our knowledge this study describes the largest population of esophageal or gastroesophageal junction cancer patients with interval distant metastases.

There are certain limitations that apply to this study that warrant caution for the interpretation of results. Firstly, selection bias may have resulted in a potential overestimation of the effect of metastasis-directed therapy on OS. Secondly, because the NCR did not record the number of metastases per metastasis location, the impact of this potential prognostic factor on OS could not be assessed. Thirdly, because the NCR did not record the radiation dosage per fraction and the number of fractions, this study was not able to discriminate between SBRT and palliative radiation therapy which may have resulted in an underestimation of the effect of MDT on OS. Fourthly, because NCR did not record the performance status after nCRT we were not able to use performance status as a matching variable in the propensity score matching. Finally, for some patients the first modality of treatment may have been registered only due to registration practices. Therefore, this study may represent an underestimation of the complete (multimodality) treatment strategy.

In conclusion, esophageal or gastroesophageal junction cancer patients with interval distant metastases after nCRT have a poor prognosis with a median overall survival of 10.0 months after the diagnosis of the primary tumor. In comparison to 600 matched patients with synchronous distant metastases, patients with interval distant metastases had comparable overall survival from the moment of diagnosis of the primary tumor.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Patient characteristics stratified for type of management.

	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age[1]	1.00 (0.98-1.02)	0.734		
Sex				
Male	Ref			
Female	1.21 (0.82-1.75)	0.332		
Baseline performance score				
WHO 0	Ref			
WHO 1-2	1.06 (0.78-1.44)	0.669		
Missing	1.20 (0.77-1.86)	0.418		
Number of comorbidities[1]	1.01 (0.89-1.13)	0.880		
Clinical tumor stage				
cT1-cT2	Ref			
cT3-cT4	1.10 (0.78-1.54)	0.583		
Missing	1.54 (0.60-3.89)	0.363		
Clinical nodal stage				
cN0	Ref		Ref	
cN1	1.09 (0.76-1.57)	0.632	1.06 (0.72-1.57)	0.772
cN2-cN3	1.37 (0.94-1.98)	0.092	1.49 (0.99-2.22)	0.053
Year of diagnosis primary tumor[1]	1.02 (0.94-1.10)	0.589		
Location primary tumor				
Superior or mid third esophagus	Ref			
Lower third esophagus	0.69 (0.41-1.16)	0.160		
Gastroesophageal junction	0.53 (0.28-1.01)	0.057		
Esophagus not specified	0.59 (0.21-1.61)	0.303		
Signet ring cell carcinoma				
No	Ref		Ref	
Yes	2.37 (1.41-4.00)	<.001	1.92 (1.12-3.28)	**0.017**
Histology				
Adenocarcinoma	Ref			
Squamous cell carcinoma	1.15 (0.78-1.74)	0.456		
Differentiation grade				
Well/moderate	Ref		Ref	
Poor	1.84 (1.30-2.61)	0.001	1.96 (1.35-2.83)	**<0.001**
Not specified	1.35 (0.92-1.95)	0.115	1.29 (0.88-1.91)	0.194
Type of dissemination				
Single hematogenous location	Ref			
Peritoneum only	1.10 (0.75-1.62)	0.611		
Extra-regional lymph node only	1.02 (0.64-1.64)	0.916		
Non-specified single location	0.92 (0.48-1.79)	0.813		
Multiple locations	1.03 (0.71-1.50)	0.869		
Management				
Best supportive care	Ref		Ref	
Metastasis-directed therapy (MDT)	0.37 (0.27-0.50)	<0.001	0.36 (0.26-0.49)	**<0.001**
Resection of the primary tumor only	0.51 (0.32-0.85)	0.009	0.55 (0.33-0.94)	**0.027**
Resection primary tumor plus MDT	0.22 (0.11-0.45)	<0.001	0.20 (0.10-0.38)	**<0.001**
Method of confirmation				
No pathology	Ref			
Pathology (i.e. histology or cytology)	0.80 (0.57-1.10)	0.169		
Not specified	1.04 (0.63-1.73)	0.872		

MDT, metastasis-directed therapy; BSC, best supportive care.

Supplementary table 2. Characteristic synchronous and interval metastases.

Characteristics	Interval distant metastases (n = 208) No. (%)	Synchronous distant metastases (n = 605) No. (%)
Median age	66	64
Sex		
Male	37 (17.8%)	115 (19.0%)
Female	171 (82.2%)	490 (81.0%)
Baseline performance score		
WHO 0-1	174 (83.7%)	506 (83.6%)
WHO 2-4	4 (1.9%)	5 (0.8%)
Missing	30 (14.4%)	94 (15.5%)
Year of diagnosis primary tumor		
2010-2014	48 (23.1%)	146 (24.1%)
2015	43 (20.7%)	132 (21.8%)
2016	58 (27.9%)	155 (25.6%)
2017	59 (28.4%)	172 (28.4%)
Location of primary tumor		
Superior or mid third thoracic esophagus	16 (7.7%)	57 (9.4%)
Lower third thoracic esophagus	161 (77.4%)	453 (74.9%)
Gastroesophageal junction	25 (12.0%)	81 (13.4%)
Thoracic esophagus not specified	6 (2.9%)	14 (2.3%)
Clinical tumor stage		
cT1	2 (1.0%)	4 (0.7%)
cT2	49 (23.6%)	152 (25.1%)
cT3	146 (70.2%)	417 (68.9%)
cT4	7 (3.4%)	25 (4.1%)
Not specified	4 (1.9%)	7 (1.2%)
Clinical nodal stage		
cN0	53 (25.5%)	132 (21.8%)
cN1	82 (39.4%)	236 (39.0%)
cN2	57 (27.4%)	194 (32.1%)
cN3	16 (7.7%)	43 (7.1%)
Histology		
Adenocarcinoma	178 (85.6%)	516 (85.3%)
Squamous cell carcinoma	30 (14.4%)	89 (14.7%)
Signet ring cell carcinoma		
No	161 (77.4%)	467 (77.2%)
Yes	17 (8.2%)	49 (8.1%)
Well/moderate	30 (14.4%)	89 (14.7%)
Poor	63 (30.3%)	180 (29.8%)
Not specified	88 (42.3%)	251 (41.5%)
Type of dissemination		
Single hematogenous location	57 (27.4%)	174 (28.8%)
Peritoneum only	79 (38.0)	227 (37.5%)
Extra-regional lymph node only	45 (21.6)	24 (4.0%)
Non-specified single location	25 (12.0)	190 (31.4%)
Multiple locations	49 (23.6	164 (27.1%)

Acknowledgements

CH 06.

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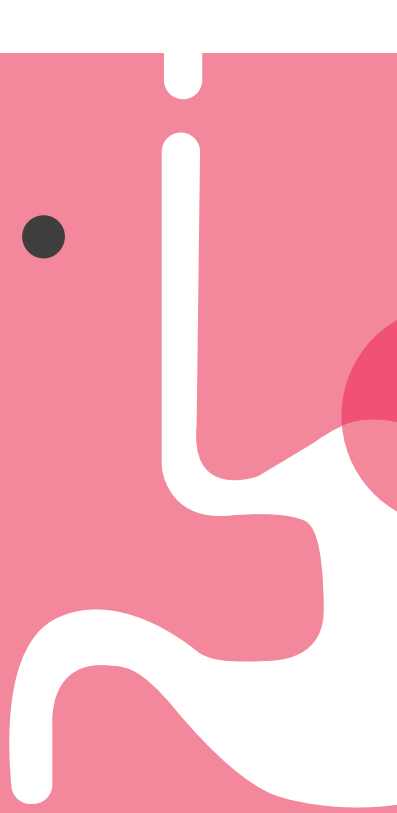
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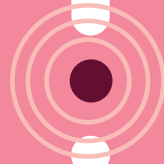
Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy

Journal of Cachexia, Sarcopenia and Muscle, 2019.

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Background: Palliative systemic treatment in patients with advanced or metastatic esophagogastric cancer may result in improved overall survival and quality of life but can also lead to considerable toxicity. In various cancer types, severe muscle mass depletion (sarcopenia) and poor muscle strength are associated with decreased survival and increased chemotherapy-related toxicity. The aim of this study is to determine the impact of body composition on survival and chemotherapy toxicity in esophagogastric cancer patients treated with first-line palliative chemotherapy.

Methods: A total of 88 patients with advanced esophagogastric cancer treated with standard first-line palliative systemic therapy consisting of capecitabine and oxaliplatin (CapOx) between January 2010 and February 2017 were included. Skeletal muscle index (SMI), reflecting muscle mass, and skeletal muscle density (SMD), associated with muscle strength, were measured using pre-treatment of all patients and evaluation computed tomography scans after three treatment cycles of 65 patients and were used to determine sarcopenia and sarcopenic obesity (i.e. sarcopenia and body mass index >25 kg/m^2). The associations between body composition (SMI, SMD, sarcopenia, and sarcopenic obesity) and survival and toxicity were assessed using univariable and multivariable Cox and logistic regression analyses, respectively.

Results: Of 88 patients, 75% was male, and median age was 63 (interquartile range 56−69) years. The majority of patients had an adenocarcinoma (83%). Before start of treatment, 49% of the patients were sarcopenic, and 20% had sarcopenic obesity. Low SMD was observed in 50% of patients. During three cycles CapOx, SMI significantly decreased, with a median decrease of 4% (interquartile range 8.6−0.4). Median progression-free and overall survival were 6.9 and 10.1 months. SMI, SMD, sarcopenia, and sarcopenic obesity (both pre-treatment and after three cycles) were neither associated with progression-free nor overall survival. Pre-treatment SMD was independently associated with grade 3−4 toxicity (odds ratio 0.94; 95% confidence interval 0.89−1.00) and sarcopenic obesity with grade 2−4 neuropathy (odds ratio 3.82; 95% confidence interval 1.20−12.18).

Conclusion: Sarcopenia was not associated with survival or treatment-related toxicity in advanced esophagogastric cancer patients treated with CapOx. Pre-treatment sarcopenic obesity was independently associated with the occurrence of grade 2−4 neurotoxicity and skeletal muscle density with grade 3−4 toxicity.

INTRODUCTION

Esophagogastric cancer is often diagnosed when curative treatment options are not available.[1,2] Palliative chemotherapy is considered standard treatment because it can improve survival and quality of life in incurable esophagogastric cancer patients.[3,4] Currently, doublet therapy with a fluoropyrimidine and platinum compound is recommended as first-line palliative chemotherapy, providing a survival benefit of several months.[5,6] Unfortunately, chemotherapy often causes toxicity, which may result in dose reductions, suspension, and discontinuation of chemotherapy and can thereby compromise treatment efficacy. Excess toxicity may also lead to a reduction in quality of life. The identification of patient or tumour

characteristics that are related to toxicity and survival has the potential to improve quality of care by enabling more individually aligned treatment plans.

A characteristic of increasing interest is the loss of skeletal muscle mass. In various cancer types, the depletion of skeletal muscle mass (sarcopenia) is associated with decreased survival and increased risk of complications after surgery and systemic treatment-related toxicity.[7–10] Muscle mass can be easily determined by assessment of skeletal muscle index (SMI) using computed tomography (CT) scans that are routinely acquired for pre-treatment staging and treatment evaluation. Furthermore, muscle strength or quality is associated with skeletal muscle density (SMD), which can be measured then as well.[11–14]

Previous studies in esophagogastric cancer patients during curative treatment found that sarcopenia was associated with increased chemoradiotherapy-related toxicity, increased post-operative complications, and decreased survival rates.[15–20] Furthermore, during neoadjuvant treatment, sarcopenic obesity has been associated with higher risk of dose reductions.[21] However, studies investigating the association between muscle mass and outcome in the palliative setting are limited. Only one study investigated SMD in a small study population in gastric cancer patients and found that low SMD is associated with poor survival.[11] No studies in the palliative have investigated the association between muscle mass depletion and toxicity. Investigating the relation between muscle mass loss and outcome in advanced esophagogastric cancer patients seems relevant because weight loss is common during palliative treatment (due to cancer-related cachexia and dysphagia resulting in malnutrition), which could lead to the loss of skeletal muscle mass.[22,23]

The aim of our study was to explore associations between skeletal muscle mass and density, sarcopenia and sarcopenic obesity, and survival and chemotherapy toxicity in esophagogastric cancer patients treated with first-line palliative chemotherapy.

MATERIAL AND METHODS

Study population

Between January 2010 and July 2017, all patients in the Academic Medical Center with incurable esophageal, gastroesophageal junction, or gastric cancer that received at least one cycle of standard first-line palliative systemic therapy consisting of capecitabine and oxaliplatin (CapOx) were included in the study (n = 118). Patients that did not have a CT scan or a positron emission tomography-CT scan containing images of the third lumbar vertebra within 60 days prior to start of treatment (n = 25) and patients that had palliative systemic treatment before a scan was made (n = 5) were excluded. A total of 88 patients with at least one useful CT scan were ultimately included, of which 65 had a second (evaluation) CT scan performed after three (n = 60) or two (n = 5) cycles of chemotherapy (Figure 1).

Figure 1. Flowchart displaying patient selection.

Advanced esophagogastric cancer patients treated with CapOx (*n*=118)

Exclusion of patients without aviable CT scan within 60 days before start of treatment (*n*=25) or without prior palliative systemic treatment (*n*=5)

Included patients with at least one useful CT scan prior to treatment (*n*=88)

Patients with an ecaluation CT scan after 2 or 3 cycles CapOx (*n*=65)
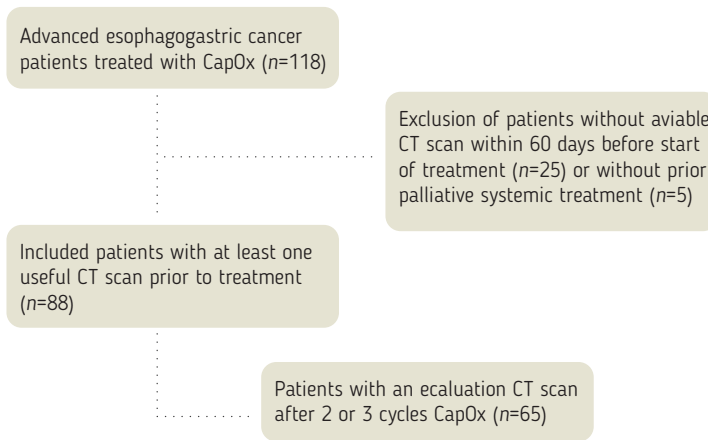
CapOx, capecitabine/oxaliplatin; CT, computed tomography.

Treatment

Standard first-line palliative systemic therapy consisted of the fluoropyrimidine capecitabine (1000 mg/m2 , taken orally two times a day from Days 1–14) and platinum compound oxaliplatin (130 mg/m2 , administered intravenously on Day 1) in a three weekly cycle, with a maximum of six successive cycles followed by capecitabine monotherapy. Optionally, oxaliplatin could be reintroduced in case of progressive disease during capecitabine monotherapy. Treatment was discontinued in case of disease progression, inacceptable toxicity, or on patient's request. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (version 4.03) by recording the highest Common Terminology Criteria for Adverse Events grade of each adverse event throughout all cycles of first-line treatment.[24] Survival was calculated from the day metastatic disease was histologically confirmed or, if not available, diagnosed by imaging (n = 2), to date of death (overall survival), date of radiological progression according to Response Evaluation Criteria in Solid Tumors, clinical progression on CapOx or capecitabine monotherapy (progression-free survival; PFS), and lost-to-follow-up or end of follow-up (19 March 2018).

Skeletal muscle index and skeletal muscle density assessment

Pre-treatment CT scans (CT 1) and evaluation CT scans after the second or third treatment cycle (CT 2) with administration of intravenous contrast were assessed for body composition. According to the CT protocol in our centre, patients were scanned in the late portal venous phase, as routinely performed in cancer patients, with a tube voltage of 120 kV, regularly used in contrast-enhanced scans. The medical imaging software Slice-O-Matic® (version 5.0; Tomovision, Montreal, Quebec, Canada) was used to identify and demarcate the skeletal muscle compartments at the L3 level using predetermined cut-off points for Hounsfield units (HU) (-29 to +150).[8,14,25] Using two single-slice axial images, the average surface areas of the psoas muscles, abdominal wall muscles, and paraspinal muscles, in which transverse and

spinous processes were visible, were used to determine muscle area. CT scans were analysed by a trained investigator (M. P.). SMI (cm² /m²) was determined by normalizing the obtained muscle area (cm²) for squared body height (m²). SMD was expressed as mean HU-value of the skeletal muscle cross sectional areas.

We used specific cut-off values for SMI and SMD that are correlated with reduced survival in a large cohort consisting of patients with solid tumours, taking into account BMI and sex as defined by Martin et al.[8] Sarcopenia was defined as SMI 25 kg/m² ; in female patients, sarcopenia was set at SMI < 41 HU in non-overweight patients (BMI 25 kg/m² for both sexes. Sarcopenic obesity was defined as sarcopenia combined with overweight or obesity (BMI >25 kg/m²).

Statistical analysis

Patient and tumour characteristics are presented as mean with standard deviation, median with interquartile range (IQR), or counts and percentages. SMI and SMD of CT 1 and CT 2 were compared using the paired t-test or Wilcoxon signed rank test, whichever was appropriate. Correlations between continuous variables were determined using Pearson's correlation coefficient in case of normally distributed data and Spearman in non-normally distributed data. The association of SMI and SMD with survival, toxicity, and response on chemotherapy was tested using Cox proportional hazard and logistic regression, respectively. Variables were added as confounders to multivariable regression analyses if the association/correlation of the variable with both the determinant and the outcome had a P value lower than 0.2.

For all other analyses, a P value lower than 0.05 was regarded as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (Version 24.0 IBM Corp. Armonk, NY, USA).

RESULTS

Patient characteristics

Characteristics of the 88 included patients are displayed in Table 1. Seventy-five percent of the patients were male, and median age at diagnosis of metastatic disease was 62.2 years (IQR 56–69). The majority of the patients had an adenocarcinoma (83% vs. 17% squamous cell carcinoma), and 47 (53%) of the tumours were localized in the oesophagus, 25 (28%) around the gastro-esophageal junction, and 16 (18%) in the stomach, respectively. A total of 143 (93%) scans were performed in our centre; all scans were assessed by expert radiologists from our centre. Median time between the baseline CT (CT 1) and start of the first CapOx cycle was 18 days (IQR 7.5–32).

The majority of the patients had one to three (n = 39, 44%) or four to six cycles (n = 40, 46%) of CapOx, and 42% of the patients continued with capecitabine monotherapy after CapOx. In 56 patients (63%), doses of capecitabine and/or oxaliplatin were reduced or postponed due to toxicity. Thirty-two patients (36%) had grade 3–4 toxicity (including hematologic toxicity); 18 patients (21%) experienced peripheral sensory neuropathy grade 2 or higher.

Table 1. Patient characteristics and body composition.

Baseline characteristics	All patients (n = 88) No. (%)
Men	66 (75.0%)
Age in years, median (IQR)	63.0 (56–69)
Tumour location	
Oesophagus	47 (53.4%)
Gastro-esophageal junction	25 (28.4%)
Stomach	16 (18.2%)
Histology	
Adenocarcinoma	73 (83.0%)
Squamous cell carcinoma	15 (17.0%)
WHO performance status	
0 or 1	78 (88.6%)
≥2	10 (11.4%)
Reported weight loss before start of treatment	
<8%	49 (55.7%)
≥8%	38 (43.2%)
Unknown	1 (1.1%)
Prior curative treatment	40 (45.5%)
Metastatic dissemination	
Only lymphatic	29 (33.0%)
Hematogenous	59 (67.0%)
Number of metastatic sites—no (%)	
0 or 1	37 (42.0%)
≥2	51 (58.0%)
Treatment and toxicity	
Days between CT 1 and start of CapOx, median (IQR)	18 (7.3–29.0%)
Days between CT 1 and CT 2—median (IQR)	79 (66.5–89.0%)
Number of completed CapOx cycles	
1–3	39 (44.3%)
4–6	40 (45.5%)
>6	9 (10.2%)
Capecitabine monotherapy	37 (42.0%)
Toxicity grade 3 or 4	32 (36.4%)
Neuropathy grade 2–4	18 (20.5%)
Hematologic toxicity grade 3–4	21 (23.9%)
Dose reduction or delay	56 (63.3%)

CapOx, capecitabine/oxaliplatin; IQR, interquartile range.

Body composition

Table 2 shows SMI, SMD, BMI, and the number of sarcopenic and sarcopenic obese patients in CT 1 and CT 2 for all patients, men and women. Mean pre-treatment SMI was 46.9 cm2/m2 for all patients, and 48.0 and 38.4 cm2/m2 for male and female patients, respectively, which differed significantly (P < 0.001; Table 2). Mean pre-treatment SMD for the entire group was 37.8 HU and did not differ between men and women in CT 1 (P = 0.265). Fifty percent of all patients had a SMD below cut-off value (Table 2), reflecting poor quality of muscle tissue. Nearly half of the patients had sarcopenia before start of treatment (48.9%), and 19.7% had sarcopenic obesity.

Skeletal muscle index was significantly lower on the second CT scan in the whole group and for male and female patients independently (P < 0.001, P < 0.001, and P = 0.011, respectively), with a median difference of -4.0% (IQR -8.6 – -0.4%) for all patients. SMD and BMI were comparable in CT 1 and CT 2 (P = 0.840 and P = 0.122, respectively). The proportion of patients with sarcopenia increased over time (CT 1 49% vs. CT 2 55%) in all patients (Table 2). The amount of sarcopenic obese patients increased from 19% in CT 1 to 22% in CT 2 (P < 0.001).

Table 2. Comparison of body composition between CT 1 and CT 2 and between men and women (CT 1).

Body composition	All patients			Male			Female			
	CT 1 (n = 88)	CT 2 (n = 65)	P value	CT 1 (n = 66)	CT 2 (n = 50)	P value*	CT 1 (n = 22)	CT 2 (n = 15)	P value*	P value#
SMI cm²/m² - mean (SD)	46.9 (9.9)	44.4 (10.0)	<0.001[a]	48.0 (9.3)	46.6 (9.8)	<0.001[a]	39.9 (4.6)	37.0 (6.3)	0.011[a]	<0.001[b]
SMD, HU - mean (SD)	37.8 (8.9)	38.6 (9.0)	0.840[a]	38.4 (9.0)	39.5 (8.7)	0.851[a]	35.9 (8.5)	35.4 (9.9)	0.942[a]	0.265[b]
BMI, kg/m² - median (IQR)	23.4 (21.6–26.1)	23.2 (21.7–26.1)	0.122[c]	23.4 (21.4–26.1)	23.2 (21.7–26.1)	0.265[c]	24.1 (22.6–26.4)	23.2 (22.0–26.3)	0.120[c]	0.512[d]
BMI category										
Underweight (<18.5 kg/m²)	5 (5.7%)	3 (4.6%)		3 (4.5%)	2 (4.0%)		2 (9.1%)	1 (6.7%)		
Normal weight (20–24.9 kg/m²)	54 (61.4%)	43 (66.2%)		42 (63.6%)	33 (66.0%)		12 (54.4%)	10 (66.7%)		
Overweight (≥25 kg/m²)	29 (32.9%)	19 (29.2%)	<0.001[e]	21 (31.8%)	15 (30.0%)	<0.001[e]	8 (36.4%)	4 (26.7%)	<0.001[e]	0.629[e]
Sarcopenia	43 (48.9%)	36 (55.4%)	<0.001[e]	29 (43.9%)	25 (50.0%)	<0.001[e]	14 (63.6%)	11 (73.3%)	0.033[f]	0.109[e]
Sarcopenic obesity	17 (19.3%)	14 (21.5%)	<0.001[f]	13 (19.7%)	12 (24.0%)	<0.001[f]	4 (18.2%)	2 (13.3%)	0.029[f]	0.574[f]
Low SMD – no (%)	44 (50.0%)	30 (46.2%)	<0.001[f]	28 (42.4%)	21 (42.0%)	<0.001[e]	16 (72.7%)	9 (60.0%)	0.011[f]	0.014[e]

*Comparison between CT 1 and CT 2 in male and female patients. #Comparison between male and female patients in CT 1.
[a]Paired t-test. [b]Unpaired t-test. [c]Wilcoxon signed rank test. [d]Mann–Whitney U-test. [e]X² test. [f]Fisher's exact test.
BMI, body mass index; CT, computed tomography; HU, Houndsfield units; IQR, interquartile range; SD, standard deviation; SMD, skeletal muscle density; SMI, skeletal muscle index.

Table 3. Univariable and multivariable Cox regression analysis.

	Progression-free survival						Overall survival					
	Univariable analysis			Multivariable analysis[a]			Univariable analysis			Multivariable analysis[b]		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SMI CT 1, cm²/m²	1.01	0.99-1.03	0.243	0.99	0.97-1.02	0.647	1.02	0.99-1.04	0.231	0.99	0.97-1.02	0.588
SMI CT 2, cm²/m²	1.02	1.00-1.04	0.060	1.00	0.97-1.04	0.900	1.03	1.00-1.05	0.049	1.00	0.97-1.03	0.862
ΔSMI, cm²/m²	1.02	0.94-1.11	0.601	0.94	0.86-1.02	0.116	0.97	0.90-1.05	0.544	0.97	0.88-1.06	0.481
Sarcopenia CT 1	0.72	0.47-1.11	0.136	0.78	0.47-1.30	0.343	0.70	0.44-1.10	0.123	0.94	0.59-1.50	0.787
Sarcopenia CT 2	0.56	0.33-0.95	0.031	0.76	0.41-1.41	0.385	0.53	0.30-0.91	0.022	0.88	0.47-1.64	0.686
Sarcopenic obesity CT 1	0.90	0.52-1.56	0.703	0.61	0.32-1.16	0.133	0.79	0.45-1.40	0.424	0.88	0.50-1.54	0.656
Sarcopenic obesity CT 2	0.87	0.47-1.62	0.663	0.95	0.49-1.86	0.890	0.98	0.52-1.84	0.940	0.90	0.45-1.79	0.765
SMD CT 1, HU	1.01	0.98-1.03	0.562	1.01	0.98-1.04	0.588	1.00	0.98-1.03	0.609	1.00	0.97-1.03	0.754
SMD CT 2, HU	1.01	0.98-1.04	0.540	0.99	0.96-1.02	0.528	1.00	0.98-1.03	0.765	0.98	0.95-1.01	0.255
ΔSMD, HU	1.02	0.99-1.06	0.213	0.98	0.94-1.01	0.198	1.00	0.97-1.04	0.852	1.00	0.96-1.04	0.839
Low SMD CT1	1.04	0.68-1.61	0.850	1.05	0.64-1.73	0.835	0.94	0.60-1.47	0.789	1.40	0.85-2.31	0.193
BMI CT 1, kg/m²	0.99	0.95-1.04	0.719	0.95	0.90-1.01	0.100	0.99	0.95-1.04	0.809	0.97	0.92-1.02	0.181
BMI CT 2, kg/m²	1.01	0.95-1.06	0.828	1.00	0.94-1.07	0.862	1.03	0.98-1.10	0.237	0.98	0.92-1.04	0.417
ΔBMI, kg/m²	0.93	0.73-1.17	0.533	0.84	0.64-1.10	0.205	0.91	0.70-1.17	0.460	0.86	0.67-1.09	0.204
Overweight (BMI ≥25 kg/m²)	1.03	0.65-1.64	0.890	0.84	0.50-1.42	0.513	1.03	0.64-1.67	0.895	0.96	0.60-1.55	0.868

[a] Sex, age, WHO performance status ≥2, number of metastatic sites ≥2. [b] Sex, age, WHO performance status ≥2, number of metastatic sites ≥2, hematogenous metastatic dissemination. BMI, body mass index; CI, confidence interval; CT, computed tomography; HR, hazard ratio; HU, Houndsfield units; SMD, skeletal muscle density; SMI, skeletal muscle index. Confounders multivariable analyses.

Table 4. Univariable and multivariable logistic regression analysis.

	Toxicity grade 3 or 4						Peripheral sensory neuropathy grade ≥2		
	Univariable analysis			Multivariable analysis[a]			Univariable analysis[b]		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
SMI CT 1, cm²/m²	1.01	0.97-1.06	0.600	1.00	0.96-1.06	0.734	0.99	0.93-1.05	0.645
SMI CT 2, cm²/m²	1.00	0.95-1.06	0.930	1.00	0.95-1.05	0.924	0.97	0.91-1.04	0.376
ΔSMI, cm²/m²	0.96	0.83-1.10	0.521	0.97	0.84-1.11	0.633	0.98	0.84-1.14	0.784
Sarcopenia CT 1	0.88	0.37-2.11	0.778	0.87	0.36-2.11	0.764	1.87	0.65-5.38	0.248
Sarcopenia CT 2	1.59	0.57-4.44	0.379	1.48	0.52-4.23	0.462	0.75	0.24-2.32	0.618
Sarcopenic obesity CT 1	1.29	0.44-3.80	0.647	1.19	0.39-3.60	0.760	3.82	1.20-12.18	0.024
Sarcopenic obesity CT 2	0.94	0.27-3.21	0.916	0.91	0.26-3.22	0.886	1.30	0.35-4.91	0.699
SMD CT 1, HU	0.94	0.89-0.99	0.019	0.94	0.89-1.00	0.037	1.02	0.97-1.09	0.435
SMD CT 2, HU	0.95	0.89-1.00	0.080	0.95	0.90-1.01	0.109	1.07	0.99-1.14	0.074
ΔSMD, HU	0.99	0.93-1.05	0.724	0.99	0.93-1.06	0.741	0.98	0.91-1.04	0.464
Low SMD CT1	1.81	0.75-4.37	0.186	1.75	0.72-4.28	0.219	0.57	0.20-1.63	0.294
BMI CT 1, kg/m²	1.06	0.96-1.17	0.243	1.04	0.95-1.15	0.403	0.97	0.86-1.10	0.675
BMI CT 2, kg/m²	1.03	0.92-1.15	0.611	1.03	0.92-1.15	0.649	0.85	0.71-1.03	0.099
ΔBMI, kg/m²	0.80	0.52-1.22	0.306	0.88	0.56-1.38	0.567	1.03	0.64-1.65	0.902
Overweight (BMI ≥25 kg/m²)	1.11	0.44-2.78	0.830	0.87	0.33-2.35	0.790	1.87	0.65-5.39	0.249

Confounders multivariable analyses. [a] WHO performance status ≥2. [b] There were no confounders, so only univariable analysis was performed.
BMI, body mass index; CI, confidence interval; CT, computed tomography; HU, Houndsfield units; OR, odds ratio; SMD, skeletal muscle density; SMI, skeletal muscle index.

Survival

One patient was excluded for survival analyses because trastuzumab was added to CapOx after the third treatment cycle. Median progression-free survival of remaining patients (n = 87) was 6.9 months (IQR 3.7–10.3), and overall survival was 10.1 months (IQR 5.0–16.1).

In both univariable and multivariable regression analyses, SMI and SMD (pre-treatment and after three cycles) were not independently associated with progression-free or overall survival. Sarcopenia in CT 2 was significantly associated with progression-free survival in univariable analysis [hazard ratio 0.56; 95% confidence interval (CI) 0.33–0.95] but not in multivariable analysis. Sarcopenia (pre-treatment), sarcopenic obesity, low SMD, and BMI did not impact PFS and overall survival, neither did the difference in SMI (ΔSMI), SMD (ΔSMD), or BMI (ΔBMI) between CT 2 and CT 1 (Table 3).

Toxicity

Univariable and multivariable logistic regression analyses for grade 3–4 toxicity and grade 2–4 peripheral sensory neuropathy are presented in Table 4.

Pre-treatment SMD (CT 1) was associated with the occurrence of grade 3–4 toxicity [odds ratio (OR) 0.94; 95% CI 0.89–1.00] in both univariable and multivariable logistic regression analyses, and sarcopenic obesity (CT 1) with grade 2 or more peripheral sensory neuropathy (OR 3.82; 95% CI 1.20–12.18). All other parameters were not independently related to (neuro)toxicity.

DISCUSSION

In this first study exploring skeletal muscle features of incurable esophagogastric cancer patients treated with first-line palliative systemic therapy with CapOx, sarcopenia and low muscle density were observed in (nearly) half of our patients (48.9% and 50.0%, respectively). SMI, SMD, sarcopenia, sarcopenic obesity, or BMI (pre-treatment and after three cycles of CapOx) and change in SMI were not related to progression-free or overall survival, whereas a higher SMD was independently associated with a lower risk of grade 3–4 toxicity. Sarcopenic obesity was significantly related with neuropathy.

Although several studies in lung cancer, gastrointestinal cancer, and lymphoma patients, both pre-treatment SMI[7,8,26] and SMD[8,11,27–30] were associated with overall survival. We did not observe this association, either due to limited power of our study or the relatively large number of overweight patients in our population with baseline sarcopenia [17 of 43 (39.5%); Table 2] that could have been a protective factor for survival, a phenomenon that is referred to as the obesity paradox.[8,31] Other causes of the specifics of esophagogastric cancer patients have to be identified in future studies. In addition, the difference in skeletal muscle mass index pre-treatment and after three cycles of CapOx (ΔSMI) was not associated with survival, in contrast to earlier findings in metastatic colorectal patients who received first-line treatment with CapOx.[30] However, ΔSMI tended towards statistical significance in multivariable analysis for PFS (hazard ratio 0.94; 95% CI 0.86–1.02), indicating increase of muscle mass could prolong PFS. Possibly, either the limited time between the two CT scans and duration of treatment or the small group of patients resulted in these differences in outcome.

A decrease in SMD was independently associated with a higher chance of grade 3 or 4 toxicity. SMD is associated with strength or quality of muscle mass: a lower SMD is related to fat infiltration in muscles or myosteatosis, which is a pathological condition.[9,27,32,33] Myosteatosis is hypothesized to be a preliminary state for sarcopenia and therefore a more accurate representative of muscle function than the SMI.[27] Half of our patients had a pre-treatment SMD that was beyond cut-off values, which is in line with the 58.5% of low SMD in the study with metastatic gastric cancer patients in which the same cut-off values of Martin et al. were used.[11]

Patients with sarcopenic obesity had greater risk of grade 2–4 peripheral sensory neuropathy (OR 3.82; 95% CI 1.20– 12.18). A possible explanation is that oxaliplatin is a lipophilic agent and accumulates in the fat tissue compartments. In patients with excess fat, this may result in longer exposure to the drug that could lead to increased risk of neuropathy in sarcopenic obesity patients.[34,35] Currently, dosing chemotherapy is performed base on body surface area, which is based on a patient's height and weight and used as an index for chemotherapy dosing, without taken body composition into account. This could result in overdosing in patients with sarcopenic obesity because of their high body surface area and decreased muscle mass, as reported in previous studies.[10,20,34,36]

In our study, we found that BMI did not differ between CT 1 and CT 2 although muscle mass decreased significantly, which supports earlier findings stating that muscle mass is not necessarily associated with BMI and that loss of muscle mass could be accompanied by growth of adipose tissue.[13,35]

Accordingly, there were significantly more patients with sarcopenia and sarcopenic obesity at the time of the evaluation CT scan than at the pre-treatment scan. Given the observed relation with sarcopenic obesity and neurotoxicity and SMD and toxicity grade 2–4, interventions to prevent decrease of SMI and SMD during palliative systemic treatment could prevent toxicity. Given the complex pathologic process of cachexia and sarcopenia and according to increasing evidence, these interventions should ideally be multimodal and at least consist of nutritional support, physical exercise perhaps combined with pharmacological interventions. This could prevent (pre) cachectic patients from developing refractory cachexia, a stage of cancer cachexia associated with progressive cancer not responding to anticancer treatment, low performance status, and short life expectancy.[23,37] In our study, we observed a median decrease of 4% in SMI and an increase of sarcopenic (obese) patients after only three cycles of chemotherapy, stressing the urgency that these preventive measures need to be applied in an early stage of treatment.

We are aware of several limitations in our study. Firstly, our study comprised a limited number of patients; nevertheless, it is the largest cohort esophagogastric cancer patients treated with palliative systemic therapy in which these analyses are performed. Secondly, patients without available CT scans were excluded from the analysis, which could lead to a possible selection bias created due to exclusion of patients without available CT scans. Furthermore, sample size was too small to perform subanalyses between sarcopenic patients with overweight and obesity, because obese sarcopenic patients may have a worse survival.[38] Moreover, we could not determine the relation between skeletal muscle features and quality of life, clinical outcomes, or muscle function or strength because these data were not prospectively collected in our study. In metastatic lung cancer patients treated with first-

line systemic therapy, clinical outcomes and global quality of life were positively associated with skeletal muscle features.[39] This deserves further study in esophagogastric cancer patients. Lastly, approximately 7% of included CT scans were not performed in our centre. Although in all CT scans intravenous contrast was used, differences in contrast enhancement phases and tube voltages might affect calculations of determinants used in our study.[40,41]

In conclusion, skeletal muscle mass and density, sarcopenia, and sarcopenic obesity are not associated with survival in advanced esophagogastric cancer patients treated with first-line chemotherapy. However, low SMD is independently associated with the occurrence of grade 3–4 toxicities and sarcopenic obesity with grade 2–4 peripheral sensory neuropathy. Research focusing on interventions to increase or prevent decrease of muscle mass index and density and adjustment of chemotherapy doses to muscle mass could be valuable in preventing chemotherapy toxicity in these patients in the future.

Ethical standards
Our study was considered Medical Research Involving Human Subjects Act (WMO) exempt by the Medical Ethics Committee of the Amsterdam UMC. Therefore, formal approval of the Medical Ethics Committee was not necessary. The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.[42]

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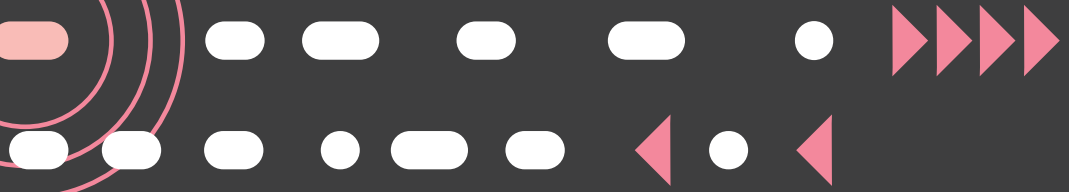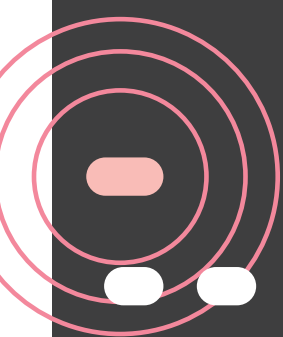
Cachexia and dietetic interventions in esophagogastric cancer patients: A population-based study

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ABSTRACT

Background: Cachexia is common in patients with esophagogastric cancer and is associated with increased mortality. Nutritional screening and dietetic interventions can be helpful in preventing evolvement of cachexia. Our aim was to study the real-world prevalence and prognostic value of pretreatment cachexia on overall survival (OS) using patient-reported weight loss, and to explore dietetic interventions in esophagogastric cancer.

Methods: Patients with esophagogastric cancer (2015–2018), regardless of disease stage, who participated in the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP) and completed patient-reported outcome measures were included. Data on weight loss and dietetic interventions were retrieved from questionnaires before start of treatment (baseline) and 3 months thereafter. Additional patient data were obtained from the Netherlands Cancer Registry. Cachexia was defined as self-reported >5% half-year body weight loss at baseline or 2% in patients with a body mass index (BMI) <20 kg/m2 according to the Fearon criteria. The association between cachexia and OS was analyzed using multivariable Cox proportional hazard analyses adjusted for sex, age, performance status, comorbidities, primary tumor location, disease stage, histology, and treatment strategy.

Results: Of 406 included patients, 48% had pretreatment cachexia, of whom 65% were referred for dietetic consultation at baseline. The proportion of patients with cachexia was the highest among those who received palliative chemotherapy (59%) or best supportive care (67%). Cachexia was associated with decreased OS (hazard ratio, 1.52; 95% confidence interval 1.11–2.09). Median weight loss after 3-month follow-up was lower in patients with cachexia who were referred to a dietician at baseline compared with those who were not (0% vs 2%; P5.047).

Conclusion: Nearly half of patients with esophagogastric cancer have pretreatment cachexia. Dietetic consultation at baseline was not reported in more than one-third of the patients with cachexia. Because cachexia was independently associated with decreased survival, improving nutritional screening and referral for dietetic consultation are warranted to prevent further deterioration of malnutrition and mortality.

INTRODUCTION

Malnutrition is defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass, and is associated with diminished physical and mental function and impaired clinical outcome.[1,2] It is reported in 48% to 85% of patients with esophagogastric cancer,[3–6] and is caused by reduced dietary intake as a result of dysphagia and odynophagia caused by tumor obstruction; treatment-related toxicity, such as mucositis, nausea, or taste changes, possibly aggravated by tumor-induced anorexia; and psychologic distress.[3,7–11] Reduced dietary intake, together with decreased physical activity and tumor-induced catabolism, are causes of cancer-related cachexia.[12] Cachexia is a multifactorial syndrome characterized by involuntary weight loss due to ongoing loss of skeletal muscle mass, that can only partly be reversed by conventional nutritional support.[13,14] It is associated with poorer compliance to chemotherapy, increased treatment toxicity, lower quality of life, and even decreased survival in patients with cancer.[12–22] Patients with cancer and major (>5%

of half-year body weight) or minor weight loss (>2%) but a low body mass index (BMI) are assumed to have cachexia.[13]

According to an international consensus statement included in the European Society for Clinical Nutrition and Metabolism (ESPEN) nutrition guideline, all patients with cancer should be screened for the risk or presence of malnutrition.[2] Patients can be identified as at high risk of malnutrition using validated screening tools, such as the Short Nutritional Assessment Questionnaire (SNAQ)[23] or the Malnutrition Universal Screening Tool (MUST).[24] For patients with poor nutritional status or a high risk of malnutrition, measures should be taken to improve the nutritional status.[2,25,26] These measures usually consist of dietetic consultation to promote a personalized diet high in energy and proteins, supplemented by the use of oral nutritional supplements or tube feeding when the intake remains insufficient.[2,11]

Information on the prevalence of cachexia and implementation of dietetic interventions in clinical practice could provide relevant insight into the need for potential improvements in nutritional care in current practice. Thus far, these data in esophagogastric cancer are scarce. Moreover, the prognostic effect of cachexia on overall survival (OS) in patients with esophagogastric cancer receiving different treatment modalities has not been explored using real-world data. The aim of this study was to explore the prevalence of pretreatment cachexia, association of pretreatment cachexia with OS, and use of dietetic interventions in patients with esophagogastric cancer using patient-reported outcome measures (PROMs) in a real-world setting (ie, a large national patient cohort).

MATERIALS AND METHODS

Data Collection
Patients with an adenocarcinoma or squamous cell carcinoma of the esophagus, gastroesophageal junction, or stomach diagnosed in 2015 through 2018 in the Netherlands were asked to participate in the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP), for which PROMs are prospectively collected after informed consent is provided by the patient.[27] Data on patient and tumor characteristics, treatment, and survival were extracted from the Netherlands Cancer Registry (NCR), which is a population-based registry that covers the total Dutch population of >17 million people, for which data are extracted from the hospital's electronic health record system or medical records by trained data managers. Data on vital status were obtained through annual linkage to the Dutch Personal Records Database and were updated until February 1, 2020.

Questionnaires
Patients included in POCOP were asked to complete computer-administered or paper questionnaires at initial diagnosis (baseline), and 3, 6, 9, 12, 18, 24, and 36 months after inclusion. Patients were considered eligible for inclusion if they completed the baseline questionnaire before resection or before or within a week after start of (neoadjuvant) treatment with chemo(radio)therapy. Results from the baseline and 3-month questionnaire were included, because these questionnaires contained the Dutch Healthy Diet Food

Frequency Questionnaire (DHD-FFQ). Information on height, weight, weight loss, and whether patients received dietetic consultation, tube feeding, or oral nutritional supplements was collected in a general questionnaire. Patients who consumed food orally were requested to complete the DHD-FFQ, a validated questionnaire based on Dutch national dietary guidelines including questions about portion sizes of bread, dairy, meat, fish, vegetables, and alcohol consumption.[28,29] A protein score was calculated based on this DHD-FFQ,[30] and varied from 0 to 10. Among the general healthy population, a protein score of 10 is regarded as sufficient intake, whereas <10 indicates insufficient intake of the protein sources included in the questionnaire.[31] For patients with disease-related malnutrition, a protein score <10 may indicate the need for nutritional support, given that their protein requirements are higher than those of healthy persons.

Weight Loss Parameters

BMI (kg/m^2) was calculated from reported heights and weights retrieved from the questionnaires. Percentage weight difference was calculated from the reported half-year weight loss in the baseline questionnaire, and from weight differences between 2 questionnaires during follow-up. Cachexia was defined as >5% body-weight loss or >2% in individuals with a BMI of <20 kg/m^2 according to international consensus criteria.[13] The criterion for cachexia that included the presence of sarcopenia was not used because data on skeletal muscle mass and strength were unavailable.

Treatment

Analyses were stratified according to treatment type: (1) neoadjuvant chemoradiotherapy (nCRT) followed by a surgical resection, (2) neoadjuvant chemotherapy (nCT) followed by a resection (± adjuvant chemotherapy), (3) a resection without neoadjuvant treatment, (4) definitive chemoradiotherapy (dCRT; ie, chemotherapy and concurrent long-term radiotherapy without a resection), (5) palliative chemotherapy, and (6) best supportive care (BSC) without chemotherapy or a resection.

Statistical Analysis

Baseline characteristics and nutritional parameters are displayed with counts and percentages or medians and interquartile ranges (IQRs) and compared using chi-square, Fisher exact, or Mann-Whitney U tests, whichever was appropriate, in patients with versus without pretreatment cachexia. OS was calculated from the day of baseline questionnaire completion until the date of death or last follow-up (February 1, 2020). OS was assessed in all patients using the Kaplan-Meier method and groups were compared using the log-rank test, and results were stratified according to treatment type. A multivariable Cox proportional hazard analysis was used to assess the independent prognostic value of cachexia on OS after adjustment for sex, age, performance status, number of comorbidities, primary tumor location, disease stage, histology, and treatment strategy. P values <.05 were considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc.).

Data Availability

Data supporting the findings of this study are available from the NCR and POCOP PROMs. Restrictions apply to the availability of these data, which were used under license for this study.[32]

RESULTS

Patient Characteristics

The total patient cohort included 406 patients with esophagogastric cancer who completed the baseline questionnaire before start of treatment (Figure 1). Of these, 244 completed the 3-month follow-up questionnaire. Median time between completion of the baseline and 3-month questionnaire was 92 days (IQR, 88–97 days).

Figure 1. Flow diagram of patient inclusion. All 406 included patients completed the baseline questionnaire; 244 (64%) of 383 patients were still alive at 3-month follow-up.
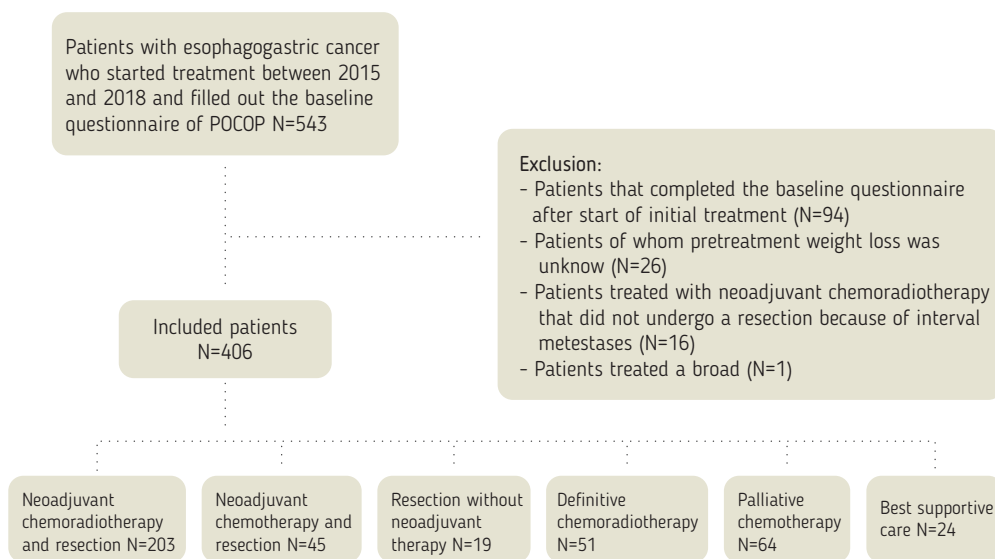
POCOP, Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients.

Table 1. Patient Characteristics at Baseline.

Characteristics	Pretreatment cachexia (n = 197) No.(%)	No pretreatment cachexia (n = 209) No (%)	P value
Female	58 (29%)	38 (18%)	0.008[a]
Age, years, median (IQR)	66 (59, 71)	66 (60, 71)	0.382[b]
<55	24 (12%)	20 (10%)	0.809[a]
55-64	62 (31%)	63 (30%)	
65-74	82 (42%)	93 (44%)	
≥75	29 (15%)	33 (16%)	
Performance status			0.010[a]
0 or 1	141 (72%)	162 (78%)	
≥ 2	15 (8%)	3 (1%)	
Unknown	41 (21%)	44 (21%)	
Comorbidities			0.707[a]
0	60 (30%)	62 (30%)	
1	49 (25%)	48 (23%)	
≥2	56 (28%)	70 (33%)	
Unknown	32 (16%)	29 (14%)	
Tumor location			0.341[a]
Esophagus	149 (76%)	156 (75%)	
Gastro-esophageal junction or cardia	25 (13%)	20 (10%)	
Stomach	23 (12%)	33 (16%)	
Histology			0.464[c]
Adenocarcinoma	147 (75%)	167 (80%)	
Squamous cell carcinoma	46 (23%)	38 (18%)	
Carcinoma NOS	4 (2%)	4 (2%)	
Stage*			0.028[a]
1	28 (14%)	56 (27%)	
2	22 (11%)	18 (9%)	
3	89 (45%)	83 (40%)	
4	47 (24%)	38 (18%)	
X	11 (6%)	14 (7%)	
Reported BMI, kg/m²			<0.001[a]
<18.5	12 (6%)	1 (0%)	
18.5-25	109 (55%)	80 (38%)	
>25	76 (39%)	128 (61%)	
Reported half-year weight loss			<0.001[a]
Stable weight (<2% weight loss)	0 (0%)	146 (70%)	
Medium weight loss (2-10%)	112 (57%)	63 (30%)	
Severe weight loss (>10%)	85 (43%)	0 (0%)	

*Baseline characteristics of included patients stratified for pretreatment cachexia (i.e. reported half-year body weightloss of >5%, or >2% in patients with a reported BMI of <20 kg/m²). *Stage according to 7th edition of the TNM.*
IQR = interquartile range.
[a] Chi square test, [b] Mann-Whitney U test, c Fisher exact test, d Disease stage according to 7th edition of the AJCC Cancer Staging Manual.

Of all 406 patients, 197 (49%) had pretreatment cachexia (Table 1), and 21% reported that they lost >10% of their body weight within 6 months before diagnosis. Compared with patients without cachexia, those with cachexia were more often female, had more frequently a performance status of ≥2, and had a higher disease stage.

Cachexia and OS

OS was significantly higher in patients without versus with pretreatment cachexia (P<.01; Figure 2), with a median survival of 41 months (25th percentile, 14.7 months) versus 19 months (25th percentile, 8.4 months), respectively. When OS was analyzed per treatment type, a numerical difference in survival between patients with and without cachexia was seen in almost all treatment groups, but this difference was not statistically significant (Supplementary Figure 1).

In multivariable analyses, after adjustment for sex, age, performance status, number

of comorbidities, primary tumor location, disease stage, histology, and treatment strategy, cachexia was independently associated with OS (adjusted hazard ratio [HR], 1.37, 95% CI, 1.03–1.83; Table 2).

Figure 2. Overall survival (OS) in all patients stratified for pretreatment cachexia after completion of the baseline questionnaire and those who completed at least the baseline questionnaire.

All patients

Number at risk

	0	6	12	18	24	30	36
No cachexia	209	192	166	147	132	83	42
Cachexia	197	166	131	103	85	54	31
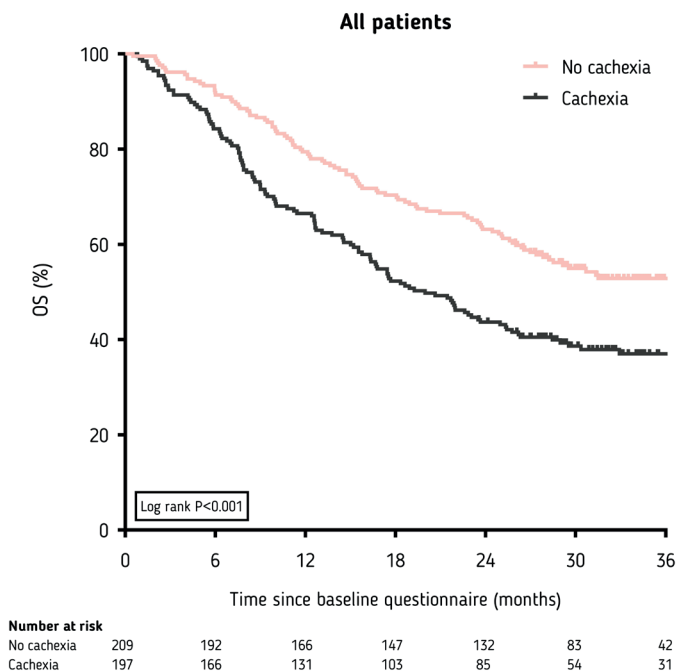
Table 2. Cox Regression Analyses for Overall Survival.

	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Pretreatment cachexia	1.60	1.23-2.08	<0.001	1.37	1.03-1.83	0.030
Female sex	1.16	0.86-1.56	0.349	1.05	0.76-1.46	0.751
Age, years						
<55	Ref			Ref		
54-64	1.23	0.70-1.81	0.633	1.09	0.67-1.77	0.744
65-74	1.08	0.68-1.71	0.743	1.08	0.67-1.74	0.748
≥75	1.67	1.01-2.78	0.048	1.51	0.85-2.69	0.163
Performance status						
0 or 1	Ref			Ref		
≥2	3.04	1.82-5.09	<0.001	1.58	0.87-2.87	0.130
Unknown	1.04	0.75-1.45	0.815	1.07	0.70-1.64	0.760
Number of comorbidities						
0	Ref			Ref		
1	1.20	0.84-1.70	0.317	1.15	0.80-1.67	0.453

≥2	0.96	0.68-1.35	0.812	0.97	0.67-1.41	0.891
Unknown	0.932	0.61-1.42	0.743	1.12	0.67-1.87	0.670
Tumor location						
Esophagus	Ref			Ref		
Gastro-esophageal junction or cardia	1.18	0.79-1.77	0.409	0.88	0.55-1.39	0.573
Stomach	1.05	0.71-1.54	0.821	1.41	0.82-2.41	0.217
Histology						
Adenocarcinoma	Ref			Ref		
Squamous cell carcinoma	1.02	0.74-1.40	0.923	0.95	0.66-1.37	0.788
Carcinoma NOS	0.85	0.32-2.30	0.754	0.77	0.28-2.16	0.619
Stage						
1	Ref			Ref		
2	1.68	0.95-2.98	0.073	1.49	0.81-2.75	0.200
3	1.78	1.17-2.71	0.007	2.16	1.37-3.40	<0.001
4	4.82	3.12-7.43	<0.001	1.54	0.84-2.81	0.161
X	1.31	0.65-2.62	0.448	1.03	0.50-2.14	0.927
Type of treatment						
nCRT and resection	Ref			Ref		
nCT and resection	0.98	0.59-1.61	0.925	0.90	0.39-1.92	0.747
Resection only	0.81	0.36-1.86	0.625	0.96	0.60-4.27	0.925
dCRT	2.09	1.41-3.11	0.002	2.08	1.32-3.72	0.002
Palliative chemotherapy	5.02	3.56-7.09	<0.001	5.54	3.78-13.25	<0.001
Best supportive care	8.00	4.98-12.85	<0.001	7.82	4.85-19.33	<0.001

Abbreviations: dCRT, definitive chemoradiotherapy; GEJ, gastroesophageal junction; HR, hazard ratio; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; NOS, not otherwise specified.

Nutritional Screening and Dietetic Consultation

A total of 65% of patients with cachexia received dietetic consultation before start of treatment compared with 27% of those without cachexia. The proportion of patients with pretreatment cachexia was highest in those who received BSC (67%), followed by those treated with palliative chemotherapy (59%), nCRT + resection (47%), dCRT (43%), nCT + resection (42%), and a resection without neoadjuvant therapy (32%) (Figure 3). A total of 71% of patients with pretreatment cachexia treated with nCRT + resection or dCRT received dietetic consultation before start of treatment compared with 68% of those treated with palliative chemotherapy, 42% of those treated with nCT + resection, and 33% who underwent a resection only. More than half of the patients treated with nCRT + resection, dCRT, palliative chemotherapy, or BSC used oral nutritional supplements (Figure 3).

Overall, the protein score was unknown in 78 patients, which includes those who received tube feeding (n=28) and other patients who did not complete the DHD-FFQ. Of the 328 remaining patients, 267 (81%) had a protein score of <10. Patients with a protein score of 10 received oral nutritional supplements half as often as those with a protein score <10 (16% vs 33%, respectively; P=.009), whereas no difference was seen in the proportion of patients who were referred for dietetic support (34% vs 35%, respectively; P=.952). A total of 152 (78%) of the 194 patients who completed the DHD-FFQ at 3 months had a protein score of <10. The proportion of patients with cachexia who had a protein score of <10 is shown in Figure 3.

Of 103 patients with pretreatment cachexia who completed the baseline and 3-month questionnaires, 60 (58%) received dietetic consultation at baseline. Median half-year pretreatment weight difference was −9% (IQR, −13% to −7%%) in the patients with cachexia

Figure 3. Dietetic interventions, use of nutritional supplements and protein score in patients with cachexia stratified per type of treatment at baseline.
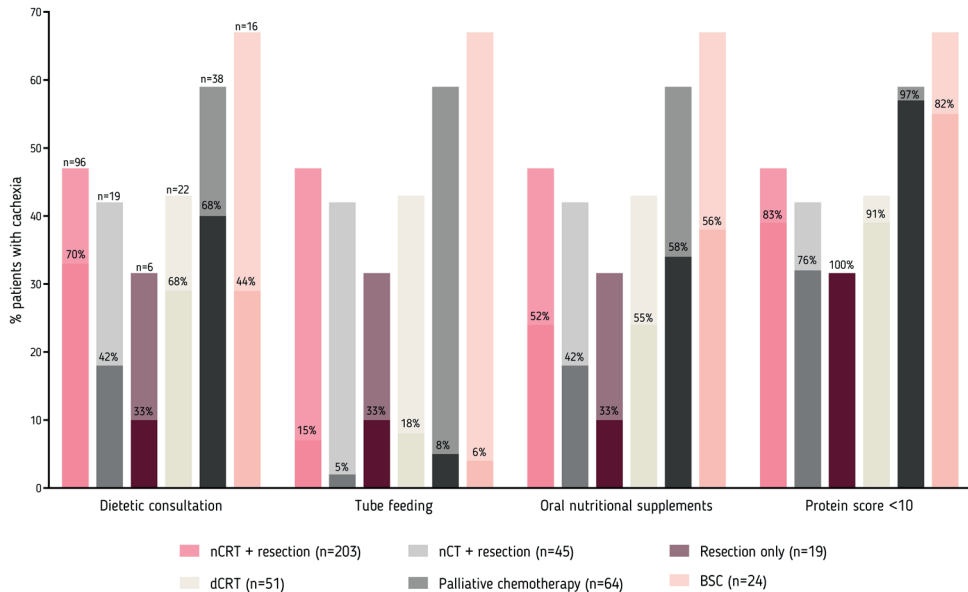
The percentages within the bars reflect the proportion of patients with pretreatment cachexia. Protein scores of patients with cachexia who completed the DHD-FFQ are shown (n=135).
Abbreviations: BSC, best supportive care; DHD-FFQ, the Dutch Healthy Diet Food Frequency Questionnaire; dCRT, definitive chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; SNAQ, Short Nutritional Assessment Questionnaire.

who received dietetic consultation at baseline, and −8% (IQR, −11% to −7%) in the 43 patients with cachexia who did not (P=.222). Weight of the patients who received dietetic consultation was stable in the 3 months thereafter (median weight difference, 0% [IQR, −3% to 2%]), and differed statistically significantly from patients who were not referred at baseline (median weight difference, −2% [IQR, −6% to 2%]; P=.047).

DISCUSSION

Pretreatment cachexia was observed in 48% of 406 patients with esophagogastric cancer and associated with decreased survival. The fact that more than one-third of patients with cachexia did not receive dietetic consultation before start of treatment is worrisome, because body weight loss at 3 months was lower in patients who were referred to a dietician compared with those who were not referred at baseline. Our findings suggest an urgent need for awareness of the importance of nutritional screening and subsequent referral for dietetic interventions at an early stage in multimodal treatment of esophagogastric cancer.

Preventing cachexia is important, because it can ultimately result in a nonreversible, refractory state that is associated with impaired response to anticancer treatment and

limited life expectancy.[12] A previous study of patients with a low initial BMI showed that even subtle weight loss can result in decreased survival,[33] independent of performance status and disease stage. The presence of pretreatment cachexia, which was defined as self-reported half-year body-weight loss of >5% or of >2% in patients with a BMI <20 kg/m^2 according to internationally accepted criteria,[13] was independently associated with shorter OS in our study, emphasizing the need for early screening and interventions and underlining the importance of awareness of the presence of cachexia among physicians to prevent (further) weight loss in every patient with esophagogastric cancer. Unfortunately, information on depletion of skeletal muscle mass and strength was not available, which possibly resulted in an underestimation of patients with cachexia because muscle mass and strength are part of one of the criteria for the determination of cancer cachexia.[13] Nevertheless, nearly one-half of the patients already had cachexia according to the criteria concerning weight loss and BMI only.[13] Ideally, assessment of weight loss, BMI, and skeletal muscle mass will be routinely performed in the future to identify all patients with cachexia.[1]

Nutritional interventions can help stop weight loss and prevent (evolvement of) cachexia.[2,9,25,26,34] We found that patients with cachexia who were referred to a dietician before start of treatment had less weight loss in the subsequent 3 months compared with patients who were not referred before start of treatment. Unfortunately, we could not evaluate the effect of dietetic support on clinical outcomes (eg, quality of life and survival) in this retrospective study. Nevertheless, we did observe that more than one-third of the patients with pretreatment cachexia were not referred to a dietician. Possible causes of nonreferral could include lack of awareness to the presence of cachexia, and inadequate or absence of nutritional screening, which could result in insufficient application of nutritional interventions.[2] Moreover, because cancer-related malnutrition can develop at any time, including during treatment,[35] nutritional risk screening should be performed on a regular basis. It is therefore recommended that each hospital involved in the treatment of cancer should incorporate standard procedures for early and routine screening for malnutrition and implement nutritional interventions for patients in both in-hospital and out-of-hospital settings.[2] This approach should ideally be multidisciplinary, in which the primary responsible physician takes care of the referral, and works closely with the dietician while staying involved in the nutritional status and interventions. These interventions usually include a protein- and energy-enriched diet, possibly supplemented by oral nutritional supplements or tube feeding, adapted to the specific needs of the patient.[2,11]

Use of conventional screening tools for nutritional risk assessment that are validated in hospitalized patients with cancer (ie, SNAQ[23] and MUST[24]) could underestimate malnutrition in the outpatient clinic.[36,37] Retrospectively completing these nutritional screening tools using data from the present study showed that SNAQ and MUST only identified three-quarters and one-half of patients who already had cachexia as being at high risk of malnutrition, respectively. The reason for this is that in patients with a low BMI, a lower percentage of body weight loss is already defined as cachexia.[13,23] An option for screening is to ascertain the presence of cachexia using just the definition that includes body weight loss and BMI, or to use screening tools that include both parameters because they take into consideration the vulnerability of patients with a low BMI,[33] such as the Patient-Generated Subjective Global Assessment Short-Form.[38]

Causes of cancer-related malnutrition and cachexia are multifactorial and include reduced food and/or protein intake, and metabolic changes due to tumor- and treatment-related factors.[10,19] We also found inadequate food intake in a large part of our population. A protein score of <10 was found in 81% of the patients who completed the DHD-FFQ. Among the general healthy population, this score indicates insufficient intake of the protein sources included in the DHD-FFQ. Moreover, in patients with cancer, a higher protein intake (1–1.5 g/kg/d) is recommended than in healthy persons,[2] suggesting that the number of patients with inadequate protein intake from these sources is even higher. Furthermore, only 33% of the patients with a protein score of <10 received oral nutritional supplements. Both findings may have contributed to the reported weight loss.

Although dietetic consultation can be helpful in preventing weight loss, it should be noted that cachexia is not completely reversible by nutritional therapy alone.[10,12] Treatment and prevention of malnutrition and cachexia should therefore occur early in the cancer treatment trajectory and multimodal, and at least consist of physical therapy in addition to dietetic consultation and provision of energy- and protein-enriched dietary advice, possibly supplemented with oral nutritional supplements or (par)enteral nutrition.[2]

A strength of this study is that real-world data were included, which provide a good indication of current practice. However, there were also some limitations. One of the limitations is that there is probably a selection bias of patients who were included in POCOP, with the result that the study population may not reflect the actual patient population and patients with a higher tumor stage or worse nutritional status may not be represented adequately. Because some results were based on patient-reported outcomes, misinterpretations due to inadequate or incomplete reporting cannot be excluded. Unfortunately, we did not know if patients were formally screened for the presence of malnutrition. Moreover, we could not calculate exact protein intake, because the protein score only includes protein sources mostly contributing to intake in a healthy population, and does not include supplements. Furthermore, it would have been interesting to compare treatment intensity and tolerability between patients with and without cachexia, but this was not possible because of the limited number of patients within the treatment groups and missing data. The small sample sizes within the treatment groups also hindered us from stratifying for treatment strategy in the Cox proportional hazard analyses. Because univariable HRs on OS cachexia showed the same pattern in all treatment groups, we put all patients in one model and adjusted for treatment strategy. Lastly, weight loss comparisons were only performed in patients who completed the baseline and 3-month questionnaire, which could have resulted in a selection bias of patients who survived a longer period and were probably in a better condition.

CONCLUSIONS

Cachexia is common in esophagogastric cancer, even before start of treatment, and associated with decreased survival. Physicians should therefore be aware of the risk, presence, and consequences of cachexia already present at initial diagnosis. In the multimodal treatment trajectory, early and adequate nutritional screening and referral for dietetic support are of major importance to prevent weight loss and improve survival outcomes, and are indicated for

every patient with esophagogastric cancer in both the in-hospital and out-of-hospital setting.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Overall survival (OS) of patients stratified for pretreatment cachexia by treatment type: (A) neoadjuvant chemoradiotherapy + resection, (B) neaodjuvant chemotherapy + resection, (C) resection only, (D) definitive chemoradiotherapy, (E) palliative chemotherapy, and (F) best supportive care.

3e. Palliative chemotherapy

3f. Best supportive care

Number at risk

	0	6	12	18	24	30	36		0	6	12	18	24	30	36
No cachexia	26	20	12	7	6	1	1		8	5	3	3	1	0	0
Cachexia	38	24	15	6	4	3	1		16	8	3	1	0	0	0

Disclaimer

According to the Central Committee on Research Involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the scientific committee of the Dutch Upper GI Cancer Group. Patients who participated in the Prospective Observational Cohort Study of Oesophageal-Gastric Cancer Patients (POCOP) provided written informed consent.

Disclosures

Rob Verhoeven has disclosed that he has received grant/research support from Bristol-Myers Squibb and Roche. Martijn van Oijen has disclosed that he has received grant/research support from Bristol-Myers Squibb, Merck Serono, Nordic, Roche, and Servier. Hanneke van Laarhoven van Laarhoven has disclosed that he has received consulting fees from Bristol-Myers Squibb, Celgene, Lilly, Nordic Pharma, and Servier, and grant/research support from Bayer, Bristol-Myers Squibb, Celgene, Lilly, Merck Serono, Merck Sharpe & Dohme, Nordic, Philips, Roche, and Servier. The remaining authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

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09.

Prognostic value of patient-reported quality of life in oesophagogastric cancer: Analysis from the population-based POCOP study

Submitted to Gastric Cancer.

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ABSTRACT

Background: Accumulating evidence of trials demonstrates that patient-reported health-related quality of life (HRQoL) at diagnosis is prognostic for overall survival (OS) in oesophagogastric cancer. However, real-world data are lacking. Moreover, differences in disease stages and tumor specific symptoms are usually not taken into consideration. The aim of this population-based study was to assess the prognostic value of HRQoL, including tumour-specific scales, on OS in patients with potentially curable and advanced oesophagogastric cancer.

Methods: Data were derived from the Netherlands Cancer Registry and the patient reported outcome registry (POCOP). Patients included in POCOP between 2016-2018 were stratified for potentially curable (cT1-4aNallM0) or advanced (cT4b or cM1) disease. HRQoL was measured with the EORTC QLQ-C30 and the tumour-specific OG25 module. Cox proportional hazards models assessed the impact of HRQoL, sociodemographic and clinical factors (including treatment) on OS.

Results: 924 patients were included. Median OS was 38.9 months in potentially curable patients (n=795) and 10.6 months in patients with advanced disease (n=129). Global Health Status was independently associated with OS in potentially curable patients (hazard ratio 0.89, 99% confidence interval 0.82-0.97), together with several OG-25 domains (dysphagia, eating restrictions, odynophagia, and body image). In advanced disease, the QLQ-C30 Summary Score was the strongest independent prognostic factor (hazard ratio 0.75, 99% confidence interval 0.59-0.94), followed by role functioning, fatigue, pain and insomnia.

Conclusion: In a real-world setting, HRQoL was prognostic for OS in patients with potentially curable and advanced oesophagogastric cancer. Several HRQoL domains, including the Summary Score and several OG-25 items, could be used to develop or update prognostic models.

INTRODUCTION

The prognostic value of health-related quality of life (HRQoL) on overall survival (OS) has been described in patients with several types of cancer[1–4], including oesophagogastric cancer.[3,5–10] Most knowledge regarding the prognostic value of HRQoL in oesophagogastric cancer originates from RCTs[3,5,6,8–10] rather than from population-based studies.[7] As the typical trial patient reflects only 5-10% of the general population due to stringent inclusion criteria of RCTs, trial populations may not adequately represent the real-world cancer population.[11,12] Moreover, the prognostic value of HRQoL may vary between patients with potentially curable and advanced (i.e. irresectable or metastatic) oesophagogastric cancer. In patients with advanced oesophagogastric cancer participating in RCTs, an association between fatigue[10], reflux[10], social functioning[6], physical functioning[13] and OS was found, while physical symptoms[9] were prognostic for OS in potentially curable patients. Since the majority of the patient reported outcome (PRO) data were collected in patients with advanced disease, results of potentially curable patients are scarce. Population-based data could add valuable information to those collected in RCTs on the prognostic value of HRQoL in both patient subgroups.

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 is the most commonly used questionnaire to measure HRQoL in oesophagogastric cancer.[14] It can be supplemented by the QLQ-OG25 questionnaire – a module assessing typical symptoms within oesophagogastric cancer.[15] To our knowledge, the prognostic value of OG-25 module has not been studied. In addition, the QLQ-C30 Summary Score was recently developed, and combines scores of symptom and functioning scales of the QLQ-C30 into a single score.[16] While recent results of a population-based study showed a strong prognostic value of the Summary Score in Dutch patients with colorectal, prostatic and haematological malignancies[17], its prognostic value within oesophagogastric cancer has yet to be determined.

Since 2016, clinical and PRO data of Dutch oesophagogastric cancer patients are collected in the Prospective Observational Cohort Study of Oesophageal-gastric cancer Patients (POCOP), including the QLQ-C30 and OG25 questionnaires.[18] The aims of this population-based study were to assess the independent prognostic value of the recently developed Summary Score, the frequently used Global Health Status (GHS) and the other QLQ-C30 and QLQ-OG25 domains on OS in patient with potentially curable (cT1-4a, M0) and advanced (cM1 or cT4b) oesophagogastric cancer in real world, alongside sociodemographic and clinical prognostic factors.

METHODS

Design and data source
Clinical data regarding the patient, tumour, and treatment were derived from the nationwide Netherlands Cancer Registry (NCR). Information on vital status was obtained by linkage to the Dutch municipality registry in February 2020. Baseline PROMs data of the included patients were extracted from the POCOP-registry.[15] All patients provided written informed consent for study participation and linkage with the NCR.

We included patients who were diagnosed with cancer in the oesophagus, gastro-oesophageal junction or stomach (C15 and C16 according to the 3rd version of the ICD-10[19]) between 2016 and 2018, in order to have enough follow-up data on survival times. Patients were eligible for inclusion irrespective of treatment type, but were excluded if the baseline questionnaire was completed more than seven days after start of initial treatment. The baseline PROMs were sent via mail (paper) or email (electronic questionnaire using the PROFILES platform[20]) dependent on patients' preferences.

HRQoL
The 30-item QLQ-C30 (v3.0) is a validated cancer-specific questionnaire, to be completed by the patient.[21] It contains five functional scales, a global QoL scale (GHS), three symptom scales and six single items.[21] A scoring procedure was applied according to the EORTC scoring manual.[22] Herewith, scores were linearly transformed to a score between 0 and 100. The QLQ-C30 Summary Score was calculated as the mean of the combined thirteen QLQ-C30 scale and item scores (excluding GHS and financial difficulties). Higher functioning scores, GHS and Summary Scores indicate better HRQoL, whereas higher symptom scores represent

more severe symptoms. The QLQ-OG25 scales and items are scored similarly, in which a higher score represents more severe symptoms.

Clinical and sociodemographic factors

Clinical and sociodemographic variables included age at diagnosis, marital status, ECOG performance status (PS), body mass index and weight loss in the month before diagnosis, the presence of peritoneal or liver metastases, number of metastatic sites, number of comorbidities, clinical disease stage, tumour differentiation grade and treatment type. Selection of these variables was based on a systematic review5 and clinical data availability in the NCR and POCOP registry.[18] Initial treatments for potentially curable patients, i.e. those with a cT1-4a, Nall, M0 disease stage, consisted of: 1) resection (with or without (neo) adjuvant chemotherapy or chemoradiotherapy [CRT; chemotherapy with concurrent long scheme radiotherapy, i.e. ≥23 fractions or a duration of ≥28 days]) , 2) chemoradiotherapy only, i.e. without a resection, and 3) other treatments (systemic treatment, radiotherapy, best supportive care [BSC]). Initial treatments for patients with advanced (i.e. metastatic [cM1] or irresectable [cT4b]) disease consisted of : 1) systemic therapy (chemotherapy and/or targeted therapy with or without radiotherapy, 2) BSC (including radiotherapy and stent placement) or 3) other (resection of primary tumour or metastases).

Statistical analysis

The primary endpoint was OS defined from the date of diagnosis till the date of death by any cause. OS was calculated from date of diagnosis, because baseline variables were included at diagnosis and patients could enter at any time in the POCOP cohort (after diagnosis, during treatment or during follow-up). Patients alive at the time of analysis were censored at the date of last follow-up (February 1, 2020). Our primary HRQoL variables of interest were the novel Summary Score and the GHS. Functioning and symptoms scales/items were of secondary interest.

Cox's proportional hazard regression models were used to assess the impact of HRQoL and other clinical and sociodemographic variables on OS. The hazard ratios (HRs) of all HRQoL scales were reported to represent a clinically meaningful difference of 10 points.[23]

To start, a multivariable model with clinical and sociodemographic variables5 was constructed using backwards selection (starting with full model and removal of variables if p>0.05). To investigate the added value of HRQoL variables, first, univariate analyses were performed to assess the association of HRQoL with OS. Second, HRQoL variables (p<0.05 in step 1) were added to the multivariable clinical/sociodemographic model separately to control for effects of prognostic clinical and sociodemographic variables (p<0.01).[5] Third, a final multivariable model was fitted with forced entry of the clinical and sociodemographic variables, and multiple HRQoL variables (p<0.01 in step 2) to also account for associations among HRQoL scores.[7] HRs of HRQoL items were regarded to be statistically significant at p<0.01. Nagelkerke's R2 was used to address the outcome variance explained by clinical, sociodemographic and HRQoL variables. An increase of 5% in explained variance for HRQoL variables with adjustment for clinical factors was considered clinically relevant.[24] All analysis were stratified per patient group, i.e. potentially curable versus advanced disease, and performed in Stata 16.1 (StataCorp, College Station, TX).

RESULTS

Patient characteristics
Of all included patients (n=924), 787 (85.2%) completed the baseline questionnaire before the start of treatment and 137 (14.8%) within seven days of starting treatment. Mean GHS scores (73.7 versus 73.6, Student's t-test, p=0.91) did not differ significantly between patients with a true versus non-true (i.e. within seven days of starting treatment) baseline questionnaire. OS was also comparable (29.9 versus 30.5 months, log-rank: p=0.88), suggesting no association of questionnaire compliance or worsened GHS scores with early death in the overall cohort.

Of the entire cohort, 795 (86%) had potentially curable disease (Table 1). In the potentially curable and advanced subgroup, 277 (34.8%) and 105 (81.4%) patients died and median survival was 38.9 and 10.6 months, respectively. Potentially curable patients were treated with surgery alone (5.7%), surgery plus CRT (59.9%) surgery plus CT (14%) or CRT alone (17.5%). Twenty-four patients (3%) received systemic therapy, radiotherapy or BSC, due to for example poor PS, interval metastases or on patient's request. Patients with advanced disease at diagnosis were treated with systemic therapy (59.7%), BSC including radiotherapy, stent and/or pain management (27.9%) and other treatments e.g. resection of metastases (12.4%).

Table 1. Patient, tumour and treatment characteristics.

Characteristics	Patients with potentially curable disease (n = 795)		Patients with advanced disease (n = 129)	
	No.	%	No.	%
Age (mean, SD)	66.5 (8.4)	-	65.9 (8.8)	-
Gender				
Male	611	76.9	94	72.9
Female	184	23.1	35	27.1
Performance status				
0-1	653	82.1	92	71.3
2-4	32	4	13	10.1
Unknown	110	13.8	24	18.6
Comborbidities				
0	183	23	37	28.7
1	199	25	34	26.4
≥2	235	29.6	33	25.6
Unknown	178	22.4	25	19.4
Weight loss in kilograms (mean, SD)	2.2 (3.6)	-	3.3 (3.9)	-
Tumour location				
Oesophagus	585	73.6	67	51.9
Gastro-oesophageal junction	101	12.7	20	15.5
Stomach	109	13.7	42	32.6
Histology				
Adenocarcinoma	656	82.5	114	88.4
Squamous cell carcinoma	139	17.5	15	11.6
Histological differentiation grade				
1	29	3.7	6	4.7
2	296	37.2	33	25.6
3/4	294	37	52	40.3
Unknown	176	22.1	38	29.5
Clinical stage				
1	65	8.2	-	-
2	202	25.4	-	-
3	396	49.8	2	1.6
4	89	11.2	127	98.5
Unknown	43	5.4	-	-
Number of distant metastatic sites				
0	-	-	9	7.0
1	-	-	80	62.0
≥2	-	-	40	31.0
Initial treatment				
Resection (+/- systemic treatment or chemoradiotherapy)	632	79.5	-	-
Chemoradiotherapy	139	17.5	-	-
Palliative treatment (systemic treatment, radiotherapy or BSC)	24	3	-	-
Systemic treatment (+/- radiotherapy)	-	-	77	59.7
BSC (+/- radiotherapy)	-	-	36	27.9
Other	-	-	16	12.4

SD, standard deviation; BSC, best supportive care.

Table 2. Mean and standard deviation of baseline HRQoL scores per patient subgroup.

HRQoL	n	Missing items (%)	Mean (SD)	n	Missing items (%)	Mean (SD)
	Patients with potentially curable disease Baseline			Patients with advanced disease Baseline		
EORTC QLQ-C30						
Summary Score	786	1.1%	84.7 (12.7)	124	3.9%	80.6 (12.7)
Global Health Status	790	0.6%	74.3 (17.8)	127	1.6%	70.4 (17.3)
Functioning EORTC QLQ-C30						
Physical functioning	794	0.1%	87.4 (15.8)	128	0.8%	84.6 (17.1)
Role functioning	794	0.1%	83 (24.6)	128	0.8%	76 (25.9)
Emotional functioning	792	0.4%	77.9 (19.7)	127	1.6%	74.1 (19.5)
Cognitive functioning	792	0.4%	89.7 (16.8)	127	1.6%	89.5 (15.5)
Social functioning	792	0.4%	85.3 (21.2)	127	1.6%	80.6 (24.5)
Symptoms EORTC QLQ-C30						
Fatigue	793	0.3%	23.7 (21.6)	128	0.8%	30.8 (22.2)
Nausea and vomiting	793	0.3%	10.7 (18.2)	128	0.8%	14.2 (20.2)
Pain	794	0.1%	14.5 (18.9)	129	0.0%	18.9 (21.3)
Dyspnea	794	0.1%	11.6 (20.4)	128	0.8%	13.5 (20.3)
Insomnia	793	0.3%	22.3 (27.6)	128	0.8%	25.5 (27.3)
Appetite loss	790	0.6%	19.4 (27.2)	127	1.6%	30.7 (33.8)
Constipation	791	0.5%	12.6 (22.2)	128	0.8%	16.9 (24.4)
Diarrhea	792	0.4%	6.5 (16.5)	127	1.6%	7.3 (17.8)
Financial difficulties	788	0.9%	6.4 (16.9)	127	1.6%	6.3 (17.2)
Symptoms EORTC QLQ-OG25						
Dysphagia	793	0.3%	21.4 (22.9)	125	3.1%	27.5 (25.1)
Eating restrictions	790	0.6%	30.8 (27.6)	125	3.1%	40.7 (31.3)
Reflux	789	0.8%	6.9 (16.9)	125	3.1%	6 (12.6)
Odynophagia	787	1.0%	23.6 (25.7)	125	3.1%	24.1 (25.1)
Pain and discomfort	788	0.9%	17.4 (23.6)	125	3.1%	21.3 (22.7)
Anxiety	791	0.5%	50.7 (25.8)	127	1.6%	56.7 (26.3)
Eating with others	788	0.9%	15.3 (27.8)	122	5.4%	16.4 (28.2)
Dry mouth	791	0.5%	13.7 (23.2)	125	3.1%	19.5 (28.8)
Trouble with taste	789	0.8%	11.6 (23.5)	124	3.9%	17.8 (27.4)
Body Image	791	0.5%	9.3 (20.6)	125	3.1%	18.1 (26.9)
Trouble swallowing saliva	793	0.3%	9.7 (21.6)	129	0.0%	12.9 (25.5)
Choked when swallowing	792	0.4%	6.7 (17.6)	129	0.0%	4.9 (13.2)
Coughing	788	0.9%	20.1 (22.4)	129	0.0%	18.3 (22)
Trouble talking	789	0.8%	3.9 (12.5)	127	1.6%	6 (15.9)
Worrying about weight loss	791	0.5%	18.9 (26.5)	128	0.8%	31.8 (31.3)

SD, standard deviation.

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Health-related quality of life

Missing HRQoL data on item level (not on patient level) ranged from 0.1%-5.4% for the baseline questionnaire (Table 2). For the cT1-4a/M0-subgroup, mean symptom scores were highest for anxiety (50.9), eating restrictions (30.8), and fatigue (23.7). For the advanced disease subgroup, mean symptom scores were highest for anxiety (56.7), eating restrictions (40.7), and worrying about weight loss (31.8).

Figure 1. Survival curve stratified per patient subgroup and EORTC QLQ-C30 Summary Score.
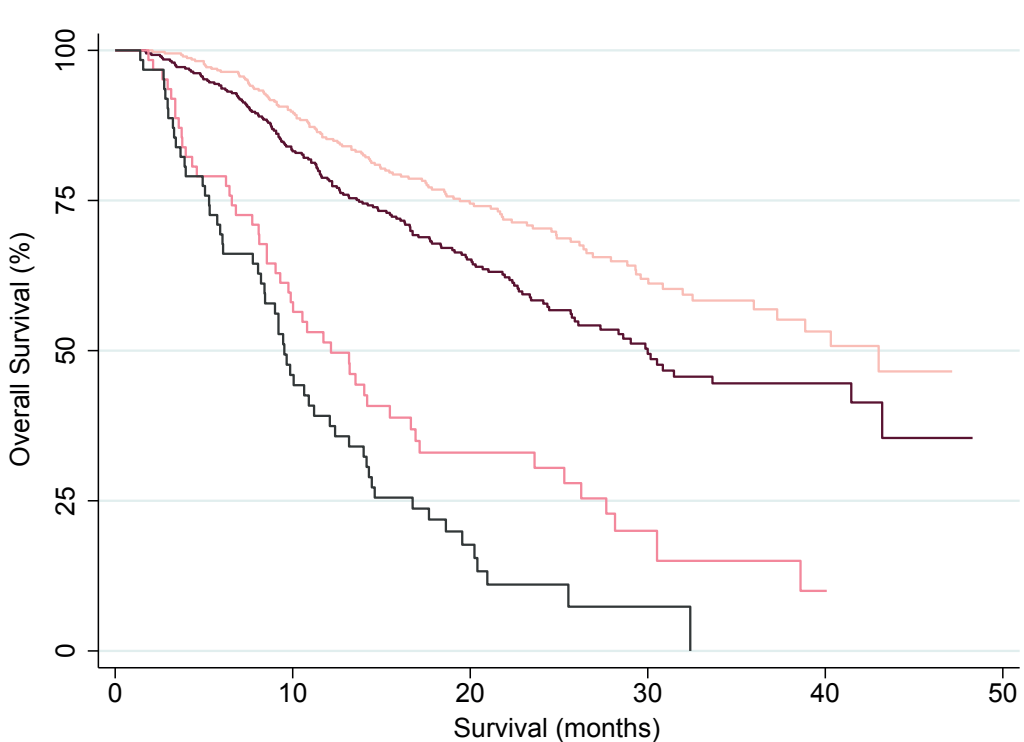
The light pink line presents patients with cT1-4aNM0 disease with a Summary Score above median. The red line presents patients with cT1-4a, N all, M0 disease with a Summary Score below median. The pink line presents patients with cT4b/cM1 disease with a Summary Score above median. The grey line presents patients with cT4b/cM1 disease with a Summary Score below median.

Prognostic value of the Summary Score and Global Health Status scale

Figure 1 shows the association between the Summary Score and OS stratified per patient subgroup (log-rank: p=0.002 and p=0.03 for the potentially curable and advanced disease subgroup, respectively). In the cT4b/M0-subgroup, the Summary Score was only significantly associated with OS in univariable Cox regression analysis (Table 3). In the cT4b/M1-subgroup, the Summary Score was significantly associated with OS in both uni- and multivariable analysis. Adjusted for clinical factors, for every 10-point increase in the Summary Score a 25% reduction in the risk of death at any given time was observed (HR 0.75, 99% CI 0.59-0.94, p=0.001).

Figure 2. Survival curve stratified per patient subgroup and EORTC QLQ-C30 Global Health Status score.
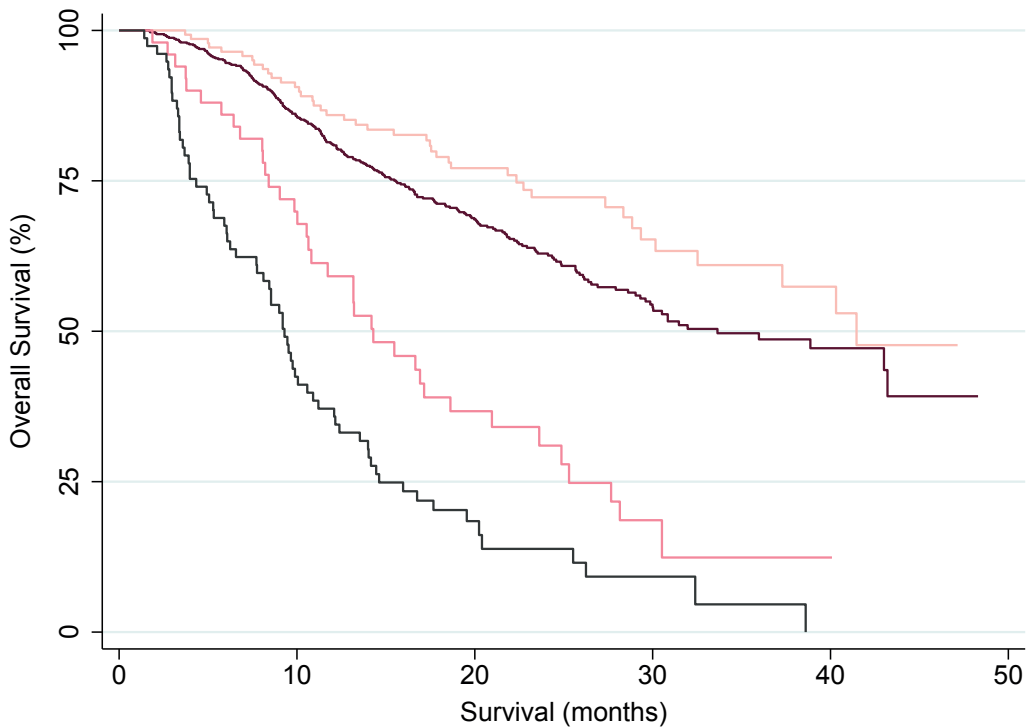
The pink line presents patients with potentially curable disease with a GHS score above median. The red line presents patients with potentially curable disease with a GHS score below median. The pink line presents patients with advanced disease with a GHS score above median. The grey line presents patients with advances disease with a GHS score below median.

Figure 2 shows the association between GHS and OS stratified per patient subgroup (log-rank: p=0.04 and p=0.005 for the potentially curable and advanced disease subgroup, respectively). In the potentially curable subgroup, Cox regression showed a significant association with OS in uni- and multivariable analysis. Adjusted for clinical factors, for every 10-point increase in the GHS score an 11% reduction in the risk of death at any given time was observed (HR 0.89, 99% CI 0.82-0.97, p<0.001). In the subgroup of patients with advanced disease, GHS was only significantly associated with OS in univariate analysis. This effect did not remain when adjusted for other clinical factors (Table 3).

Table 3. Unadjusted and adjusted cox regression analysis of EORTC QLQ-C30 and OG25 symptom and functioning scales and items.

HRQoL	Patients with potentially curable disease		Patients with advanced disease	
	HR (99% CI)	P value	HR (99% CI)	P value
Unadjusted analysis of primary HRQoL variables				
Summary Score	0.88 (0.79-0.98)	0.003	0.76 (0.62-0.92)	<0.001
Global Health Status	0.89 (0.82-0.96)	<0.001	0.82 (0.70-0.95)	0.001
HRQoL variables adjusted for clinical variables				
Summary Score	0.95 (0.84-1.06)	0.22	0.75 (0.59-0.94)	0.001
Global Health Status	0.89 (0.82-0.97)	0.001	0.88 (0.75-1.04)	0.054
Appetite loss	1.06 (1.00-1.12)	0.006	1.08 (1.00-1.18)	0.013
Role functioning	0.96 (0.91-1.02)	0.089	0.89 (0.80-1.00)	0.008
Fatigue	1.02 (0.95-1.10)	0.397	1.16 (1.03-1.31)	0.002
Pain	1.07 (0.99-1.16)	0.026	1.16 (1.02-1.32)	0.003
Insomnia	0.99 (0.94-1.05)	0.720	1.13 (1.02-1.25)	0.002
Dysphagia	1.12 (1.05-1.19)	<0.001	1.03 (0.93-1.15)	0.420
Eating restrictions	1.10 (1.04-1.16)	<0.001	1.07 (0.98-1.18)	0.054
Odynophagia	1.06 (1.01-1.13)	0.004	1.08 (0.97-1.20)	0.052
Body Image	1.08 (1.01-1.16)	0.002	1.05 (0.95-1.16)	0.208
All HRQoL items adjusted for clinical and other HRQoL variables				
Summary Score	NA	NA	0.75 (0.59-0.94)	0.001
Eating restrictions	1.10 (1.04-1.16)	<0.001	NA	NA

Hazard ratios are given for every 10-point increase in HRQoL scores. Clinical covariates for the potentially curable subgroup were: treatment type, clinical stage and tumour differentiation grade. Clinical covariates for advanced disease-subgroup were: treatment type, performance status, peritoneal metastases, age, and marital status. HRQoL, health-related quality of life; HR, hazard ratio; CI, confidence interval.

Prognostic value of QLQ-C30 & OG25 symptom and functioning scores

Table 3 shows the prognostic value of nine symptom and functioning scales/items that yielded additional prognostic information independent of clinical variables. In the potentially curable subgroup, appetite loss, dysphagia, eating restrictions, body image and odynophagia were independently associated with OS, with HRs ranging from 1.06-1.12. In the advanced disease subgroup, role functioning, fatigue, pain, and insomnia were independently associated with OS, with HRs ranging from 1.13-1.16 for symptom items, and 0.89 for role functioning.

When adjusting for associations between multiple HRQoL scores alongside clinical variables, only eating restrictions (HR 1.10, 99% CI 1.04-1.16, p<0.001) remained significantly associated with survival in the potentially curable subgroup and the Summary Score in the advanced disease subgroup (HR 0.75, 99% CI 0.59-0.94, p=0.001).

Explained variance

Figure 3 shows which percentage of outcome variance was explained by clinical and baseline HRQoL variables. In the potentially curable subgroup, clinical variables (treatment type, clinical stage, differentiation grade) explained 24.4% of the variance in OS. Adding HRQoL variables to the model explained 2.5% additionally for GHS, 1.0% for appetite loss, 3.3% for dysphagia, 3.8% for eating restrictions, 2.4% for odynophagia and 1.8% for body image,

separately. In the advanced disease subgroup, clinical variables (treatment type, PS, peritoneal metastases, age and marital status) explained 24.6% of the variance in OS. In addition, role functioning added 3.6%, fatigue 4.8%, pain 4.1% and insomnia 4.7%, separately. The Summary Score explained most of the OS variance, i.e. 5.6% additionally within this subgroup.

Figure 3. Explained variance in overall survival of HRQoL variables in addition to sociodemographic and clinical variables.
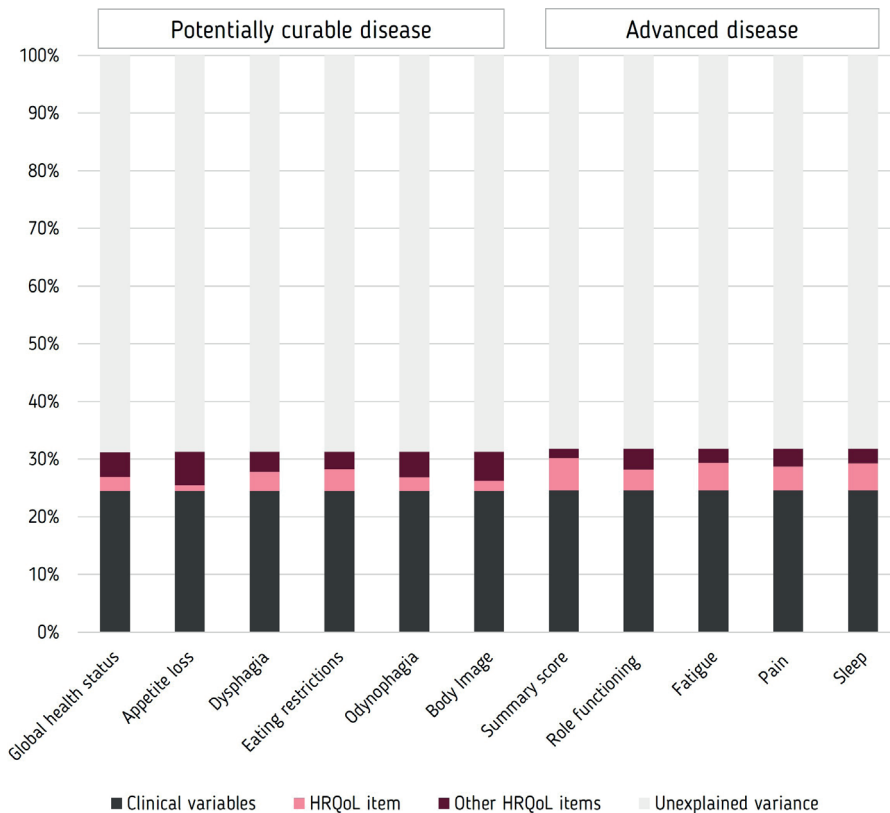
Displayed are only HRQoL scales and items that showed significant prognostic value in multivariate cox regression analysis. Clinical covariates for patients with potentially curable disease were: treatment type, clinical stage and tumour differentiation grade. Clinical covariates for patients with advanced disease were treatment type, performance status, peritoneal metastases, age, and marital status. HRQoL = health-related quality of life.

DISCUSSION

Several studies have reported on the prognostic value of HRQoL in oesophagogastric cancer patients participating in trials.[3,5–10] Our results show that several QLQ-C30 HRQoL scales, including the Summary Score, and some OG-25 items, are significantly associated with OS in the real-world setting as well.

For potentially curable patients, GHS was an independent prognostic factor. GHS is one of the most commonly used HRQoL-endpoints in clinical trials within oesophagogastric cancer. In addition, four symptoms of the QLQ-OG25, i.e. dysphagia, eating restrictions,

odynophagia and body image, were independent prognostic factors for OS, highlighting the importance of the use of this questionnaire in addition to the QLQ-C30. It could be argued that dysphagia, eating restrictions and odynophagia could be associated with tumour size and/or topography. However, these scores remained independent prognostic factors even when adjusting for clinical stage. Its specific relation to tumour size could not be investigated in our study population due to a lack of data on the precise size of the tumour, and possible mechanical obstruction. Interestingly, body image was also prognostic for OS, which is in line with recent results in pancreatic cancer patients.[24] It is hypothesized that body image is associated with nutritional status, and that involuntary weight loss resulting in cachexia may induce a negative perception of one's body.[25] A strong association between cancer-associated weight loss and cachexia with OS has been observed in many cancer types,[26–28] including in this POCOP population.[29]

In patients with advanced oesophagogastric cancer, the Summary Score was independently associated with OS. The population-based study of Husson et al. also found that the Summary Score was the strongest prognostic factor across several cancer types, with a HR of 0.77, which is comparable with the HR of 0.75 we observed.[17] Moreover, we found that pain was independently associated with OS. As argued by Mierzynska et al., patient reported pain might be more sensitive during specific disease stages than medical imaging results, indicating that pain could be indicative of progression even before growth could be measured by medical imaging techniques.[3]

Whereas previous studies suggested that the prognostic value of HRQoL may vary across cancer types,[2,17] our study shows that it can also vary within one cancer type, i.e. between patients with potentially curable and advanced disease. Physically focused symptoms, like dysphagia, eating restrictions and odynophagia had prognostic value in potentially curable patients, while symptoms with regard to role functioning, fatigue, insomnia and pain had prognostic value for patients with late stage disease.

Although physical functioning is one of the most reported prognostic domains of the QLQ-C30 across different cancer types,[3] we did not find it to be an independent prognostic factor when adjusting for other variables, including treatment type and/or PS. This might be due to multicollinearity between PS, received treatment and physical functioning. The same interrelationship may hold for dysphagia, eating restrictions and odynophagia, which may explain that only eating restrictions was retained in the final model.

Strengths of this population-based study are its multicentre design, representing the majority of the hospitals in the Netherlands. The amount of missing data at the item level was very limited.[3] In our analyses, we tested the prognostic value of HRQoL alongside established prognostic clinical and sociodemographic factors, as recommended by Mierzynska et al.[3] Since clinical practice and decision making are mainly based on clinical, sociodemographic and/or pathological information, we applied this approach to our analysis as well. Within this clinically driven treatment framework, we believe it is key to investigate the extent to which HRQoL can add additional information regarding prognostication. With regard to the additional explained variance in OS, only the Summary Score was found to explain >5% of the survival outcome in patients with distant metastases. While a 5% threshold is somewhat arbitrary, our findings show that although statistically significant, the added value of most HRQoL scales are only modest. This finding is supported by other studies across a range of cancer types.[3,30]

This study has some limitations. We also included patients who filled out PROMS within seven days after starting initial treatment. Officially, these data are therefore not true baseline values. However, there was no statistically significant association between OS and HRQoL between patients with true and non-true baseline data. Absolute HRQoL and OS values were also comparable between these two groups. Therefore, we see no additional risk of bias. Additionally, we only included patients who were participating in POCOP and hence were willing to complete questionnaires. Our sample consisted of fewer patients (14%) with advanced disease in comparison to the population prevalence of advanced disease at diagnosis, which is 40-50%.[31,32] This potential selection bias may therefore hamper the external validation of this study.

Conclusion
HRQoL was significantly associated with OS in patients with potentially curable and advanced oesophagogastric cancer in a real-world setting. The HRQoL domains that were found to be prognostic, including the recently developed Summary Score and several OG-25 items, could be used to develop or update prognostic models in oesophagogastric cancer.

Disclaimer
According to the Central Committee on Research Involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the scientific committee of the Dutch Upper GI Cancer Group. Patients who participated in the Prospective Observational Cohort Study of Oesophageal-Gastric Cancer Patients (POCOP) provided written informed consent.

Conflicts of interest
Rob Verhoeven reports grants from BMS and Roche. Nadia Haj Mohammad reports a consult/advisory role for BMS, MSD Servier, Eli Lilly, Astra Zeneca, reserach grant from Servier. Martijn van Oijen reports grants from Amgen, BMS, Lilly, Nordic, Merck, Roche and Servier. Hanneke van Laarhoven reports a consult/advisory role for BMS, Celgene, Lilly, Merck, Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

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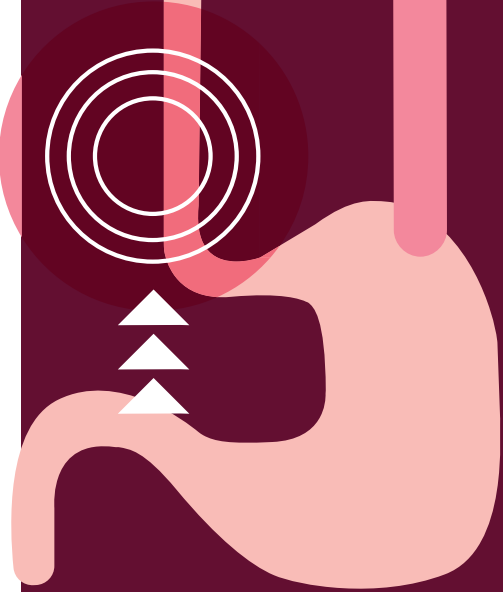
Gender differences in treatment allocation and survival of advanced gastroesophageal cancer:
A population-based study

Journal of the National Cancer Institute, 2021.

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ABSTRACT

Background: Biological sex and gender have been reported to impact incidence and overall survival (OS) of curatively treated gastroesophageal cancer. The aim of this study was to compare palliative treatment allocation and OS between women and men with advanced gastroesophageal cancer.

Methods: Patients with an unresectable (cT4b) or metastatic (cM1) esophageal (including cardia) adenocarcinoma (EAC) or squamous cell carcinoma (ESCC), or gastric adenocarcinoma (GAC) diagnosed in 2015-2018 were identified in the Netherlands Cancer Registry. Treatment allocation was compared using chi-squared tests and multivariable logistic regression analyses, and OS using the Kaplan-Meier method with log-rank test and Cox proportional hazard analysis.

Results: Of patients with EAC (n=3,077), ESCC (n=794) and GAC (n=1,836), 18.0%, 39.4% and 39.1% were women, respectively. Women received less often systemic treatment compared to men in EAC (42.7% vs. 47.4%, P=0.045) and GAC (33.8% vs. 38.8%, P=0.031), but not in ESCC (33.2% vs. 39.5%, P=0.074). Women had a lower probability of receiving systemic treatment in GAC in multivariable analyses (odds ratio 0.78, 95% confidence interval 0.62-1.00), but not in EAC (odds ratio 0.87, 95% confidence interval 0.70-1.08) and ESCC (odds ratio 0.82, 95% confidence interval 0.58-1.15). Median OS was lower in women with EAC (4.4 vs. 5.2 months, P=0.037), but did not differ after adjustment for patient and tumor characteristics and systemic treatment administration.

Conclusion: We observed statistically significant and clinically relevant gender differences in systemic treatment administration and OS in advanced gastroesophageal cancer. Causes of these disparities may be sex-based, i.e. related to tumor biology, as well as gender-based, e.g. related to differences in treatment choices.

INTRODUCTION

Gastroesophageal cancer occurs more frequently in men.[1–3] In the Netherlands, approximately 750 women are diagnosed with an esophageal or gastroesophageal junction (GEJ)/cardia carcinoma annually, compared to 2200 men.[1] This difference is smaller in gastric cancer, with a yearly incidence of 450 women and 700 men.[1]

While the overrepresentation of men in the incidence of gastroesophageal cancer has been described frequently,[2-4] less is known about gender differences in outcomes in this patient population. Overall, men have poorer outcomes in a wide range of cancer types.[1–6] However, poorer survival in women have been described in gastric cancer,[7,8] whereas similar survival rates in women have been observed in esophageal cancer,[4,9] and even better outcomes in women <55 years with esophageal squamous cell carcinoma.[9]

Causes of disparities in incidence and outcomes between men and women with gastroesophageal cancer can be either based on biological, i.e. sex-, or sociocultural, i.e. gender-related factors. Biological factors include differences in the distribution of molecular subtypes or genetic causes.[10] Gender based causes may include individual exposure to risk factors, such as obesity, smoking and alcohol,[9,11] but also treatment choices and factors associated with the need for and access to health care.[12]

Earlier studies comparing outcomes between women and men in metastatic gastroesophageal cancer did not consider the use of palliative systemic treatment,[8,9] while this may differ and influence survival. Exploration of differences in both clinical characteristics and the probability of receiving treatment in advanced gastroesophageal cancer could help understanding possible differences in outcome. The aim of this population-based study was to compare patient and tumor characteristics as well as treatment allocation and overall survival (OS) between women and men in a nationwide cohort of patients with unresectable or metastatic gastroesophageal cancer.

MATERIAL AND METHODS

Data collection
Patients of ≥18 years with a histologically confirmed esophageal (including GEJ/cardia) adenocarcinoma (EAC) or squamous cell carcinoma (ESCC), or gastric adenocarcinoma (GAC), diagnosed with synchronous metastases (cM1) or an unresectable carcinoma (cT4b) at initial diagnosis between 2015 and 2018 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 nationwide network and registry of histo- and cytopathology (PALGA) that comprises all histologically confirmed cancer diagnoses. The hospital in which the initial diagnostic assessment was performed was considered the hospital of diagnosis. Patient and tumor characteristics at initial diagnosis, including gender identity, and information about initial treatment and follow-up were extracted from the hospital's medical records by specially trained data managers. Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020. Clinical staging was performed according to the TNM 7th (2015-2016) and 8th edition (2017-2018).[13,14] Dutch guidelines recommend initial staging with gastroscopy with biopsies and CT scan in all patients, and endoscopic ultrasonography, fluorodeoxyglucose positron emission tomography (FDG-PET)/CT and diagnostic laparoscopy on indication.[15,16]

Type of treatment was subdivided in the following categories: systemic treatment; radiotherapy on the primary tumor (without systemic treatment); radiotherapy on metastases; or surgical resection. Systemic treatment was also subdivided in chemoradiotherapy (i.e. systemic treatment with long scheme radiotherapy, i.e. ≥23 fractions) and systemic treatment without long-term radiotherapy. If none of these treatments was applied, patients were assumed to have received best supportive care only.

Statistical analysis
All analyses were fully stratified for primary tumor location in combination with histology, i.e. EAC, ESCC and GAC. Patient and tumor characteristics were displayed with counts and percentages or medians and interquartile ranges (IQRs) for men and women separately. Differences were analyzed using chi-squared, Fisher's exact or Mann-Whitney U tests, whichever was appropriate. Unadjusted differences in the probability of receiving systemic treatment between genders were analyzed with chi-squared tests. To identify possible

differences in systemic treatment administration among age groups, also age-stratified chi-squared tests were performed. Additionally, multivariable logistic regression analyses were used to identify the adjusted difference in the probability of receiving systemic treatment between genders. Age, performance status, number of comorbidities, Lauren classification (only for EAC and GAC subgroups), tumor stage, metastases locations, and hospital volume were included in the full model as covariates. Hospital volume is associated with the probability of receiving curative or palliative treatment for gastroesophageal cancer in The Netherlands,[17–19] and was calculated using the number of patients diagnosed with gastroesophageal cancer per hospital in 2015-2018, subdivided in quartiles based on these volumes. Statistical significance of the adjusted differences between genders was determined with likelihood-ratio tests, comparing the full model to the full model without gender.

OS was calculated from day of diagnosis in survival analyses for all EAC, ESCC and GAC patients, and log-rank tests were performed to compare OS between genders. Multivariable Cox proportional hazard analyses were used to determine the effect of gender on overall survival, by comparing the models including gender, the interaction between gender and systemic treatment, treatment and clinical covariates (age, performance status, number of comorbidities, tumor stage, Lauren classification [in EAC and GAC], metastases locations, and hospital volume), with a model including systemic treatment and clinical covariates only, using likelihood-ratio tests. P values <0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

RESULTS

Patient selection
After exclusion of patients with a carcinoma not otherwise specified (NOS) (n=503), 14,503 patients with an gastroesophageal adenocarcinoma or squamous cell carcinoma were identified (Figure 1). Carcinoma NOS was equally distributed among men and women. Of all 5,707 patients with a cT4b and/or cM1 tumor included, most patients had an EAC (n=3,077, 53.9%), followed by GAC (n=1,836, 32.1%) and ESCC (n=794, 13.9%). Of EAC, ESCC and GAC patients, 18.0%, 39.4% and 39.1% were women, respectively.

Figure 1. Flowchart of patient selection.

Patients with advanced gastroesophageal cancer diagnosed in 2015 – 2018 (N=6,020)		Excluded: Patients with a carcinoma not otherwise specified N=313
Patients with advanced gastroesophageal cancer N=5,707		

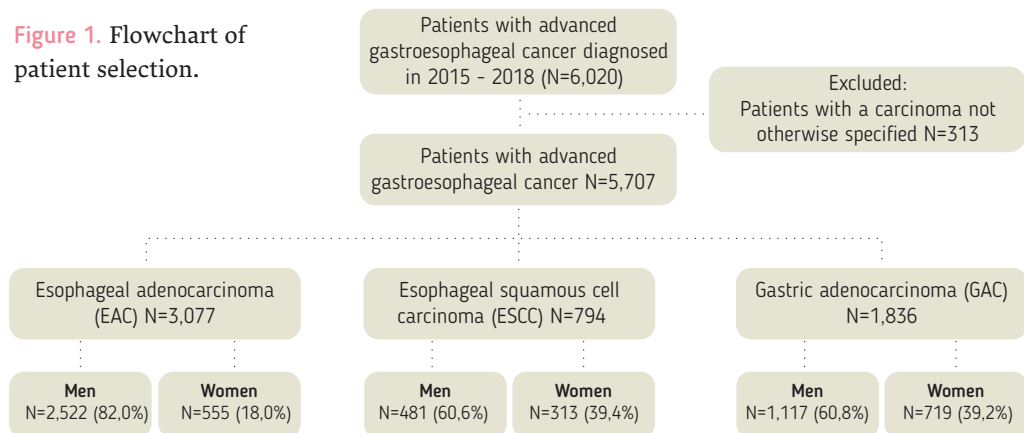| Esophageal adenocarcinoma (EAC) N=3,077	Esophageal squamous cell carcinoma (ESCC) N=794	Gastric adenocarcinoma (GAC) N=1,836
Men N=2,522 (82,0%) / **Women** N=555 (18,0%)	**Men** N=481 (60,6%) / **Women** N=313 (39,4%)	**Men** N=1,117 (60,8%) / **Women** N=719 (39,2%)

Table 1. Baseline characteristics of included patients (n=5,707).

Characteristics	EAC (n = 3,077)			ESCC (n = 794)			GAC (n = 1,836)		
	Men n = 2,522 No. (%)	Women n = 555 No. (%)	P value	Men n = 481 No. (%)	Women n = 313 No. (%)	P value	Men n = 1,117 No. (%)	Women n = 719 No. (%)	P value
Age, years			0.011			0.005			0.009
≤55	329 (13.0%)	78 (14.1%)		42 (8.7%)	22 (7.0%)		134 (12.0%)	108 (15.0%)	
56-65	695 (27.6%)	153 (27.6%)		154 (32.0%)	81 (25.9%)		201 (18.0%)	121 (16.8%)	
66-75	947 (37.5%)	173 (31.2%)		209 (43.5%)	129 (41.2%)		401 (35.9%)	211 (29.3%)	
>75	551 (21.8%)	151 (27.2%)		76 (15.8%)	81 (25.9%)		381 (34.1%)	279 (38.8%)	
Performance status			0.085			0.720			0.067
0-1	1325 (52.5%)	263 (47.4%)		236 (49.1%)	146 (46.6%)		483 (43.2%)	272 (37.8%)	
≥2	403 (16.0%)	101 (18.2%)		92 (19.1%)	59 (18.8%)		188 (16.8%)	137 (19.1%)	
Unknown	794 (31.5%)	191 (34.4%)		153 (31.8%)	108 (34.5%)		446 (39.9%)	310 (43.1%)	
Number of comorbidities			0.045			0.172			0.002
0	1174 (46.6%)	284 (51.2%)		203 (42.2%)	144 (46.0%)		487 (43.6%)	362 (50.3%)	
1	756 (30.0%)	168 (30.3%)		153 (31.8%)	109 (34.8%)		355 (31.8%)	211 (29.3%)	
≥2	467 (18.5%)	76 (13.7%)		100 (20.8%)	49 (15.7%)		218 (19.5%)	100 (13.9%)	
Unknown	125 (5.0%)	27 (4.9%)		25 (5.2%)	11 (3.5%)		57 (5.1%)	46 (6.4%)	
Tumor stage			0.063			0.624			0.413
cT4bM0	26 (1.0%)	11 (2.0%)		88 (18.3%)	53 (16.9%)		67 (6.0%)	50 (7.0%)	
cM1	2496 (99.0%)	544 (98.0%)		393 (81.7%)	260 (83.1%)		1050 (94.0%)	669 (93.0%)	
Lauren classification			0.153						0.010
Intestinal	1118 (44.3%)	241 (43.4%)		-	-		383 (34.3%)	201 (28.0%)	
Diffuse	352 (14.0%)	99 (17.8%)		-	-		356 (31.9%)	281 (39.1%)	
Mixed	46 (1.8%)	12 (2.2%)		-	-		39 (3.5%)	24 (3.3%)	
Indeterminate	72 (2.9%)	12 (2.2%)		-	-		10 (0.9%)	10 (1.4%)	
Unknown	934 (37.0%)	191 (34.4%)		-	-		329 (29.5%)	203 (28.2%)	
Signet ring cell carcinoma	98 (3.9%)	32 (5.8%)	0.046	-	-		132 (11.8%)	128 (17.8%)	<0.001[b]
Differentiation grade			0.296			0.114			0.175
Good/moderate	637 (25.3%)	135 (24.3%)		159 (33.1%)	122 (39.0%)		158 (14.1%)	87 (12.1%)	
Poor	1088 (43.1%)	259 (46.7%)		156 (32.4%)	82 (26.2%)		636 (56.9%)	440 (61.2%)	
Unknown	797 (31.6%)	161 (29.0%)		166 (34.5%)	109 (34.8%)		323 (28.9%)	192 (26.7%)	
HER2 status			0.362						0.124
Positive	378 (15.0%)	78 (14.1%)		-	-		98 (8.8%)	47 (6.5%)	
Negative	1145 (45.4%)	239 (43.1%)		-	-		555 (49.7%)	348 (48.4%)	
Unknown	999 (39.6%)	238 (42.9%)		-	-		464 (41.5%)	324 (45.1%)	
Metastases locations			0.007			0.330			0.553
0	26 (1.0%)	11 (2.0%)		88 (18%)	53 (17%)		67 (6%)	50 (7%)	
1	1249 (49.5%)	305 (55.0%)		234 (49%)	169 (54%)		660 (59%)	409 (57%)	
≥2	1247 (49.4%)	239 (43.1%)		159 (33%)	91 (29%)		390 (35%)	260 (36%)	
Extraregional lymph node metastases	1230 (48.8%)	264 (47.6%)	0.608	233 (48.4%)	154 (49.2%)	0.834	316 (28.3%)	172 (23.9%)	0.039
Liver metastases	1347 (53.4%)	281 (50.6%)	0.235	124 (25.8%)	60 (19.2%)	0.031	406 (36.3%)	177 (24.6%)	<0.001
Peritoneal metastases	251 (10.0%)	65 (11.7%)	0.216	15 (3.1%)	6 (1.9%)	0.303	552 (49.4%)	401 (55.8%)	0.008
Lung metastases	592 (23.5%)	112 (20.2%)	0.095	125 (26.0%)	85 (27.2%)	0.715	127 (11.4%)	78 (10.8%)	0.729
Bone metastases	495 (19.6%)	87 (15.7%)	0.031	68 (14.1%)	42 (13.4%)	0.775	76 (6.8%)	58 (8.1%)	0.310
Other metastases locations	394 (15.6%)	75 (13.5%)	0.211	52 (10.8%)	28 (8.9%)	0.482	104 (9.3%)	107 (14.9%)	<0.001

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; IQR, interquartile range. P values are of chi-squared tests.

CH 10.

Baseline characteristics

In all subtypes, patients >75 years were more frequently women (Table 1). Women with EAC and GAC had less comorbidities than men. Women with GAC had more often a diffuse type tumor (39.1%) compared to men (31.9%), and less often an intestinal tumor type (28.0% vs. 34.3%; P=0.010). The proportion of diffuse GACs declined with increasing age in both genders. In women, this proportion declined gradually from 50.9 in patients ≤55 years to 30.5% in patients >75 years, compared to 44.0% to 28.4% respectively, in men. A signet cell histology was relatively more frequently found in women with EAC (5.8% vs. 3.8%, P=0.046) and GAC 17.8% vs. 11.8%, P<0.001). Women with EAC less often had distant metastases at two or more locations (43.1% vs. 49.4%, P=0.007). Women with ESCC and GAC had less often liver metastases (19.2% vs. 25.8%, P=0.031, and 24.6% vs. 36.3%, P<0.001, respectively), while peritoneal metastases of GAC were more often diagnosed in women (55.8% vs. 49.4%, P=0.008). There were no differences in performance and HER2 status between women and men in any of the groups.

Table 2. Treatment characteristics of included patients stratified for tumor location and histology.

Treatment	EAC (n = 3,077)			ESCC (n = 794)			GAC (n = 1,836)		
	Men n = 2,522 No. (%)	Women n = 555 No. (%)	P value	Men n = 481 No. (%)	Women n = 313 No. (%)	P value	Men n = 1,117 No. (%)	Women n = 719 No. (%)	P value
Systemic treatment (including chemoradiotherapy)	1,195 (47.4%)	237 (42.7%)	0.045	190 (39.5%)	104 (33.2%)	0.074	433 (38.8%)	243 (33.8%)	0.031
Systemic treatment (but not chemoradiotherapy[a])	1,115 (44.2%)	217 (39.1%)	0.028	91 (18.9%)	53 (16.9%)	0.478	431 (38.6%)	241 (33.5%)	0.028
Chemoradiotherapy[a]	80 (3.2%)	20 (3.6%)	0.604	99 (20.6%)	51 (16.3%)	0.131	2 (0.2%)	2 (0.5%)	0.657
Radiotherapy primary tumor (without systemic treatment)	495 (19.6%)	113 (20.4%)	0.695	131 (27.2%)	104 (33.2%)	0.070	68 (6.1%)	26 (3.6%)	0.019
Radiotherapy metastases	217 (8.6%)	33 (5.9%)	0.038	36 (7.5%)	23 (7.3%)	0.943	18 (1.6%)	19 (2.6%)	0.125
Surgical resection	39 (1.5%)	12 (2.2%)	0.304	18 (3.7%)	10 (3.2%)	0.683	76 (6.8%)	40 (5.6%)	0.286
Best supportive care only	769 (30.5%)	196 (35.3%)	0.027	144 (29.9%)	99 (31.6%)	0.613	571 (51.1%)	419 (58.3%)	0.003

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma. P values are of Chi square tests. [a] Chemoradiotherapy was defined as systemic treatment with concurrent long-term radiotherapy.

Treatment

Among women with EAC, 42.7% received systemic treatment (including chemoradiotherapy), compared to 47.4% of men with EAC (P=0.045), a difference that was observed in GAC as well (38.8% vs. 33.8%, P=0.031; Table 2 and Figure 2). The proportion of women treated with systemic therapy in ESCC was not statistically significant lower (33.2%) than in men (39.5%, P=0.074). The proportion of women that received best supportive care only was larger in EAC (35.3% vs. 30.5%, P=0.027) and GAC (58.4% vs. 51.1%, P=0.003), and did not differ in ESCC (31.6% vs 29.9%, P=0.613).

When stratified for age, the proportion of women ≤55 years that received systemic treatment was statistically significant higher in EAC compared to men (79.5% vs. 65.7%, P=0.018; Figure 2), and did not differ in ESCC (59.1% vs 54.8%, P=0.740) and GAC (67.6% vs. 63.4%, P=0.499). Women with EAC of 56-65 years less often received systemic treatment compared to men (50.3% vs. 61.3%, P=0.012). Among women with ESCC aged >75 years,

Figure 2. Systemic treatment administration (including chemoradiotherapy) stratified for gender and age in patients with EAC, ESCC and GAC.
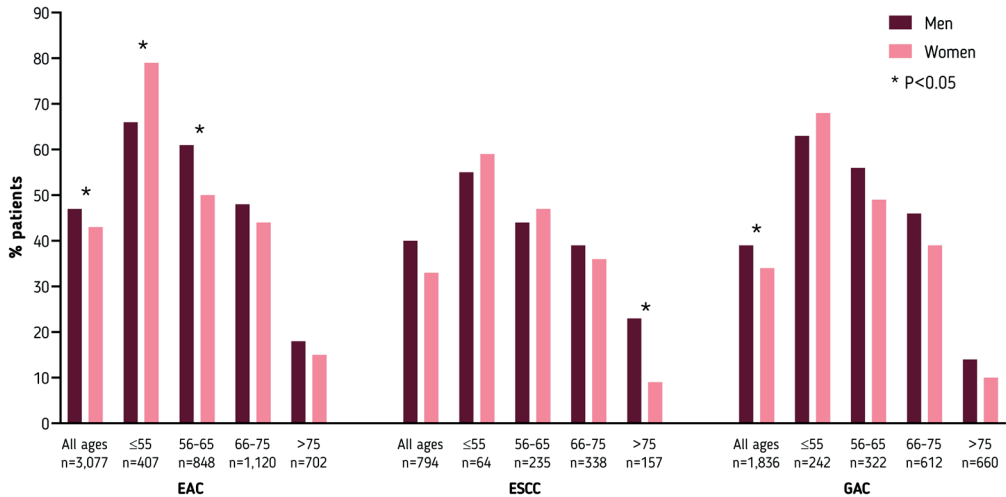
Statistically significant differences between men and women are marked with asterisks. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma.

the proportion that received systemic treatment was 8.6%, compared to 22.4% of men (P=0.017). When we restrict our analyses to patients aged 76-80 years in the highest age subgroup (i.e. >75 years), as the proportion women >80 years in this subgroup was larger than in men, systemic treatment administration in women compared to men did not statistically significantly differ in EAC (33.3% vs. 26.2%, respectively, P=0.272), ESCC (11.9% vs. 27.5%, P=0.064) or GAC (17.3% vs. 21.8%, P=0.323).

The adjusted odds ratios (ORs) for receiving systemic treatment for women with EAC, ESCC and GAC were 0.86 (95% confidence interval [CI] 0.69-1.06), 0.81 (95% CI 0.57-1.14) and 0.79 (95% CI 0.62-1.00; Table 3), respectively. Accordingly, the results of the likelihood-ratio tests were in line with these results: GAC (X^2 (1) = 4.01, P=0.045), EAC (X^2 (1) = 1.95, P=0.163) and ESCC (X^2 (1) = 1.47, P=0.226).

Increasing age and higher performance status were independently associated with a lower probability of systemic treatment administration in all groups. In EAC and ESCC, being diagnosed in a high-volume hospital was associated with a higher chance of receiving systemic treatment. If hospital volume was not added to the model, then the adjusted ORs for women with EAC, ESCC and GAC were 0.86 (95% CI 0.96-1.07), 0.81 (95% CI 0.58-1.14) and 0.80 (95% CI 0.63-1.00), respectively.

Overall survival

A statistically significant difference in median OS to the disadvantage of women compared to men was observed in EAC (4.4 [IQR 1.9, 9.9] months vs. 5.2 [IQR 2.0, 11.0] months, P=0.037), but not in ESCC (5.9 [IQR 2.5, 12.5] vs. 5.4 [IQR 10.9, 2.3] months, P=0.855) and GAC (3.8 [IQR 1.5, 8.6] vs. 4.0 [IQR 1.4, 9.8] months, P=0.173; Figure 3).

Median OS of patients who received systemic treatment did not differ between women and men with EAC (8.0 [IQR 3.7, 15.0] vs. 8.6 [IQR 4.1, 16.2] months, P=0.632), ESCC (11.1 [IQR 3.8, 18.4] vs. 8.9 [IQR 4.6, 20.0] months, P=0.812) or GAC (7.2 [IQR 3.7, 12.4] vs. 7.9 [IQR 3.4, 14.0] months, P=0.345; Figure 4).

After comparison of multivariable Cox regression models, women did not have an increased risk of dying after adjustment for clinical covariates, systemic treatment, and the interaction between gender and systemic treatment (EAC: HR 0.99, 95% CI 0.88-1.12, X^2 (1) = 0.24, P=0.888; ESCC: HR 0.93, 95% CI 0.78-1.12, X^2 (1) = 0.72, P=0.697; GAC: HR 0.97, 95% CI 0.86-1.10; X^2 (1) = 0.23, P=0.891; Table 4). The association between systemic treatment and OS was statistically significant in all groups, whereas no independent association between gender or the interaction between gender and systemic treatment was observed in any of the groups (Table 4).

Table 3. Multivariable logistic regression analyses for the probability of receiving systemic treatment (including chemoradiotherapy) in EAC, ESCC and GAC patients.

	EAC (n = 3,077)				ESCC (n = 794)				GAC (n = 1,836)			
	OR	95% CI		P value	OR	95% CI		P value	OR	95% CI		P value
Gender												
Men	Ref				Ref				Ref			
Women	0.86	0.69	1.06	0.163[b]	0.81	0.57	1.14	0.226[c]	0.79	0.62	1.00	0.046[d]
Age	0.93	0.92	0.94	<0.001	0.94	0.92	0.96	<0.001	0.91	0.91	0.93	<0.001
Performance status												
0-1	Ref			<0.001	Ref			<0.001	Ref			<0.001
≥2	0.18	0.14	0.23		0.28	0.17	0.44		0.29	0.21	0.40	
Unknown	0.29	0.24	0.34		0.21	0.14	0.32		0.24	0.19	0.31	
Number of comorbidities												
0	Ref			0.004	Ref			0.801	Ref			<0.001
1	0.88	0.74	1.06		0.95	0.65	1.39		0.99	0.77	1.28	
≥2	0.65	0.53	0.82		0.79	0.49	1.27		0.55	0.39	0.78	
Unknown	1.07	0.72	1.57		1.04	0.45	2.33		0.57	0.34	0.94	
Lauren classification												
Intestinal	Ref			0.010	N/A				Ref			0.447
Diffuse	0.73	0.57	0.93						0.85	0.64	1.14	
Mixed	1.24	0.67	2.34						0.74	0.39	1.38	
Indeterminate	0.81	0.50	1.34						0.45	0.12	1.65	
Unknown	0.75	0.63	0.90						0.80	0.60	1.07	
Stage												
cT4bM0	0.93	0.45	2.07		1.26	0.70	2.28		0.73	0.43	1.25	
cM1	Ref			0.865	Ref			0.431	Ref			0.250
Hospital volume[a]												
Q1	0.76	0.57	1.00		0.55	0.29	1.05		0.93	0.63	1.38	
Q2	1.12	0.89	1.40		0.43	0.26	0.72		1.24	0.92	1.66	
Q3	1.15	0.93	1.40		0.75	0.51	1.10		0.81	0.61	1.07	
Q4	Ref			0.029	Ref			0.007	Ref			0.073
Extraregional lymph node metastases	0.90	0.76	1.07	0.216	1.11	0.72	1.70	0.634	0.82	0.62	1.08	0.161
Liver metastases	1.20	1.03	1.43	0.046	1.04	0.66	1.61	0.880	1.10	0.83	1.48	0.504
Peritoneal metastases	0.74	0.57	0.98	0.038	0.63	0.20	1.97	0.425	0.85	0.64	1.13	0.262
Lung metastases	0.91	0.74	1.10	0.319	0.73	0.48	1.10	0.135	0.91	0.63	1.31	0.604
Bone metastases	0.81	0.62	1.00	0.053	0.44	0.25	0.78	0.004	0.55	0.35	0.86	0.009
Other metastases locations	0.61	0.48	0.77	<0.001	0.58	0.31	1.09	0.090	1.10	0.78	1.57	0.585

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; OR, odds ratio; CI, confidence interval.
[a] Volume of hospital of diagnosis. N/A, not applicable. Per hospital the volume of gastro-esophageal cancer patients that was diagnosed with gastro-esophageal cancer between 2015 and 2018, was calculated. Subsequently, hospitals were categorized into quartiles (Q1-4) according to these volumes, which resulted in hospitals in which <25 (Q1), 25-61 (Q2), 61-140 (Q3) and >140 (Q4) patients were diagnosed in 2015-2018. Likelihood-ratio tests comparing the full model and the full model without gender:
[b] EAC: X^2 = 1.95, P=0.163;
[c] ESCC: X^2 =1.47, P=0.226;
[d] GAC: X^2 = 4.01, P=0.045.

Figure 3. Kaplan Meier curves for OS in patients with EAC, ESCC and GAC, stratified for gender.

OS of patients with cT4b or cM1 EAC

Men (n=2,522)
Women (n=555)

Log rank P=0.037

OS (%)
Time since diagnosis (months)

Number at risk
Men	2.522	1.160	565	290	155	80
Women	555	215	114	55	26	17

OS of patients with cT4b or cM1 ESCC

Men (n=481)
Women (n=313)

Log rank P=0.855

OS (%)
Time since diagnosis (months)

481	221	105	66	40	27
313	157	83	38	17	13
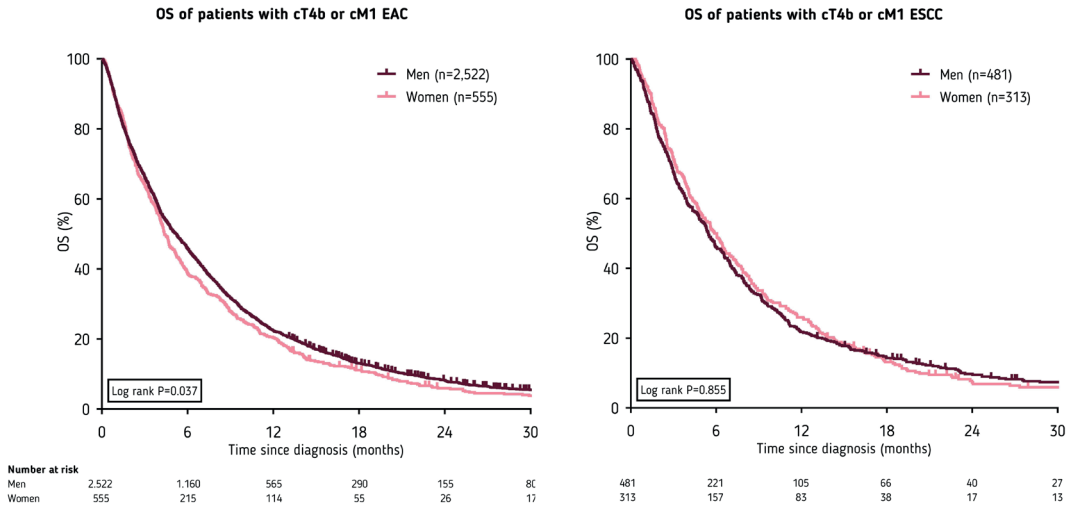
Figure 4. Kaplan Meier curves for OS in patients with EAC, ESCC and GAC who received systemic treatment (including chemoradiotherapy), stratified for gender.

OS of patients with EAC who received systemic treatment

Men (n=1,195)
Women (n=237)

Log rank P=0.632

OS (%)
Time since start of systemic treatment (months)

Number at risk
Men	1.195	785	424	226	114	62
Women	237	144	82	44	23	15

OS of patients with ESCC who received systemic treatment

Men (n=190)
Women (n=104)

Log rank P=0.812

OS (%)
Time since start of systemic treatment (months)

190	125	74	46	31	23
104	70	46	25	15	11
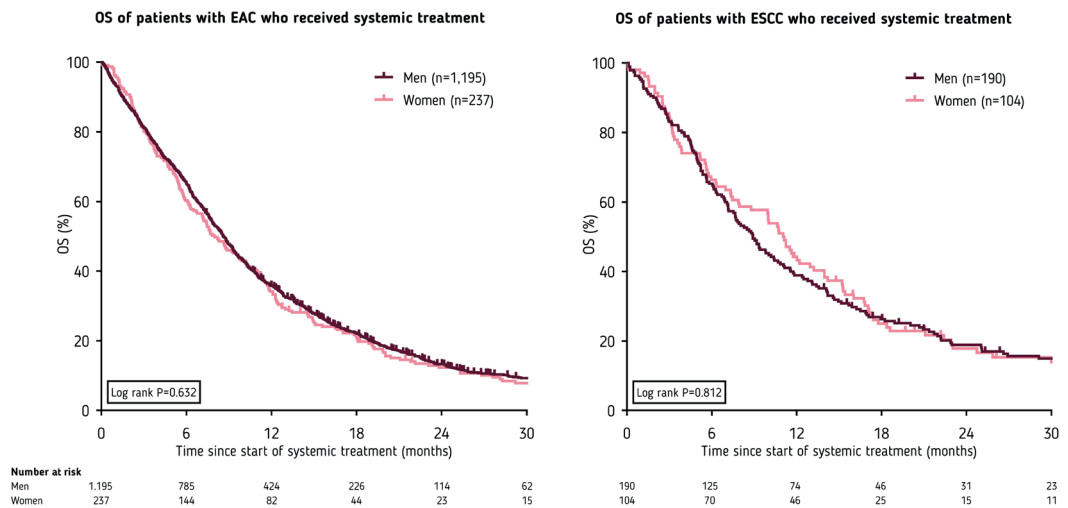
OS of patients with cT4b or cM1 GAC
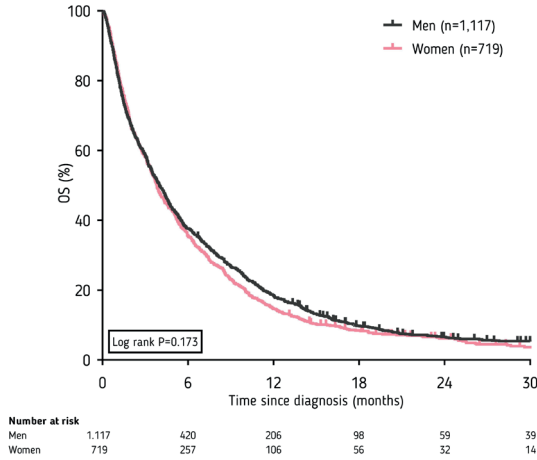
EAC, esophageal adenocarcinoma; ESCC,
esophageal squamous cell carcinoma; GAC,
gastric adenocarcinoma; OS, overall survival.

OS of patients with GAC who received systemic treatment

EAC, esophageal adenocarcinoma; ESCC,
esophageal squamous cell carcinoma; GAC,
gastric adenocarcinoma; OS, overall survival.

Table 4. Multivariable Cox proportional hazard regression analyses for overall survival in EAC, ESCC and GAC patients.

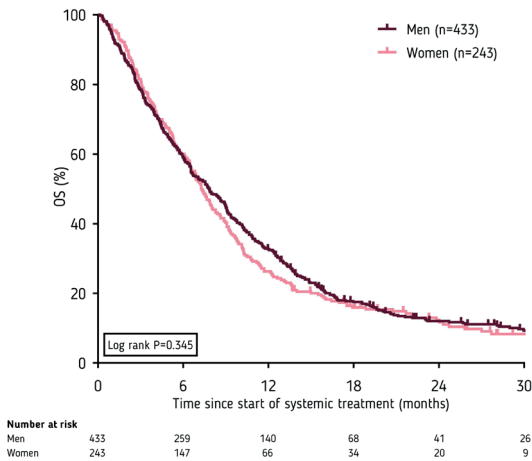|	EAC (n = 3,077)				ESCC (n = 794)				GAC (n = 1,836)			
	HR	95% CI		P value	HR	95% CI		P value	HR	95% CI		P value
Gender												
Men	Ref			0.904[b]				0.460[c]	Ref			0.640[d]
Women	0.99	0.88	1.12		0.93	0.78	1.12		0.97	0.86	1.10	
Systemic treatment	0.32	0.27	0.38	<0.001	0.41	0.31	0.53	<0.001	0.39	0.33	0.46	<0.001
Gender * Systemic treatment	0.96	0.79	1.16	0.659	0.88	0.64	1.22	0.442	0.96	0.79	1.18	0.727
Age	1.00	0.99	1.00	0.028	0.99	0.99	1.00	0.113	1.00	1.00	1.01	0.249
Performance status												
0-1	Ref				Ref				Ref			
≥2	1.66	1.49	1.85		1.79	1.46	2.19	<0.001	1.37	1.19	1.57	<0.001
Unknown	1.62	1.49	1.77	<0.001	1.64	1.38	1.96	<0.001	1.51	1.35	1.68	<0.001
Number of comorbidities												
0	Ref				Ref				Ref			
1	1.11	1.02	1.22	0.015	1.06	0.90	1.26	0.487	1.10	0.98	1.23	0.120
≥2	0.90	0.81	1.01	0.063	1.07	0.87	1.31	0.526	1.05	0.91	1.21	0.520
Unknown	0.95	0.80	1.13	0.558	1.22	0.85	1.75	0.292	0.93	0.75	1.15	0.483
Lauren classification												
Intestinal	Ref				-				Ref			
Diffuse	1.38	1.24	1.55	<0.001					1.29	1.13	1.46	<0.001
Mixed	1.65	1.26	2.16	<0.001					1.05	0.80	1.37	0.742
Indeterminate	1.03	0.82	1.30	0.801					0.82	0.51	1.30	0.395
Unknown	1.09	1.00	1.18	0.050					1.28	1.13	1.45	<0.001
HER2 status												
Negative	Ref				-				Ref			
Positive	0.75	0.67	0.84	<0.001					0.97	0.80	1.16	0.704
Unknown	1.16	1.06	1.26	<0.001					1.13	1.01	1.27	0.037
Stage												
cT4bM0	1.05	0.73	1.51	0.789	1.28	0.98	1.66	0.066	0.67	0.53	0.85	0.001
cM1	Ref				Ref				Ref			
Hospital volume[a]												
Q1	1.14	1.00	1.29	0.043	1.05	0.80	1.39	0.735	1.35	1.14	1.59	<0.001
Q2	1.09	0.98	1.20	0.126	0.98	0.79	1.21	0.843	1.45	1.27	1.65	<0.001
Q3	1.11	1.01	1.21	0.025	0.98	0.82	1.18	0.854	1.34	1.19	1.51	<0.001
Q4	Ref				Ref				Ref			
Extraregional lymph node metastases	1.27	1.17	1.37	<0.001	1.08	0.90	1.29	0.391	1.18	1.05	1.33	0.005
Liver metastases	1.77	1.63	1.92	<0.001	1.88	1.56	2.28	<.0001	1.42	1.26	1.60	<0.001
Peritoneal metastases	1.85	1.64	2.10	<0.001	2.18	1.39	3.42	<0.001	1.32	1.17	1.48	<0.001
Lung metastases	1.22	1.12	1.33	<0.001	1.25	1.04	1.50	0.018	1.09	0.94	1.27	0.266
Bone metastases	1.42	1.29	1.56	<0.001	1.28	1.03	1.59	0.027	2.06	1.71	2.49	<0.001
Other metastases locations	1.33	1.19	1.47	<0.001	1.41	1.11	1.81	0.006	1.18	1.05	1.33	0.005

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; HR, hazard ratio; CI, confidence interval . [a] Volume of hospital of diagnosis. Per hospital the volume of gastroesophageal cancer patients that was diagnosed with gastro-esophageal cancer between 2015 and 2018, was calculated. Subsequently, hospitals were categorized into quartiles (Q1-4) according to these volumes, which resulted in hospitals in which <25 (Q1), 25-61 (Q2), 61-140 (Q3) and >140 (Q4) patients were diagnosed in 2015-2018.
Likelihood-ratio tests comparing the full model and the full model without gender and the interaction between gender and systemic treatment: [b] EAC: X^2 =0.24, P=0.888; [c] ESCC: X^2 =0.72, P=0.697; [d] GAC: X^2 = 0.23, P=0.891.

DISCUSSION

In addition to the well-known disparity in gastroesophageal cancer incidence between women and men, our results in a nationwide cohort of patients with unresectable or metastatic gastroesophageal cancer reveal statistically significant and clinically relevant gender differences in both patient characteristics (e.g. less comorbidities in women), tumor characteristics (e.g. more often a diffuse histology in women), patterns of metastasis (e.g. less often liver metastasis and more often peritoneal metastasis in women), and treatment allocation (less systemic treatment administration in women). Most important, while women have a decreased risk of dying in many cancer types,[2-4] we observed an increased risk of dying in women with EAC. As these survival disparities were not observed in women and men who received systemic treatment and in multivariable analyses after adjustment for clinical covariates and systemic treatment, this gap could at least partly be explained by the smaller proportion of women treated with systemic therapy, which was observed especially in patients >55 years. Our findings support the assumption that both sex- and gender-based factors could contribute to disparities in treatment allocation and outcomes of patients with unresectable and metastatic esophageal and gastric cancer. A clear distinction between sex-based causes, e.g. differences in tumor biology, and gender-based factors, i.e. those related to sociocultural factors and behavior, is important to understand these differences.

Sex-based causes of the observed survival gap could include different exposure to sex hormones, as well as differences in tumor biology. An explanation could be the suggested protective effect of female sex hormones, i.e. estrogens, as a more aggressive cancer biology has been observed in men and postmenopausal women compared to premenopausal women in several cancer types, including esophageal cancer.[9,20] Interestingly, we observed that women were more often diagnosed with a diffuse type GAC and signet cell ring EAC and GAC, which is in line with earlier studies,[7,21] and may have contributed to their poorer survival rates.[22] Moreover, women more often had peritoneal and less often liver metastasis, which is in line with colorectal cancer, and likely to reflect differences in tumor biology, as peritoneal metastases are more frequently found in patients with a diffuse histology tumor.[23,24] Other sex differences in tumor biology of gastroesophageal cancer are increasingly reported as well. For example, women with GAC have more frequently a microsatellite instable (MSI) tumor, whereas tumors associated with the Epstein-Barr virus (EBV) are more frequently found in men.[21] In addition, sex differences in efficacy and toxicity of systemic treatment have been reported,[5,30,31] and may have contributed to difference in survival as well. Unfortunately, data on toxicity, as well as MSI, were not available in our study. More research on differences in biology and treatment response is necessary to understand differences in outcome, and improve the balance between efficacy and toxicity for both men and women.

Female sex hormones may not only influence tumor biology or treatment response, but also play a role in the development of gastroesophageal cancer. Although risk factors such as abdominal adiposity and gastroesophageal reflux disease are more common in men, they cannot fully explain the overrepresentation of men in the incidence of EAC.[6,10,25] To illustrate, men have a 2.5 times greater risk to develop a Barrett's esophagus, but a 3-7 times greater risk to subsequently develop EAC.[11] In addition, higher incidence rates of ESCC in women compared to men have been reported, despite lower prevalence of the behavioral risk factors

smoking and alcohol.[26] It is therefore suggested that female sex hormones decrease the risk of esophageal and gastric cancer.[9,20,27–29]

Interestingly, the overall proportion of women with EAC and GAC that received systemic treatment was significantly lower than the proportion of men, and numerically lower in ESCC. Hospital volume was found to play a role in the probability of receiving systemic treatment in EAC and ESCC, but did not influence the gender disparity in multivariable analysis. Besides performance status, age and a diffuse histology, being a woman was independently associated with a lower chance of receiving systemic treatment in GAC (OR 0.79), and, although not statistically significant, odds ratios were below one in EAC (OR 0.86) and ESCC (OR 0.79). Moreover, the survival difference in favor of men with EAC, which was not observed in multivariable analysis after adjustment for clinical covariates, systemic treatment and the interaction between gender and systemic treatment, suggests that women are undertreated. These differences are worrisome, because systemic treatment not only prolongs survival,[32] but also improves the patients' quality of life.[33] On the other side of the equation, some men could be overtreated, as best supportive care only may be the best option in selected patients, e.g. those with a short life expectancy.[34] Both over- and undertreatment are examples of suboptimal care, and require further examination.

To understand the gender-based causes for the statistically significant and clinically relevant difference in treatment allocation observed in our study, we propose a research agenda based on the Andersen healthcare utilization model, a framework that describes three domains of determinants for health services.[12,35] The first domain consists of predisposing factors, i.e. beliefs and preferences of the individual. Gender has earlier been identified as the most independent predictor of patients preferences.[36] Because e.g. women have appeared to be more likely to prefer palliative care,[37] this may have impacted treatment choices. Factors enabling or impeding health care use are the second domain, and include access to health insurance or family support. In the Dutch population of ≥55 years, women are overrepresented and less often married than men.[38,39] Being single has been associated with a higher probability of refraining from esophageal cancer treatment.[40,41] We hypothesize that lack of spousal support may contribute to different treatment choices. A factor that may also impede access in these patients, is that physicians may be influenced by stereotypes and biased in treatment propositions and recommendations. For example, single patients have been offered treatment less often because of the assumption that they do not have enough support.[42] Gender stereotypes are also known to exist in medical diagnosis and decisions: physicians are more likely to interpret symptoms in women as psychosocial, and illnesses in men are investigated and treated more extensively, despite the same severity of symptoms.[43–45] Awareness of these unconscious biases among physicians is urgently needed in order to narrow the treatment gap.[45] The third domain includes the need factors. Differences in the need for care may exist, e.g. due to differences in perception of disease symptoms between men and women.[46] Future qualitative studies that explore a patient's disease perception and preferences as well as environmental/social factors, and physicians' possible unconscious biases in proposing and recommending treatments, could be valuable in identifying causes for this disparity.

In conclusion, not only patient characteristics, such as comorbidities, but also tumor characteristics, such as histology, as well as palliative systemic treatment allocation

and overall survival differ significantly between men and women with advanced EAC. While behavioral factors influence for example the presence of comorbidities, other differences, such as the higher frequency of women with signet cell GAC cannot be explained by differences in behavior and support the hypothesis of a sexual dimorphism in cancer susceptibility and biology.[6,20] An independent association between gender and OS was not observed after adjustment for clinical covariates, treatment and the interaction between gender and treatment, suggesting the observed inferior survival in women with EAC might result from less frequent systemic treatment administration. Thus, more consequent systemic treatment administration in women may constitute an example for an opportunity to improve patient outcomes. The reasons for differences in treatment allocation, including potential differences in individual preferences and beliefs and the relative contributions of both physicians and patients, need further investigation.

Ethical approval
According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper GI Cancer Group. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[39]

Declaration of interests
Rob Verhoeven reports grants from BMS and Roche. Dorothea Wagner has received consulting fees from BMS, Servier Suisse, Merck, MSD, Bayer, EMD Serono, Lilly, Celgene, Shire, Pierre-Fabre, and Pfizer, non-financial support (for congress participations) from Sanofi, Astra-Zeneca, AbbVIE and Ipsen and an educational grant from Roche to EORTC. Valery Lemmens received educational grants and unrestricted research grants from Roche. Martijn van Oijen reports grants from Amgen, BMS, Lilly, Nordic, Merck, Roche and Servier. Suzanne Gisbertz reports a research grant from Olympus and consulting fees from Medtronic. Mark van Berge Henegouwen reports research grants from Olympus and Stryker, in addition to consulting fees from Medtronic, Mylan and Johnson and Johnson. Hanneke van Laarhoven reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

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11.

General discussion – Bridging the efficacy-effectiveness gap

CURRENT PERSPECTIVES ON SYSTEMIC TREATMENT IN ESOPHAGOGASTRIC CANCER

Systemic therapy is the cornerstone of palliative treatment in patients with metastatic or unresectable esophagogastric cancer. Results of several pivotal randomized controlled trials (RCTs) have resulted in (inter)national guideline recommendations for systemic treatment administration.[1-5] Although a global consensus on the optimal initial systemic treatment strategy has not been formed, the majority of the patients receive combination therapy consisting of two or three cytotoxic agents in the first line, with the addition of trastuzumab in case of HER2 overexpression (CHAPTER 2). The results of the studies included in this thesis confirm the survival benefit of combination chemotherapy over monotherapy in synchronous metastatic esophagogastric cancer patients in daily clinical practice, as well as the addition of trastuzumab to chemotherapy in patients with HER2 positive tumors (CHAPTER 2 & 3). However, an added value of triplet compared to doublet chemotherapy was not observed, as we did not find a benefit in terms of survival, while triplets induced more toxicity than doublet chemotherapy (CHAPTER 2). Based on these data, first-line doublet therapy is the preferred strategy in patients with metastatic esophagogastric cancer. Recent results revealing that the addition of an immune checkpoint inhibitor (ICI) to first-line doublet chemotherapy can improve survival in esophagogastric cancer patients with a combined positive score (CPS) ≥ 5 [6-8] will probably further increase the use of doublet chemotherapy.

Compared to the results of the RCTs that have been performed in esophagogastric cancer patients, survival rates of our real-world population were considerably lower. We observed a median overall survival of 7.7 months since start of treatment in esophagogastric cancer patients who received first-line triplet therapy (CHAPTER 2). In RCTs, median overall survival varied between 9.3 and 11.2 months in patients who received anthracycline triplets,[9,10] up to 14.6 months in patients who received a taxane triplet.[11] The median overall survival of patients who received doublets varied from 9.5 to 15.3 months in RCTs,[10-13] whereas this was 7.4 months in Dutch patients in daily clinical practice (CHAPTER 2). In patients with a HER2 positive tumor who were treated with a trastuzumab-containing regimen, overall survival was 13.8 months in the ToGA trial,[14] compared to 11.2 months in real world (CHAPTER 2). In second-line treatment, median overall survival in patients treated with paclitaxel and ramucirumab in the RAINBOW trial was 9.6 months,[15] compared to 6.1 months in daily clinical practice (CHAPTER 4). Thus, although RCTs are considered the reference standard for studying the causal relationships between interventions and outcomes, results may not resemble patient outcomes in clinical practice. The difference between these two outcomes is called the efficacy-effectiveness gap.[16]

MIND THE GAP

The efficacy-effectiveness gap is a phenomenon that comes along with the study design of RCTs that apply stringent inclusion criteria. These RCTs provide information on the efficacy and safety of drugs in a selected population under ideal study conditions, whereas whether the effectiveness of an intervention holds up in a real-world situation can be studied in population-based studies.[17] Trial results may not be applicable to patients who are treated

in clinical daily practice because this real-world patient is likely to be more frail, older, or has more comorbidities than patients included in clinical trials.[16] Medical interventions can therefore be considered efficacious if they work under controlled circumstances, but are effective if they work in clinical practice.[17]

The efficacy-effectiveness gap more frequently applies to diseases of which the incidence rises when age increases, or when risk factors such as obesity, smoking and alcohol use contribute to its development,[16] e.g. esophagogastric cancer. In these diseases, the trial population is more likely to differ substantially from the real-world population because of a higher chance they do not meet the stringent trial inclusion criteria. In RCTs, patients with substantial comorbidity, e.g. due to smoking or alcohol use, or with a poor performance status (i.e. ≥2) are often not considered eligible for participation,[15,18–20] or represent only a minor proportion of <5%.[11–13,19] In our cohort, approximately 12% of the patients that received first- or second-line systemic treatment and with a known performance status had a performance status of 2 or higher (CHAPTER 2 & 4). Moreover, the median age of the patients in the pivotal trials ranging from 59-63 years[9–11,14,15,18,20,21] is lower than in our real-world studies (64 years; chapter 1, 2 & 3). Although patients with higher age or performance status may not always be eligible for trial inclusion, our results confirm systemic treatment can thus still be administered in these patients in clinical practice. However, the treatment may be less well tolerated due to their condition leading to dose or treatment alterations, and therefore become less effective. As a result, the treatment efficacy determined in RCTs may be an overestimation of effectiveness when this treatment will be applied in these frail patients in daily clinical practice. Moreover, although the inclusion of women in clinical oncological trials has increased, the majority of participants are still men.[22,23] Underrepresentation of women in clinical trials could reveal unexpected results in daily clinical practice, hereby contributing to the efficacy-effectiveness gap for women specifically. In esophagogastric cancer incidence, women represent 29% of the Dutch patient population. The proportion women in the majority of the trials varied mostly between 24% and 31%,[15,19,24] and was lower in two major trials (19%).[9,25] Also, only 24% of our real-world patient population that received systemic treatment were women (CHAPTER 1, 2 & 3), which supports the hypothesis that women are undertreated in daily clinical practice as stated in CHAPTER 10.

For esophagogastric cancer specifically, the inclusion of patients with unresectable nonmetastatic disease alongside patients with metastatic disease in several trials[9,10,13,14,25] may have contributed to the observed efficacy-effectiveness gap, because patients with unresectable nonmetastatic disease have usually a better prognosis than patients with metastatic disease.[26–30] Other differences between RCTs and real-world studies that may contribute to the efficacy-effectiveness gap in general, include disparities in the definition of overall survival, i.e. from start of randomization in RCTs versus start of treatment in real-world studies. Moreover, trial participants are often treated in specialized, high-volume centers, where there is close monitoring and treatment of adverse events, hereby improving patient outcomes.[16] This volume-outcome relationship has also been described in the curative treatment of esophagogastric cancer,[31,32] as well as in the palliative setting (CHAPTER 3 & 4).

CH 11.

The gap may also apply for the harms of treatment. For example, frail patients may be more susceptible to experience toxicity of systemic treatment. We observed that chemotherapy toxicity was more often found in overweight patients with cachexia, i.e. skeletal muscle mass depletion, or patients with a low skeletal muscle density (CHAPTER 7). As women have a different body composition with less muscle mass and more fat mass compared to men, women may experience more often treatment-related toxicity.[33] In addition, cachexia at initial diagnosis was observed in nearly 60% of the patients with esophagogastric cancer who received palliative systemic treatment, and more often observed in patients with a poor performance status (CHAPTER 8). Systemic treatment toxicity may therefore be underestimated in clinical trials, because patients with a poor performance status who have a higher probability of having cachexia, may be excluded from trial participation.

BRIDGING THE GAP

Strict eligibility criteria hinder the participation of frail and elderly people with comorbidities in RCTs, limiting RCT data generalizability. Physicians should therefore be aware of an efficacy-effectiveness gap when informing patients about the benefits and harms of an intervention, especially in patients that may not be entirely represented by participants of RCTs. In order to narrow the efficacy-effectiveness gap, expansion of inclusion criteria in RCTs should be considered, in order to more adequately reflect the real-world population. For example, our real-world results most closely resemble the outcomes of the FLOT65+ trial, in which only (Western) patients of 65 years and older were included, as well as patients with a performance status of 2 or higher, which was 8% in this trial.[34] Furthermore, research should be more focused on effectiveness, with the aim to answer the question 'does it work?', instead of 'can it work?' in efficacy studies.[17] Population-based studies for which for example registry-based data are used, could add valuable information on effectiveness in real world alongside efficacy results of RCTs. The use of prediction models that are based on population-based data in clinical practice could contribute to better and fair communication on expectations between the physicians and patients. The usability of a population-based prediction model in esophagogastric cancer called SOURCE is currently being investigated in clinical practice in order to support shared decision-making.[35]

Observational studies have several limitations. Comparison of study results on systemic treatment may be hampered by the lack of agreement on the definition of a treatment line. Although several population-based studies on systemic treatment in esophagogastric cancer have been published, the definition of a treatment line usually differed between these studies. For example, Hess et al. regarded discontinuation of a regimen for at least 42 days as the end of a treatment line.[36] However, in our studies, if the same (or equivalent) systemic agents were administered after a therapy break, regardless of the duration of this break, we considered this as the continuation of a treatment line (CHAPTER 2, 3 & 4). In order to enable fair comparisons between observational studies, as well as between observational studies and RCTs, an international consensus on the definition of a systemic treatment line between experts in this field is warranted. Moreover, there are several biases that could be present due to the lack of randomization, e.g. a selection bias or unknown confounding.[37] Therefore, analysis and interpretation of these data should be performed carefully, and chances of

bias should be limited. In our studies, we aimed to minimize the chance of selection bias and confounding by including the nationwide esophagogastric cancer population treated with systemic treatment, and by adjusting for patient characteristics such as performance status and comorbidities in multivariable analyses, respectively. However, performance status was still missing in a considerable part of the patients, probably due to inadequate reporting in medical records, which could have led to a bias due to non-optimal adjustment in multivariable survival analyses. Accurate registration of performance status, comorbidities and other prognostic factors such as weight loss, as well as predictive factors such as skeletal muscle mass are therefore of major importance to increase the value of population-based studies, for example by improving systemic treatment dosing based on skeletal muscle mass hereby preventing toxicity. Routinely collection of patient reported outcome measures (PROMs) in clinical practice could be helpful in obtaining these patient data before, during and even after treatment, e.g. on treatment-related toxicity, which is currently performed in the Prospective Observational Cohort study of Oesophageal-gastric cancer Patients (POCOP).[38] Moreover, the use of artificial intelligence techniques such as natural language processing to retrieve information on e.g. performance status from medical records automatically, could decrease the registration burden and expedite data extraction.[39]

FUTURE PERSPECTIVES IN ESOPHAGOGASTRIC CANCER

The studies included in this thesis underline the added value and clinical relevance of population-based studies for the evaluation of systemic treatment, by revealing the gap between efficacy in clinical trials versus effectiveness in real world. Nevertheless, the results confirm the effectiveness of systemic treatment administration in advanced gastroesophageal cancer patients in daily clinical practice, and contribute to improved decision-making in systemic treatment in esophagogastric cancer by enabling fair communications on prognosis in these patients. Although chemotherapy will remain important in the palliative care of esophagogastric cancer, accumulating evidence on the efficacy of ICIs will probably change the systemic treatment landscape in esophagogastric cancer in the coming years.[6,7] The effectiveness of these agents should be evaluated in clinical practice in the future to guard a possible efficacy-effectiveness gap. Moreover, the uptake of biomarker testing, e.g. CPS, in case the use of immune checkpoint inhibitors is considered, should be studied as we observed that the biomarker HER2 was only tested in 88% of the patients, six years after introduction of HER2-targeted treatment (CHAPTER 3). We observed that hospital volume was positively associated with the probability of being tested for HER2, but also with receiving beyond first-line treatment, and better survival rates in all metastatic esophagogastric cancer patients who received systemic treatment (CHAPTER 3 & 4). The association between hospital volume and treatment and patient outcomes was already known in the curative setting,[31,32] but adds to accumulating evidence that this is applicable in the palliative setting as well.[40] Both adequate access to multidisciplinary sources, as well as the higher inclusion rate of patients in trials as discussed earlier, probably contributed to improved patient outcomes. These results suggest that involving high-volume hospitals in decision-making of palliative treatment may contribute to better treatment outcomes in this patient population. Regional multidisciplinary collaboration networks have the potential to improve patient selection not only for curative

but also for palliative treatments by uniting expertise, e.g. on biomarker testing, and facilitating the inclusion of patients in trials regardless of hospital of diagnosis, in order to improve outcomes for patients with esophagogastric cancer.

Further steps could be taken to improve personalization of systemic treatment. Future population-based studies investigating treatment effectiveness should take into account the heterogeneity of esophagogastric tumors, for example the four molecular subtypes of gastric cancer, i.e. the Epstein-Barr virus positive, microsatellite instable, genomically stable, and chromosomal instable subtypes, of which the latter is similar to the esophageal adenocarcinoma and could be evaluated together with these tumors.[41,42] Moreover, study endpoints should be focused on quality of life as well rather than survival alone, as quality of life is regarded as an important outcome in these patients and may even impact overall survival (CHAPTER 9). Ideally, patient-reported outcomes are routinely collected in all patients receiving systemic treatment in daily clinical practice, in order to use these outcomes to evaluate the impact of treatment on quality of life alongside survival outcomes.

Furthermore, more research into causes of differences in tumor biology, toxicity, and survival between men and women, taking into account the differences in skeletal muscle mass between genders as well, as differences in tumor biology and response to oncological drugs (e.g. immunotherapy) between men and women have been identified[43,44], but are insufficiently examined. Taken together with the observed differences in treatment administration and OS between genders in real world (CHAPTER 10), the revelation of both biological and sociocultural based factors, including unconscious biases of physicians, could contribute to equality and personalization of treatment in both genders.

Moreover, interventions should be considered to prevent or improve skeletal muscle mass depletion and cachexia. To reduce systemic treatment toxicity, skeletal muscle mass features should be routinely used to optimize dosing of systemic treatment agents. Although cachexia is often perceived as an unavoidable consequence of progressive cancer, it can be prevented by adequate detection and early interventions. Recently, suggestions for multimodal strategies to identify weight loss or (pre)cachexia have been made, e.g. by routinely assessment of PROMs in clinical practice and measurement of body composition, which is supported by our findings (CHAPTERS 8 & 9), as well as suggestions of multimodal treatment to prevent (progression of) cachexia.[45] The evaluation of this multidisciplinary and multimodal approach consisting of at least early application of nutritional interventions and education, exercise, symptom management with or without tumor-directed treatment (Figure 1)44 on the outcomes of patients with esophagogastric cancer could be evaluated in a real-world study using registry data and PROMs.

CONCLUDING REMARKS

Systemic treatment is effective in patients with advanced esophagogastric cancer in terms of overall survival in daily clinical practice. A considerable efficacy-effectiveness gap was identified when our real-world results are compared to those of RCTs, to the disadvantage of the real-world population. The esophagogastric cancer patient is often of high age, frail, with multiple comorbidities, and therefore non-eligible for participation in clinical trials, which probably contributes to this efficacy-effectiveness gap. Population-based data are therefore

important in determining treatment effectiveness in clinical practice, alongside the RCT data on treatment efficacy. The efficacy-effectiveness gap should be taken into consideration when informing patients about benefits and harms of treatments in order to provide fair communication about expectations and prognosis. To monitor the gap, the use of population-based data should become more common, provided that these data are well analyzed and interpreted, and possible biases that come along with observational studies are taken into account. To narrow the gap, trial eligibility criteria should be expanded, and multidisciplinary, regional collaborations that include high-volume centers could contribute to accessibility to trial participation for all patients regardless of hospital of diagnosis. Lastly, our studies support a multidisciplinary approach towards patients with advanced esophagogastric cancer that should not be focused on tumor-directed therapy alone but should also include early identification of (pre)cachexia, nutrition, exercise, symptom management, and strategies to maintain quality of life, in order to improve treatment tolerability and survival.

Figure 1. A comprehensive approach to the care of patients with esophagogastric cancer as suggested by Roeland et al.[45]
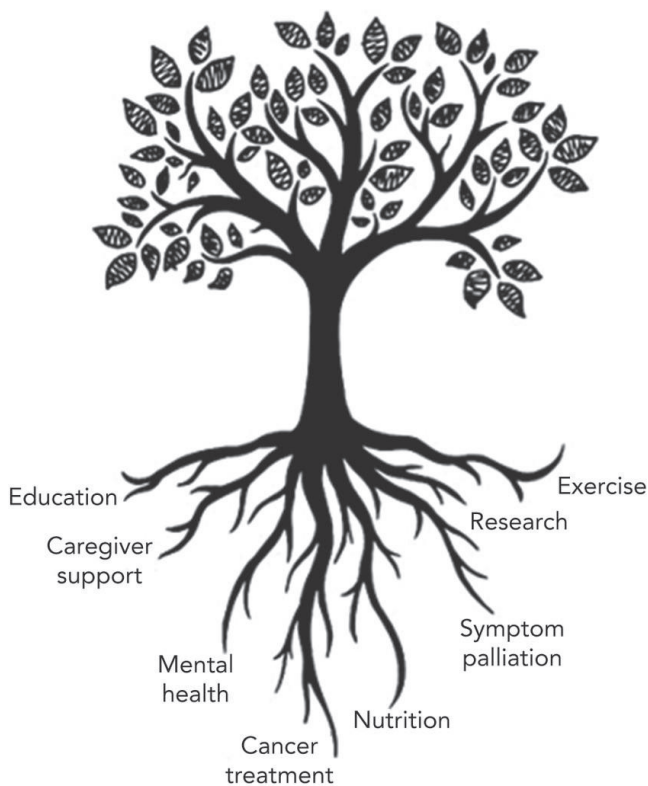
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CH 11.

Summary

This thesis includes studies that focus on the palliative treatment of patients with advanced esophagogastric (i.e. esophageal and gastric) cancer in daily clinical practice. Most results regard systemic treatment, which consists of either chemotherapy, targeted therapy or both. Rather than curation, palliative treatment aims to prolong survival, optimize quality of life and reduce symptom burden.

The first study aims to explore the use and effectiveness of first-line systemic treatment strategies in synchronous metastatic esophagogastric cancer patients, for which nationwide, population-based data of the Netherlands Cancer Registry were used (CHAPTER 2). First-line treatment strategies were categorized in monotherapy (one cytotoxic agent), doublet chemotherapy (two cytotoxic agents), triplet chemotherapy (three cytotoxic agents) and trastuzumab-containing regimens (trastuzumab with or without chemotherapy). First-line triplet chemotherapy was not superior to doublet chemotherapy in terms of overall survival, but was associated with more toxicity. Patients with a HER2-positive tumor who received a trastuzumab-containing regimen had the best survival rates compared to patients with HER2-negative tumors who received systemic treatment without trastuzumab. A large heterogeneity in use of treatment regimens was observed, with a total of 44 different first-line regimens. Such a heterogeneity is undesirable as it may impede the choices on beyond first-line systemic treatment, e.g. when agents that are recommended for beyond first-line treatment are used in first line.

Building on these results, we studied whether metastatic esophagogastric cancer patients who received systemic treatment were tested for HER2 status in clinical practice (CHAPTER 3). We observed a yearly increase in HER2 testing since publication of the landmark trial in 2010, from 18% in 2010 to 88% of the patients in 2016. A large heterogeneity in the proportion of HER2 tested patients between the hospitals in 2015-2016 was found, varying from 29%-100%. A high hospital volume, i.e. a high number of patients diagnosed with esophagogastric cancer per hospital, was associated with a higher probability of HER2 testing. Patients who were tested for HER2 had a better survival compared to non-tested patients, regardless of HER2 status. Overall survival of all patients who received systemic treatment increased statistically significant over time, from 6.9 months in patients diagnosed in 2010-2013 to 7.9 months in 2014-2016. The increased determination of HER2 status resulting in administration of trastuzumab may have contributed to the improved survival in these patients over time.

Patients in whom first-line treatment has failed could benefit from beyond first-line systemic treatment. In CHAPTER 4, the use of beyond first-line treatment in patients with metastatic esophagogastric adenocarcinoma is described. Again, a large heterogeneity of 44 administered regimens was observed. Treatment in a hospital with a higher number of esophagogastric cancer patients who received systemic treatment, was associated with a higher chance of beyond first-line treatment administration. The overall survival of all patients who were treated with palliative systemic treatment was higher in patients treated in a hospital with a high administration of beyond first-line treatment compared to a low administration of beyond first-line treatment. This suggests that factors other than patient, tumor and treatment characteristics may contribute to improved survival, for example well-organized structures and availability of multidisciplinary resources in high-volume hospitals. Moreover, we analyzed the effect of second-line treatment strategies on overall survival, and

observed a superior survival in patients who received second-line paclitaxel and ramucirumab, compared to a taxane alone, which is in line with results of clinical trials.

In CHAPTER 5 AND 6, the management and outcomes of patients with esophageal and gastric cancer who started treatment with curative intent and developed interval distant metastases, i.e. metastases detected during neoadjuvant treatment or surgery, was described. In patients with esophageal or gastroesophageal junction (GEJ) cancer who started neoadjuvant chemoradiotherapy in whom interval metastases were detected, independent prognostic factors for inferior survival were signet ring cell carcinoma and a poor tumor differentiation grade. Median overall survival since detection of metastases was 5.3 months. After detection of metastases, patients who received best supportive care only (41%) had a shorter survival compared to patients who received radiotherapy, surgical, or systemic treatment. Overall survival since diagnosis was comparable between patients with interval metastases and a matched cohort of patients with synchronous distant metastases (10.2 versus 9.4 months, respectively). In GEJ and gastric cancer patients who started neoadjuvant systemic treatment (without concurrent radiotherapy) and in whom interval metastases were detected, median overall survival since detection of metastases was 5.5 months. Overall survival from start of neoadjuvant systemic treatment did not differ from a propensity score matched cohort of synchronous metastatic GEJ or gastric cancer patients who received palliative systemic treatment. In conclusion, survival of esophagogastric patients with interval metastases is poor, and comparable to synchronous metastatic patients. Improvement of initial staging to detect metastases may avoid unnecessary surgical procedures and potentially improve systemic treatment outcomes in these patients.

In various cancer types, sarcopenia, i.e. severe muscle mass depletion, and skeletal muscle density, reflecting muscle strength, are associated with decreased survival and increased chemotherapy-related toxicity. CHAPTER 7 includes results on advanced esophagogastric cancer patients who received first-line systemic treatment consisting of capecitabine and oxaliplatin. Nearly half of the patients had sarcopenia before start of treatment. Although we did not observe an association between sarcopenia or low skeletal muscle density and survival; pre-treatment sarcopenic obesity (i.e. sarcopenia and a body mass index of >25kg/m2) was independently associated with the occurrence of neurotoxicity and skeletal muscle density with severe treatment-related toxicity. Future research focusing on interventions to increase or prevent decrease of skeletal muscle mass and density, which probably requires a multimodal approach, as well as adjustment of chemotherapy doses to muscle mass could be valuable in preventing chemotherapy toxicity in these patients.

An underlying condition of sarcopenia can be cachexia, which is a multifactorial syndrome that is characterized by involuntary skeletal muscle mass loss and inflammation. The prognostic significance of cachexia at initial diagnosis and the use of dietetic interventions in patients with esophagogastric cancer are determined in CHAPTER 8. Results are based on patient reported outcomes measures of a population-based cohort of esophagogastric cancer patients who participated in the Prospective Observational Cohort Study of Oesophageal-gastric cancer Patients (POCOP). Cachexia was defined as self-reported half-year body weight loss of >5% at initial diagnosis, or >2% in patients with a BMI <20 kg/m2 according to international consensus. Out of a total of 406 included patients, nearly half (49%) of esophagogastric cancer patients had pretreatment cachexia. The proportion of

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cachectic patients was the highest among patients that received palliative chemotherapy (59%) or best supportive care (67%). Cachexia was independently associated with lower overall survival. Dietetic consultation at baseline was not reported in over a third of the cachectic patients, although cachectic patients who were referred to a dietician experienced less median weight loss after three months follow-up compared to patients that were not. Therefore, improving nutritional screening and referral for dietetic consultation are warranted to prevent further weight loss and improve outcomes in esophagogastric cancer patients.

In CHAPTER 9, the prognostic value of health-related quality of life in esophagogastric cancer patients was assessed using patient-reported outcome measures collected in POCOP. Health-related quality of life was associated with overall survival in patients with both potentially curable and advanced esophagogastric cancer alongside sociodemographic and clinical characteristics. We observed that dysphagia, odynophagia, eating restriction and body image were prognostic in patients with potentially curable cancer, whereas fatigue and pain were prognostic in patients with advanced esophagogastric cancer. These results underline the prognostic value of quality of life in esophagogastric cancer, and confirm the extrapolation of results from clinical trials towards daily clinical practice.

Although differences in the incidence of esophagogastric cancer between men and women have been acknowledged regularly, less is known about disparities in treatment and survival. In CHAPTER 10, we explored gender differences in treatment allocation and overall survival of advanced esophagogastric cancer. Of all patients diagnosed with advanced esophagogastric cancer between 2015 and 2018, the proportion of women with esophageal and gastric adenocarcinoma that received palliative systemic treatment was statistically significantly lower compared to men (43% vs. 47% and 34% vs 39%, respectively), while this did not statistically differ in esophageal squamous cell carcinoma although it was numerically lower (33% vs. 40%). Being a woman was independently associated with a lower probability of receiving systemic treatment in gastric adenocarcinoma. Women with esophageal adenocarcinoma had a significantly lower median overall survival than men in univariable analysis, but not after adjustment for clinical covariates and systemic treatment administration. These statistically significant and clinically relevant disparities in palliative treatment allocation and overall survival between men and women with advanced gastroesophageal cancer have probably both biological and sociocultural causes, for which more research is warranted.

13.

Nederlandse samenvatting ● ⟩⟩ ●

Dit proefschrift bevat studies die zich richten op de palliatieve behandeling van patiënten met vergevorderde slokdarm- of maagkanker in de dagelijkse praktijk. Een palliatieve behandeling heeft niet als doel om te genezen, maar is gericht op het verlengen van de levensduur, optimaliseren van de kwaliteit van leven en het verminderen van symptomen. De studies in dit proefschrift zijn in het bijzonder gericht zijn op de palliatieve systemische behandeling, die kan bestaan uit zowel chemotherapie als doelgerichte- of immunotherapie.

De eerste studie heeft als doel het gebruik en de effectiviteit van de initiële, ofwel eerstelijns systemische behandelstrategieën bij patiënten met uitgezaaide slokdarm- en maagkankerpatiënten te onderzoeken. Hiervoor werden landelijke gegevens van de Nederlands kankerregistratie gebruikt (HOOFDSTUK 2). Eerstelijns behandelstrategieën werden onderverdeeld in monotherapie (één middel chemotherapie), doublet chemotherapie (een combinatie van twee verschillende middelen chemotherapie), triplet chemotherapie (drie verschillende middelen) en trastuzumab-bevattende behandelingen (trastuzumab met of zonder chemotherapie). Er werd een grote variatie van 45 verschillende eerstelijns behandelschema's waargenomen. Eerstelijns triplet chemotherapie resulteerde niet in een langere overleving dan doublet chemotherapie, maar was wel geassocieerd met meer ernstige bijwerkingen. Patiënten waarbij de tumor expressie van het HER2-eiwit vertoonde en die hiervoor systemische behandeling kregen die gericht was op dit HER2-eiwit, namelijk een trastuzumab-bevattende behandeling, hadden de beste overlevingskansen. Daarom hebben we onderzocht of de HER2-status van slokdarm- en maagkankerpatiënten die een systemische behandeling kregen in de dagelijkse praktijk werd getest (HOOFDSTUK 3). We zagen een jaarlijkse toename van het aandeel patiënten dat een HER2-test kreeg sinds de publicatie van het baanbrekende onderzoek in 2010, van 18% in 2010 naar 88% van de patiënten in 2016. Er werd een grote variatie in het aandeel patiënten dat een HER2-test kreeg tussen de ziekenhuizen in 2015-2016 gevonden, variërend van 29%-100%. Een hoog ziekenhuisvolume, d.w.z. een groot aantal patiënten met de diagnose slokdarmkanker per ziekenhuis, werd in verband gebracht met een hogere kans op het krijgen van een HER2-test. De overleving van patiënten die een HER2-test hadden gekregen was langer dan die van niet-geteste patiënten, ongeacht de uitslag van de test. Bij alle patiënten die een systemische behandeling kregen nam de overlevingsduur toe van 6.9 maanden bij patiënten die in 2010-2013 werden gediagnosticeerd tot 7.9 maanden in 2014-2016. De toename in het aantal bepalingen van de HER2-status en in de toediening van trastuzumab hebben mogelijk bijgedragen aan de verbeterde overleving van deze patiënten in de loop van de tijd.

Patiënten bij wie de eerstelijns behandeling heeft gefaald, hebben mogelijk baat bij vervolgbehandeling. In HOOFDSTUK 4 wordt het gebruik van deze vervolgbehandeling, ofwel tweedelijns behandeling bij patiënten met een uitgezaaide slokdarm- en maagkanker beschreven. Ook hier werd een grote variatie in toegediende schema's waargenomen. Een hoger behandelvolume in het ziekenhuis, d.w.z. het aantal slokdarm- en maagkankerpatiënten dat per ziekenhuis een systemische behandeling kreeg, ging gepaard met een grotere kans op het krijgen van een tweedelijns behandeling. De overlevingsduur van alle patiënten die werden behandeld met palliatieve systemische therapie was langer bij patiënten die werden behandeld in een ziekenhuis die vaak tweedelijns therapie toediende, in vergelijking met ziekenhuizen die het niet vaak toediende. Dit suggereert dat andere factoren dan patiënt-, tumor- en behandelkenmerken mogelijk bijdragen aan een langere overlevingsduur, bijvoorbeeld een

goed georganiseerde structuur en multidisciplinaire benadering in hoog-volume ziekenhuizen. In HOOFDSTUK 5 EN 6 werden de behandeling en de overleving beschreven van patiënten met slokdarm- en maagkanker die een behandeling startten die gericht was op genezing, maar bij wie uitzaaiingen geconstateerd werden gedurende, of net na deze behandeling, zogenoemde intervaluitzaaiingen. Bij patiënten met maagkanker die systemische behandeling (zonder gelijktijdige bestraling) kregen en bij wie intervaluitzaaiingen werden ontdekt, was de mediane overleving sinds de detectie van de intervaluitzaaiingen 5.5 maanden. De overleving vanaf het begin van de systemische behandeling verschilde niet met die van een cohort patiënten waarbij meteen bij diagnose uitzaaiingen waren gediagnosticeerd en die palliatieve systemische behandeling kregen. Bij patiënten met slokdarmkanker die systemische therapie en bestraling kregen en waarbij intervaluitzaaiingen werden ontdekt, bleek een bepaalde type tumor, namelijk zegelringceltumor, en een slechte tumordifferentiatiegraad voorspellend voor een slechtere overleving. De gemiddelde overleving sinds de detectie van de intervaluitzaaiingen was 5.3 maanden. Patiënten die na detectie van de intervaluitzaaiingen alleen ondersteunende zorg kregen (41%) hadden een kortere overleving in vergelijking met patiënten die bestraling, een operatie, of systemische behandeling kregen. De conclusie van deze studies is dat de overleving van slokdarm- en maagkankerpatiënten met intervaluitzaaiingen slecht is. Verbetering van de technieken om de uitzaaiingen voor start van behandeling op te sporen kan onnodige operaties voorkómen en de uitkomsten van de palliatieve systemische behandeling bij deze patiënten mogelijk verbeteren.

Bij verschillende soorten kanker worden sarcopenie, ofwel ernstig verlies van skeletspiermassa, en skeletspierdichtheid, wat een maat is voor spierkracht, geassocieerd met een kortere overleving en een grotere kans op bijwerkingen van systemische behandeling. HOOFDSTUK 7 bevat de resultaten van vergevorderde slokdarm- en maagkankerpatiënten die een eerstelijns systemische behandeling hebben gekregen bestaande uit capecitabine en oxaliplatin. Bijna de helft van de patiënten had sarcopenie voor aanvang van de behandeling. Hoewel we geen verband zagen tussen sarcopenie of een lage skeletspierdichtheid en overleving, werd gezien dat patiënten met sarcopenie en overgewicht een grotere kans hadden op het krijgen van neurologische bijwerkingen van de systemische behandeling. Daarnaast werd gevonden dat een afname van skeletspierdichtheid geassocieerd was met een hogere kans op ernstige bijwerkingen van systemische behandeling. Toekomstig onderzoek gericht op interventies om verlies van skeletspiermassa en -dichtheid te verkleinen, welke waarschijnlijk een multimodale aanpak vereist, en het aanpassen van de dosering systemische therapie aan de spiermassa zou van waarde kunnen zijn bij het voorkomen van bijwerkingen bij deze patiënten.

Cachexie is een multifactorieel syndroom dat wordt gekenmerkt door onder andere progressief verlies van skeletspiermassa en inflammatie. De voorspellende waarde op overleving van cachexie bij de eerste diagnose en het gebruik van voedingsinterventies bij patiënten met slokdarm- en maagkanker worden in HOOFDSTUK 8 bepaald. De resultaten zijn gebaseerd op de resultaten van vragenlijsten die ingevuld werden door patiënten met slokdarm- en maagkanker die deelnemen aan de Prospective Observational Cohort Study of Oesophageal-gastric cancer Patients (POCOP). Cachexie werd gedefinieerd als een verlies van het lichaamsgewicht van >5% in het afgelopen half jaar, of >2% bij patiënten met een BMI <20 kg/m2. Van de geïncludeerde 406 slokdarm- en maagkankerpatiënten had bijna de helft (49%)

cachexie bij diagnose. Het aandeel cachectische patiënten was het hoogst onder de patiënten die palliatieve systemische therapie kregen (59%) of de alleen ondersteunende zorg (67%). Cachexie was geassocieerd met een verminderde algemene overleving. Verwijzing naar de diëtist bij diagnose werd niet gemeld in meer dan een derde van de cachectische patiënten, hoewel het mediane gewichtsverlies na drie maanden follow-up lager was bij cachectische patiënten die werden doorverwezen naar een diëtist in vergelijking met patiënten die niet waren doorverwezen. We concluderen daarom dat het verbeteren van voedingsscreening en doorverwijzing naar een diëtist nodig is om verder gewichtsverlies te voorkomen, en de overleving te verbeteren bij patiënten met slokdarm- en maagkanker.

In HOOFDSTUK 9 werd de voorspellende waarde van de kwaliteit van leven op de overleving van patiënten met slokdarm- en maagkanker beoordeeld met behulp van patiënt-gerapporteerde uitkomstmaten die werden verzameld in POCOP. De kwaliteit van leven werd in verband gebracht met de overleving van patiënten die een behandeling gericht op genezing, als een palliatieve behandeling kregen. We observeerden dat symptomen als moeite met slikken, pijn bij het slikken, eetbeperkingen en een verstoord lichaamsbeeld voorspellend waren voor de overleving bij patiënten die een behandeling kregen die op genezing gericht was. Daarnaast waren vermoeidheid en pijn voorspellend voor de overleving van patiënten met vergevorderde slokdarm- en maagkanker. Deze resultaten onderstrepen de prognostische waarde van kwaliteit van leven in slokdarm- en maagkanker, en bevestigen eerdere resultaten van trials in de klinische praktijk.

Hoewel de verschillen in het vóórkomen van slokdarm- en maagkanker tussen mannen en vrouwen regelmatig worden erkend, is er minder bekend over de verschillen in behandeling en overleving. In HOOFDSTUK 10 onderzochten we de verschillen tussen mannen en vrouwen in het krijgen van behandeling en de algehele overleving van patiënten met vergevorderde slokdarm- en maagkanker. We maakten hierbij onderscheid tussen adenocarcinomen van de slokdarm en de maag, en plaveiselcelcarcinomen van de slokdarm. Van alle patiënten bij wie tussen 2015 en 2018 de diagnose slokdarm- en maagkanker in een vergevorderd stadium werd vastgesteld, was het aandeel van vrouwen met een adenocarcinoom van de slokdarm en maag die een palliatieve systemische behandeling kregen statistisch gezien lager dan bij mannen, terwijl dit niet verschilde bij het plaveiselcelcarcinoom van de slokdarm. Vrouwen met een adenocarcinoom van de slokdarm hadden een kortere mediane overleving dan mannen. Onder patiënten die een palliatieve systemische behandeling kregen, verschilde de mediane overleving niet tussen mannen en vrouwen. Deze statistisch significante en klinisch relevante verschillen in het krijgen van een palliatieve behandeling en algehele overleving tussen mannen en vrouwen met vergevorderde slokdarm- en maagkanker hebben waarschijnlijk zowel biologische als socioculturele oorzaken, waarnaar meer onderzoek vereist is.

13.

APPENDICES

From presentation to paper:
Gender disparities in oncological research

International Journal of Cancer, 2019.

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ABSTRACT

Background: Gender disparities in scientific publications have been identified in oncological research. Oral research presentations at major conferences enhance visibility of presenters. The share of women presenting at such podia is unknown. We aim to identify gender-based differences in contributions to presentations at two major oncological conferences.

Methods: Abstracts presented at plenary sessions of the American Society of Clinical Oncology (ASCO) Annual Meetings and European Society for Medical Oncology (ESMO) Congresses were collected. Trend analyses were used to analyze female contribution over time. The association between presenter's sex, study outcome (positive/negative) and journals' impact factors (IFs) of subsequently published papers was assessed using Chi-square and Mann–Whitney U tests.

Results: Of 166 consecutive abstracts presented at ASCO in 2011–2018 (n = 34) and ESMO in 2008–2018 (n = 132), 21% had female presenters, all originating from Northern America (n = 17) or Europe (n = 18). The distribution of presenter's sex was similar over time (p = 0.70). Of 2,425 contributing authors to these presented abstracts, 28% were women. The proportion of female abstract authors increased over time (p < 0.05) and was higher in abstracts with female (34%) compared to male presenters (26%; p < 0.01). Presenter's sex was not associated with study outcome (p = 0.82). Median journals' IFs were lower in papers with a female first author (p < 0.05).

Conclusion: There is a clear gender disparity in research presentations at two major oncological conferences, with 28% of authors and 21% of presenters of these studies being female. Lack of visibility of female presenters could impair acknowledgement for their research, opportunities in their academic career and even hamper heterogeneity in research.

INTRODUCTION

Gender inequalities in science and medicine are increasingly brought to the fore. Despite an expanding number of women entering the field of medicine, female physicians are still at disadvantage in obtaining jobs, less rewarded than men and underrepresented in leadership positions.[1–5] In medical research, gender differences are even more pronounced: women are less likely to hold first-author positions on top publications, receive requested grants, be invited as a peer reviewer, or become a full professor.[1,4–7]

Gender discrepancies in authorships of scientific publications have been identified in many disciplines all over the world, including oncology.[2,8–12] However, results of a clinical research project are often first brought to life through a presentation at an international conference. Such a presentation gives the scientific study an actual identity through visibility of the researcher. Presentations at major international conferences are not only important for discussion of the outcomes of a study, they also provide the presenter the opportunity for recognition for as a principal investigator, and increase the chance of climbing the academic career ladder.

Female underrepresentation in presenting studies and invitation to speak at conferences has been identified in other disciplines.[13–18] The exact share of women presenting at major oncological conferences is not clear. In our study, we aimed to identify potential

gender-based differences in contributions to presentations at two major international oncological conferences: the American Society of Clinical Oncology (ASCO) Annual Meetings and European Society for Medical Oncology (ESMO) Congresses.

METHODS

Data collection

We aimed to collect consecutive abstracts of all plenary sessions of ASCO Annual Meetings and presidential sessions of ESMO Congresses between 2000 and 2018. The abstracts presented at these sessions are assumed to have the highest impact on oncological research and practice. Specific data on ASCO abstracts were available from 2011 and on ESMO abstracts from 2008. Data on ASCO abstracts, including sexes of the presenters, were provided by ASCO Center for Research and Analytics for all abstracts presented at the plenary sessions since 2011. All consecutive ESMO abstracts presented at the presidential sessions since 2008 were identified from the ESMO website (www.esmo.org) or the website of the conference.

Data extracted from the abstracts included information on presenters, names and order of authors, country of origin, study subject and results. Sexes of presenters and authors were interpreted based on their first names or, if inconclusive, based on available online information including photos and electronic portfolio of the specific author. Study results were defined as positive and negative if they met or did not meet the primary endpoints, respectively, and neither negative nor positive if results were not clear yet, or if both positive and negative results were found.

From all abstracts, the subsequently published papers were identified and corresponding impact factors (IFs) of the journals in which they were published (obtained from InCites Journal Citation Reports) were collected. One-year IFs of the year in which the article was published were used, or of the previous year in case IFs were not yet known. Any changes in authorships compared to the presented abstract were identified.

Ethical approval to perform our study was not considered to be necessary.

Statistical analysis

Descriptive statistics were used to display the distribution of presenter's and abstract author's sex. Chi-square or Fisher's exact tests where appropriate were used to compare the sex distribution in abstract presenters and authors per year. The association between presenter's or last author's sex and distribution of author's sex, study outcome and IFs were analyzed using Chi-square and Mann–Whitney U tests, respectively. A trend in contribution of both sexes in presenters and abstract authors over time was tested using the Cochran-Armitage trend test; p-values lower than 0.05 were regarded as statistically significant. Statistical 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 corresponding author upon reasonable request.

RESULTS

Presenters
Data of 166 consecutive abstracts presented at plenary sessions of ASCO Annual Meetings from 2011 and at ESMO Congresses from 2008 were collected. Included abstracts of the plenary sessions of ASCO Annual Meetings between 2011 and 2018 (n = 34) and of the presidential sessions of ESMO conferences between 2008 and 2018 (n = 132) are shown in Tables 1 and 2, respectively. References of all of these abstracts and subsequently published papers can be found in the Supplementary Material online (DOI: 10.1002/ijc.32660).

Of all 166 abstracts, 35 (21%) were presented by a woman. Although the proportion of female presenters has decreased since 2015–2016 (Fig. 1), the distribution of female and male contribution to presenters was not different over the years (p = 0.699), neither was a trend observed in contribution of both sexes over time (p = 0.350).

The majority of the presenters originated from Europe (n = 90, 54%), followed by Northern America (n = 65, 39%), Asia (n = 9, 5%) and Oceania (n = 2, 1%). All female presenters came from Northern America (n = 17) or Europe (n = 18). The share of women of all Northern American and European presenters was 26 and 20%, respectively. Per country, 17 of 62 (27%) American, 5 of 29 (17%) British, 1 of 6 (17%) Belgian, 2 of 17 (12%) French, 6 of 13 (46%) Dutch, 2 of 4 (50%) Swiss, 1 of 5 (20%) Italian presenters and the only Austrian presenter were female.

Almost a quarter of the studies presented by a female researcher (n = 35) concerned breast cancer (n = 8, 23%), lung cancer (n = 3, 9%), followed by ovarian cancer, colorectal cancer and multiple types of cancer (all: n = 4, 11%). Other subjects are shown in Tables 1 and 2. Overall, 26% of the presentations about breast cancer, 44% about ovarian cancer, 29% about colorectal cancer and 17% about lung cancer were presented by a woman.

Study outcomes were most often positive (n = 119, 71%), while 33 (20%) had negative outcomes and 14 (8%) neither positive nor negative (N/P), or nonapplicable (N/A). Outcomes were positive, negative and N/P or N/A in 71, 23 and 6% of the 35 studies presented by a female researcher, and 72, 19 and 9% of 131 abstracts with male presenters, respectively. The outcomes of presented abstracts did not differ between male and female presenters (p = 0.746). Presenter's sex was not associated with study outcome (p = 0.815).

Figure 1. Proportion of female presenters and abstract authors over time at plenary sessions of American Society of Clinical Oncology (ASCO) Annual Meetings and European Society for Medical Oncology (ESMO) Congresses.
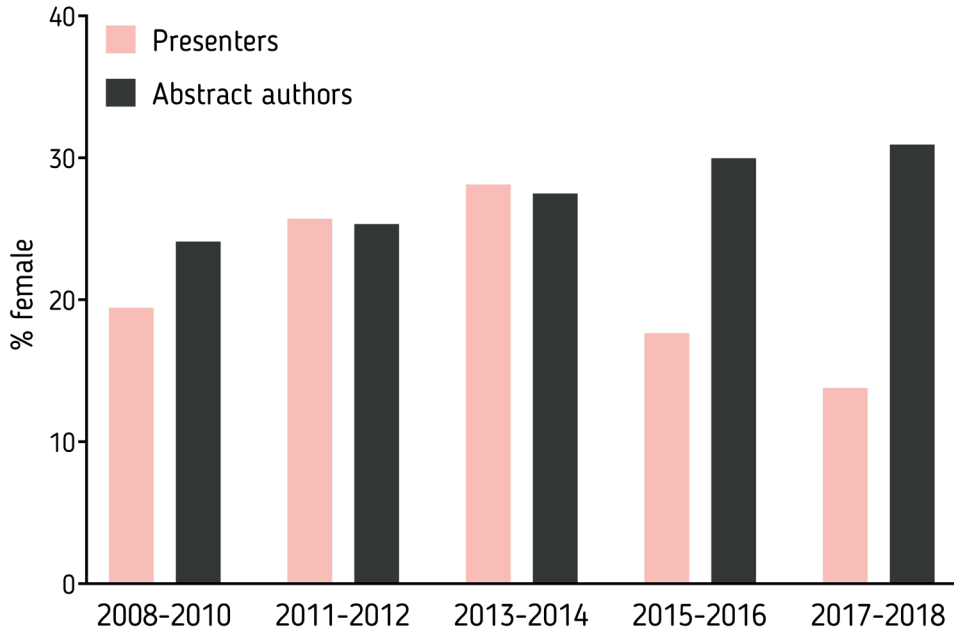
Results of 2008–2010 are based on ESMO abstracts solely. Abstract authors with unknown sex (n = 19) are not displayed.

Table 1. Abstracts presented at ASCO annual meetings.

		Presenter				Abstract						Article					
Year	Abstract no.	Name	Sex	Country of origin	Author place presenter	Sex last author	No. authors	No. male authors	No. female authors	No. authors unknown sex	Study outcome*	Journal published	Year	IF	Sex 1st author	Sex last author	Subject
2011	A-2011-1 [41]	H. Joensuu	M	Finland	First	M	18	13	5	0	P	JAMA J Am Med Assoc [42]	2012	29.978	M	M	GIST
	A-2011-2 [43]	R.L. Ladenstein	F	Austria	First	F	19	9	10	0	P	Lancet Oncol [44]	2017	36.418	F	F	Neuroblastoma
	A-2011-3 [45]	E.C. Larsen	M	USA	First	M	16	8	8	0	P	J Clin Oncol [46]	2016	24.008	M	M	Leukaemia
	A-2011-4 [47]	P.B. Chapman	M	USA	First	M	20	17	3	0	P	New Engl J Med [48]	2011	53.298	M	M	Melanoma
	A-2011-5 [49]	J.D. Wolchok	M	USA	First	F	10	9	1	0	P	New Engl J Med [50]	2011	53.298	F	M	Melanoma
2012	A-2012-1 [51]	K.L. Blackwell	F	USA	First	M	14	10	4	0	P	New Engl J Med [52]	2012	51.658	M	F	Breast cancer
	A-2012-2 [53]	M.J. Van Den Bent	M	The Netherlands	First	M	19	15	4	0	P	J Clin Oncol [54]	2013	17.879	M	M	Oligodendroglioma
	A-2012-3 [55]	M.J. Rummel	M	Germany	First	M	18	15	3	0	P	Lancet [56]	2013	39.207	M	M	Lymphoma
	A-2012-4 [57]	M. Hussain	F	USA	First	M	18	13	5	0	N	New Engl J Med [58]	2013	54.420	F	M	Prostate cancer
2013	A-2013-1 [59]	M.R. Gilbert	M	USA	First	M	20	15	5	0	N	New Engl J Med [60]	2014	55.873	M	M	Glioblastoma
	A-2013-2 [61]	S.S. Shastri	M	India	First	M	6	4	2	0	P	JNCI J Natl Cancer I [62]	2014	12.583	M	M	Cervical cancer
	A-2013-3 [63]	K.S. Tewari	M	USA	First	M	10	6	4	0	P	New Engl J Med [64]	2014	55.873	M	M	Cervical cancer
	A-2013-4 [65]	M.S. Brose	F	USA	First	M	16	12	4	0	P	Lancet [66]	2014	45.217	F	M	Thyroid cancer
	A-2013-5 [67]	R.G. Gray	M	UK	First	M	22	15	7	0	P	not (yet) published					Breast cancer
2014	A-2014-1 [68]	O. Pagani	F	Switzerland	First	F	20	10	10	0	P	New Engl J Med [69]	2014	55.873	F	F	Breast cancer
	A-2014-2 [70]	C. Sweeney	M	USA	First	M	17	15	2	0	P	New Engl J Med [71]	2015	59.558	M	M	Prostate cancer
	A-2014-3 [72]	A.P. Venook	M	USA	First	M	15	11	4	0	N	JAMA J Am Med Assoc [73]	2017	47.661	M	M	Colorectal cancer
	A-2014-4 [74]	M.J. Piccart	F	Belgium	First	F	20	15	5	0	N/P	not (yet) published					Breast cancer
2015	A-2015-1 [75]	J.D. Wolchok	M	USA	First	M	20	17	3	0	P	New Engl J Med [76]	2015	59.558	M	M	Melanoma
	A-2015-2 [77]	G.T. Armstrong	M	USA	First	M	15	9	6	0	P	New Engl J Med [78]	2016	72.406	M	M	Childhood cancers
	A-2015-3 [79]	A. D'Cruz	M	India	First	M	16	6	10	0	P	New Engl J Med [80]	2015	59.558	M	M	Oral cancer
	A-2015-4 [81]	P.D. Brown	M	USA	First	M	17	10	7	0	N	JAMA J Am Med Assoc [82]	2016	44.405	M	M	Multiple types of cancer
2016	A-2016-1 [83]	P.E. Goss	M	USA	First	F	20	11	9	0	P	New Engl J Med [84]	2016	72.406	M	F	Breast cancer
	A-2016-2 [85]	J.R. Perry	M	Canada	First	M	20	16	4	0	P	New Engl J Med [86]	2017	79.260	M	M	Glioblastoma
	A-2016-3 [87]	J.R. Park	F	USA	First	F	17	7	10	0	P	not (yet) published					Neuroblastoma
	A-2016-4 [88]	A. Palumbo	M	Italy	First	M	19	13	5	1	P	New Engl J Med [89]	2016	72.406	M	M	Multiple myeloma
2017	A-2017-1 [90]	Q. Shi	F	USA	First	M	20	16	4	0	N/P	New Engl J Med [91]	2018	70.670	M	M	Colorectal cancer
	A-2017-2 [92]	E.M. Basch	M	USA	First	F	13	6	7	0	P	JAMA J Am Med Assoc [93]	2017	47.661	M	F	Multiple types of cancer
	A-2017-3 [94]	K. Fizazi	M	France	First	M	15	11	3	1	P	New Engl J Med [95]	2017	79.260	M	M	Prostate cancer
	A-2017-4 [96]	M.E. Robson	M	USA	First	M	14	6	8	0	P	New Engl J Med [97]	2017	79.260	M	M	Breast cancer
2018	A-2018-1 [98]	J.A. Sparano	M	USA	First	M	20	14	6	0	P	New Engl J Med [99]	2018	70.670	M	M	Breast cancer
	A-2018-2 [100]	G. Bisogno	M	Italy	First	M	12	6	6	0	P	Lancet Oncol [101]	2018	35.386	M	M	Rhabdomyosarcoma
	A-2018-3 [102]	A. Méjean	M	France	First	M	20	18	2	0	P	New Engl J Med [103]	2018	70.670	M	M	Renal cell carcinoma
	A-2018-4 [104]	G. Lopes	M	USA	First	M	13	10	2	1	P	Lancet [105]	2019	59.102	M	M	Lung cancer
Total	N=34		F: N=8		F: N=7	F: N=7	569	388	178	3		N=31			F: N=5	F: N=5	

1 Abstracts presented at plenary sessions of ASCO annual meetings between 2011 and 2018. For papers published in 2019, journal IFs of 2018 were used. Abbreviations: ASCO, American Society of Clinical Oncology; F, female; GIST, gastrointestinal stroma cell tumor; IF, impact factor; M, male; N, negative; N/P, outcome did not reach significance or endpoint, but did show improvement/benefit or reached some of the outcomes; no, number; P, positive. References of ASCO abstracts can be found online.

Table 2. Abstracts presented at ESMO congresses.

		Presenter					Abstract					Article					
Year	Abstract no.	Name	Sex	Country of origin	Author place presenter	Sex last author	No. authors	No. male authors	No. female authors	No. authors unknown sex	Study outcome*	Journal published	Year	IF	Sex 1st author	Sex last author	Subject
2008	E-2008-1[106]	C. Manegold	M	Germany	First	M	10	6	4	0	P	J Clin Oncol[107]	2009	17.793	M	M	Lung cancer
	E-2008-2[108]	T. Mok	M	Hong Kong	First	M	10	6	4	0	P	New Engl J Med[109]	2009	47.050	M	M	Lung cancer
	E-2008-3[110]	R.S.J. Midgley	F	UK	First	M	10	5	5	0	N	J Clin Oncol[111]	2010	18.970	F	M	Colorectal cancer
	E-2008-4[112]	B.J. Monk	M	USA	First	M	10	8	2	0	P	J Clin Oncol[113]	2010	18.970	M	F	Ovarian cancer
	E-2008-5[114]	S. Lee	M	UK	First	F	5	1	4	0	N	J Clin Oncol[115]	2010	18.970	M	M	Glioma
	E-2008-6[116]	C. Karapetis	M	Australia	First	M	10	7	3	0	P	New Engl J Med[117]	2008	50.017	M	M	Colorectal cancer
	E-2008-7[118]	M. Löhr	M	Germany	First	M	10	9	1	0	P	Ann Oncol[119]	2012	7.384	M	M	Pancreatic cancer
	E-2008-8[120]	P.M. Patel	M	UK	First	M	10	6	4	0	N	Eur J Cancer[121]	2011	5.536	M	M	Melanoma
	E-2008-9[122]	M. Auerbach	M	USA	First	M	8	6	2	0	P	Am J Hematol[123]	2010	3.576	M	M	Multiple types of cancer
2009	E-2009-1[124]	M. van Hemelrijck	F	UK	First	M	8	6	2	0	P	J Clin Oncol[125]	2010	18.970	F	M	Prostate cancer
	E-2009-2[126]	C. van de Velde	M	The Netherlands	First	M	10	8	2	0	P	Lancet[127]	2011	38.278	M	M	Breast cancer
	E-2009-3[128]	A. M. Brunt	M	UK	First	M	10	6	4	0	P	Radiother Oncol[129]	2011	5.580	N/A	N/A	Breast cancer
	E-2009-4[130]	R. Issels	M	Germany	First	M	10	10	0	0	P	Lancet Oncol[131]	2010	17.764	M	M	Soft-tissue sarcoma
	E-2009-5[132]	A. Stopeck	F	USA	First	F	10	5	5	0	P	J Clin Oncol[133]	2010	18.970	M	F	Breast cancer
	E-2009-6[134]	M.E.L. van der Burg	F	The Netherlands	First	M	2	1	1	0	N	Lancet[135]	2010	33.633	M	F	Ovarian cancer
	E-2009-7[136]	G.G. Steger	M	Germany	First	M	10	8	2	0	P	Ann Oncol[137]	2014	7.040	M	M	Breast cancer
	E-2009-8[138]	J. Baselga	M	Spain	First	M	10	8	2	0	P	J Clin Oncol[139]	2012	18.038	M	M	Breast cancer
	E-2009-9[140]	M. Baumann	M	Germany	First	M	10	8	2	0	N/P	Radiother Oncol[141]	2011	5.580	M	M	Lung cancer
	E-2009-10[142]	D. Hailer	M	USA	First	M	10	9	1	0	P	J Clin Oncol[143]	2015	20.982	M	M	Colorectal cancer
	E-2009-11[144]	T. Maughan	M	UK	First	M	10	9	1	0	N	Lancet[145]	2011	38.278	M	M	Colorectal cancer
	E-2009-12[146]	S. Badve	M	USA	First	M	10	7	3	0	P	not (yet) published					Breast cancer
	E-2009-13[147]	P. Chapman	M	USA	First	M	10	10	0	0	P	New Engl J Med[148]	2010	53.486	M	M	Melanoma
	E-2009-14[149]	B. Johnson	M	USA	First	M	7	6	1	0	P	J Clin Oncol[150]	2013	17.879	M	M	Lung cancer
	E-2009-15[151]	A. Inoue	M	Japan	First	M	10	10	0	0	P	Ann Oncol[152]	2013	6.578	M	M	Lung cancer
	E-2009-16[153]	J. Douillard	M	France	Second	F	10	9	1	0	P	J Clin Oncol[154]	2010	18.970	M	F	Colorectal cancer
	E-2009-17[155]	C. Osborne	F	USA	First	M	10	6	4	0	P	New Engl J Med[156]	2011	53.298	F	M	Breast cancer
	E-2009-18[157]	A. Dueñas-González	M	Mexico	First	M	11	8	3	0	P	J Clin Oncol[158]	2011	18.372	M	M	Cervical cancer
	E-2009-19[159]	E. van Cutsem	M	Belgium	First	M	10	7	3	0	P	Lancet[160]	2010	33.633	M	M	Gastric cancer
	E-2009-20[161]	C. Nutting	M	UK	First	F	10	8	2	0	P	Lancet Oncol[162]	2011	22.589	M	F	Head and neck cancer
	E-2009-21[163]	A.M.M. Eggermont	M	The Netherlands	First	M	5	4	1	0	P	Eur J Cancer[164]	2012	5.061	M	M	Melanoma
	E-2009-22[165]	E.L. Kwak	F	USA	First	M	10	9	1	0	P	not (yet) published					Multiple types of cancer
2010	E-2010-1[166]	V.A. Miller	M	USA	First	M	10	8	2	0	N/P	Lancet Oncol[167]	2012	25.117	M	M	Lung cancer
	E-2010-2[168]	J. Chih-Hsin Yang	M	Taiwan	First	M	10	7	3	0	N	J Clin Oncol[169]	2011	18.372	M	M	Lung cancer
	E-2010-3[170]	E.A. Perez	F	USA	First	F	10	5	5	0	P	Breast Cancer Res[171]	2014	5.490	F	M	Breast cancer
	E-2010-4[172]	T.J. Perren	M	UK	First	M	10	9	1	0	P	New Engl J Med[173]	2011	53.298	M	M	Ovarian cancer

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Year	Code	Name		Country	Position							Journal				Cancer type
2011	E-2010-5 [174]	J.S. De Bono	M	UK	First	M	10	10	0	0	P	New Engl J Med [175]	2011	53.298	M	Prostate cancer
	E-2011-1 [176]	L. Dirix	M	Belgium	First	M	9	7	1	1	P	New Engl J Med [177]	2012	51.658	M	Basal cell carcinoma
	E-2011-2 [178]	C. Parker	M	UK	First	M	10	9	1	0	P	New Engl J Med [179]	2013	54.420	M	Prostate cancer
	E-2011-3 [180]	J. Bourhis	M	Switzerland	First	F	17	15	2	0	N	Lancet Oncol [181]	2012	25.117	F	Head and neck cancer
	E-2011-4 [182]	M. Bebin	F	UK	First	M	10	7	3	0	P	Lancet [183]	2013	39.207	M	Astrocytoma
	E-2011-5 [184]	I. Fernando	M	UK	First	M	10	8	2	0	P	not (yet) published				Breast cancer
	E-2011-6 [185]	J. Tabernero	M	Spain	First	F	12	9	3	0	P	Eur J Cancer [186]	2014	5.417	F	Colorectal cancer
	E-2011-7 [187]	C. Aghajanian	F	USA	First	F	9	2	7	0	P	J Clin Oncol [188]	2012	18.038	M	Ovarian cancer
	E-2011-8 [189]	P. Hoskin	M	UK	First	M	13	9	4	0	N	JNCI J Natl Cancer I [190]	2015	11.370	M	Prostate cancer
	E-2011-9 [191]	R. Sullivan	M	UK	First	M	10	10	0	0	N/A	Lancet Oncol [192]	2011	22.589	M	Multiple types of cancer
	E-2011-10 [193]	L. Krug	M	USA	First	M	10	9	1	0	N	Lancet Oncol [194]	2015	26.509	M	Mesothelioma
	E-2011-11 [195]	J. Baselga	M	USA	First	M	10	8	2	0	P	Ann Oncol [196]	2014	7.040	F	Breast cancer
	E-2011-12 [197]	E.J.T. Rutgers	M	The Netherlands	Last	M (= presenter)	16	9	7	0	P	Eur J Cancer [198]	2011	5.536	M	Breast cancer
	E-2011-13 [199]	H.J. Bonjer	M	The Netherlands	First	M	7	6	1	0	P	New Engl J Med [200]	2015	59.558	F	Colorectal cancer
	E-2011-14 [201]	M. Van Hemelrijck	F	UK	First	M	7	4	3	0	P	Hypertension [202]	2012	6.873	F	Multiple types of cancer
	E-2011-15 [203]	F. Amant	M	Belgium	First	F	16	9	7	0	N/P	Lancet Oncol [204]	2012	25.117	F	Multiple types of cancer
	E-2011-16 [205]	E. Papaemmanuil	F	UK	First	M	10	7	3	0	P	New Engl J Med [206]	2011	53.298	M	Myelodysplastic malignancies
	E-2011-17 [207]	M. Middleton	M	UK	First	M	10	9	1	0	N/P	Ann Oncol [208]	2015	9.269	M	Melanoma
	E-2011-18 [209]	E. van Cutsem	M	Belgium	First	M	11	9	2	0	P	Ann Oncol [210]	2015	9.269	M	Colorectal cancer
2012	E-2012-1 [211]	A. Shaw	F	USA	First	M	20	14	6	0	P	New Engl J Med [212]	2013	54.420	F	Lung cancer
	E-2012-2 [213]	A.X. Zhu	M	USA	First	M	14	13	1	0	N	J Clin Oncol [214]	2015	20.982	M	Hepatocellular carcinoma
	E-2012-3 [215]	F. Lordick	M	Germany	First	M	16	12	4	0	N	Lancet Oncol [216]	2013	24.725	M	Gastric cancer
	E-2012-4 [217]	J. Taïeb	M	France	First	M	19	16	3	0	N	Lancet Oncol [218]	2014	24.690	M	Colorectal cancer
	E-2012-5 [219]	X. Pivot	M	France	First	M	19	14	5	0	N	Lancet Oncol [220]	2013	24.725	M	Breast cancer
	E-2012-6 [221]	R. Gelber	M	USA	Second	M	24	19	5	0	N	Lancet [222]	2013	39.207	M	Breast cancer
	E-2012-7 [223]	W. Van der Graaf	F	The Netherlands	Last	F (= presenter)	19	15	4	0	N	Lancet Oncol [224]	2014	24.690	F	Soft-tissue sarcoma
	E-2012-8 [225]	R.J. Motzer	M	USA	First	M	25	18	7	0	P	New Engl J Med [226]	2013	54.420	M	Renal cell carcinoma
2013	E-2013-1 [227]	P. Autier	M	France	First	M	4	3	1	0	N	Lancet Diabetes Endocrinol [228]	2014	9.185	M	Multiple types of cancer
	E-2013-2 [229]	P. Poortmans	M	The Netherlands	First	M	10	7	3	0	P	New Engl J Med [230]	2015	59.558	M	Breast cancer
	E-2013-3 [231]	A.J. Breugom	F	The Netherlands	First	M	11	7	4	0	P	Lancet Oncol [232]	2015	26.509	F	Colorectal cancer
	E-2013-4 [233]	M. Reimers	F	The Netherlands	First	M	10	7	3	0	P	JNCI J Natl Cancer I [234]	2014	12.583	F	Colorectal cancer
	E-2013-5 [235]	G. Giaccone	M	USA	First	M	10	7	3	0	N/P	Eur J Cancer [236]	2015	6.163	M	Lung cancer
	E-2013-6 [237]	P. Ruszniewski	M	France	Second	F	13	7	6	0	P	New Engl J Med [238]	2014	55.873	F	Neuroendocrine tumors
	E-2013-7 [239]	P. Brastianos	F	USA	First	M	10	8	2	0	P	Cancer Discov [240]	2015	19.783	M	Multiple types of cancer

Year	Code	First author	Sex	Country	Position	Presenter	Total	n	n	O	Result	Journal	Year	IF	Sex	Cancer type
	E-2013-8 [241]	P. Witteveen	F	The Netherlands	First	M	10	7	3	o	N	J Clin Oncol [242]	2014	18.428	M	Ovarian cancer
	E-2013-9 [243]	A. Oza	M	Canada	First	M	13	10	3	o	N/P	Lancet Oncol [244]	2015	26.509	M	Ovarian cancer
	E-2013-10 [245]	F. Sclafani	M	UK	First	M	10	7	3	o	P	Eur J Cancer [246]	2014	5.417	M	Colorectal cancer
	E-2013-11 [247]	J.C. Soria	M	France	Last	M (= presenter)	17	12	5	o	N/A	Eur J Cancer [248]	2014	5.417	F	Multiple types of cancer
	E-2013-12 [249]	R.E. Coleman	M	UK	First	F	10	7	3	o	N/P	Lancet Oncol [250]	2014	24.690	F	Breast cancer
	E-2013-13 [251]	J. Ledermann	M	UK	First	M	10	7	3	o	P	Lancet [252]	2016	47.831	M	Ovarian cancer
	E-2013-14 [253]	P. Van Loo	M	UK	Last	M (= presenter)	10	7	3	o	P	Nat Commun [254]	2017	12.353	F	Multiple types of cancer
	E-2013-15 [255]	J.G. Eriksen	M	Denmark	First	M	10	8	2	o	N	not (yet) published				Head and neck cancer
	E-2013-16 [256]	R. Chlebowski	M	USA	First	F	11	8	3	o	P	JNCI J Natl Cancer I [257]	2016	12.589		Endometrial cancer
	E-2013-17 [258]	H.J. de Koning	M	The Netherlands	First	F	9	7	2	o	N	Ann Intern Med [259]	2014	17.810	F	Lung cancer
2014	E-2014-1 [260]	J.S. Weber	M	USA	First	M	20	17	3	o	P	Lancet Oncol [261]	2015	26.509	M	Melanoma
	E-2014-2 [262]	C. Robert	F	France	First	M	20	14	6	o	P	Lancet Oncol [263]	2015	26.509	F	Melanoma
	E-2014-3 [264]	G.A. McArthur	M	Australia	First	F	17	12	5	o	P	Lancet Oncol [265]	2016	33.900	M	Melanoma
	E-2014-4 [266]	S. Swain	F	USA	First	M	14	9	5	o	P	New Engl J Med [267]	2015	59.558	F	Breast cancer
	E-2014-5 [268]	J.F. Vansteenkiste	M	Belgium	First	M	20	19	1	o	N	Lancet Oncol [269]	2016	33.900	M	Lung cancer
	E-2014-6 [270]	T.S. Mok	M	Hong Kong	First	M	18	14	4	o	N	J Clin Oncol [271]	2017	26.303	M	Lung cancer
2015	E-2015-1 [272]	M. Sant	F	Italy	First	F	18	8	10	o	P	Eur J Cancer [273]	2015	6.163	F	Multiple types of cancer
	E-2015-2 [274]	R. Atun	M	USA	First	F	18	12	6	o	P	Lancet Oncol [275]	2015	26.509	M	Multiple types of cancer
	E-2015-3 [276]	P. Sharma	F	USA	First	M	15	12	3	o	P	Eur Urol [277]	2017	17.581	M	Renal cell carcinoma
	E-2015-4 [278]	T. Choueiri	M	USA	First	M	23	17	6	o	P	New Engl J Med [279]	2015	59.558	M	Renal cell carcinoma
	E-2015-5 [280]	C. Vrieling	F	Switzerland	First	M	11	8	3	o	P	JAMA Oncol [281]	2017	20.871	F	Breast cancer
	E-2015-6 [282]	J. Yao	M	USA	First	F	22	18	4	o	P	Lancet [283]	2016	47.831	M	Neuroendocrine tumors
	E-2015-7 [284]	P. Ruszniewski	M	France	Second last	M	14	12	2	o	P	New Engl J Med [285]	2017	79.260	M	Neuroendocrine tumors
	E-2015-8 [286]	C. Oude Ophuis	F	The Netherlands	First	M	11	8	3	o	N	Eur J Surg Onc [287]	2016	3.522	F	Melanoma
	E-2015-9 [288]	R.A. Stahel	M	Switzerland	First	M	20	15	5	o	P	Lancet Respir Med [289]	2017	21.466	M	Lung cancer
	E-2015-10 [290]	M.C. Pietanza	F	USA	First	M	15	12	3	o	P	Lancet Oncol [291]	2017	36.418	M	Lung cancer
	E-2015-11 [292]	D. Dearnaley	M	UK	First	F	20	10	10	o	N/P	Lancet Oncol [293]	2016	33.900	F	Prostate cancer
	E-2015-12 [294]	R. Sullivan	M	UK	First	M	43	37	6	o	N/A	Lancet Oncol [295]	2015	26.509	M	Multiple types of cancer
	E-2015-13 [296]	M. Carducci	M	USA	First	F	19	16	3	o	P	J Clin Oncol [297]	2016	24.008	F	Prostate cancer
	E-2015-14 [298]	J. Sparano	M	USA	First	M	20	11	9	o	P	New Engl J Med [99]	2018	70.670	M	Breast cancer
2016	E-2016-1 [299]	G.N. Hortobagyi	M	USA	First	F	20	13	7	o	P	New Engl J Med [300]	2016	72.406	M	Breast cancer
	E-2016-2 [301]	A.M. Eggermont	M	France	First	M	19	13	6	o	P	New Engl J Med [302]	2016	72.406	M	Melanoma
	E-2016-3 [303]	M. Mirza	M	Denmark	First	F	20	14	6	o	P	New Engl J Med [304]	2016	72.406	F	Ovarian cancer
	E-2016-4 [305]	K. Harrington	M	UK	First	M	11	6	5	o	P	Lancet Oncol [306]	2017	36.418	F	Head and neck cancer
	E-2016-5 [307]	C. Langer	M	USA	First	F	19	13	6	o	P	Lancet Oncol [308]	2016	33.900	M	Lung cancer
	E-2016-6 [309]	M. Reck	M	Germany	First	F	18	9	9	o	P	New Engl J Med [310]	2016	72.406	F	Lung cancer

ID	Name	Country	Sex	Author	Sex					N/P	Journal	Year	IF	Sex	Sex	Cancer type
E-2016-7 [311]	M. Socinski	USA	M	First	M	20	14	6	0	N	New Engl J Med[312]	2017	79.260	M	M	Lung cancer
E-2016-8 [313]	F. Barlesi	France	M	First	M	20	18	2	0	P	Lancet[314]	2017	53.254	M	M	Lung cancer
E-2016-9 [315]	A. Gronchi	Italy	M	First	M	19	15	4	0	P	Lancet Oncol[316]	2017	36.418	M	M	Soft-tissue sarcoma
E-2016-10 [315]	K. Fizazi	France	M	First	M	13	9	4	0	N	Lancet Oncol[317]	2017	36.418	M	M	Prostate cancer
E-2016-11 [318]	T.K. Choueiri	USA	M	First	M	12	10	2	0	P	J Clin Oncol[319]	2017	26.303	M	M	Renal cell carcinoma
E-2016-12 [320]	A. Ravaud	France	M	First	M	20	16	3	1	P	New Engl J Med[321]	2016	72.406	M	M	Renal cell carcinoma
2017 E-2017-1 [322]	L. Paz-Ares	Spain	M	First	M	20	17	3	0	P	New Engl J Med[323]	2017	79.260	M	M	Lung cancer
E-2017-2 [324]	V. Westeel	France	F	First	M	20	17	3	0	N	not (yet) published						Lung cancer
E-2017-3 [325]	S. Ramalingam	USA	M	First	M	18	12	6	0	P	New Engl J Med[326]	2018	70.670	M	M	Lung cancer
E-2017-4 [327]	A. Di Leo	Italy	M	First	M	17	10	7	0	P	J Clin Oncol[328]	2017	26.303	M	M	Breast cancer
E-2017-5 [329]	S. Gupta	India	M	First	M	20	8	12	0	N	J Clin Oncol[330]	2018	26.303	M	M	Cervical cancer
E-2017-6 [331]	D. Petrylak	USA	M	First	M	20	14	6	0	P	Lancet[333]	2017	53.254	M	F	Renal cell carcinoma
E-2017-7 [333]	B. Escudier	France	M	First	M	20	15	5	0	P	New Engl J Med[334]	2018	70.670	M	M	Renal cell carcinoma
E-2017-8 [335]	K. Lewis	USA	M	First	M	14	13	0	1	N/P	Lancet Oncol[336]	2018	36.418	M	M	Melanoma
E-2017-9 [337]	A. Hauschild	Germany	M	First	M	19	12	7	0	P	New Engl J Med[338]	2017	79.260	F	M	Melanoma
E-2017-10 [339]	J. Weber	USA	M	First	M	20	12	8	0	P	New Engl J Med[334]	2017	79.260	M	M	Melanoma
2018 E-2018-1 [340]	P. Schmid	UK	M	First	F	18	7	11	0	P	New Engl J Med[341]	2018	70.670	M	F	Breast cancer
E-2018-2 [342]	M. Cristofanilli	USA	M	First	M	19	9	10	0	P	New Engl J Med[343]	2018	70.670	M	M	Breast cancer
E-2018-3 [344]	F. André	France	M	First	M	20	11	8	1	P	New Engl J Med[345a]	2019	70.670	M	M	Breast cancer
E-2018-4 [346]	Z. Jiang	China	M	First	M	19	11	4	4	P	Lancet Oncol[347]	2019	35.386	M	M	Breast cancer
E-2018-5 [348]	A. Hoyle	UK	M	First	M	20	18	2	0	P	not (yet) published						Prostate cancer
E-2018-6 [349]	C. Parker	UK	M	First	M	19	15	4	0	N	Lancet[350]	2018	59.102	M	M	Prostate cancer
E-2018-7 [351]	R. Motzer	USA	M	First	M	20	16	3	1	P	New Engl J Med[352]	2019	70.670	M	M	Renal cell carcinoma
E-2018-8 [353]	K. Moore	USA	F	First	M	19	10	9	0	P	New Engl J Med[354]	2018	70.670	F	M	Ovarian cancer
E-2018-9 [355]	B. Burtness	USA	F	First	M	20	12	7	1	P	not (yet) published						Head and neck cancer
E-2018-10 [356]	H. Mehanna	UK	M	First	F	20	14	6	0	N	Lancet[357]	2019	59.102	M	F	Oropharyngeal cancer
E-2018-11 [358]	C. Zhou	China	M	First	M	18	8	4	6	P	Lancet Respir Med[359]	2019	22.992	M	M	Lung cancer
Total N=132		F: N=27			F: N=26	1856	1340	500	16		N=125			F: N=23	F: N=27	

[1] Abstracts presented at presidential symposia of ESMO Congresses (2006, 2008, 2010, 2012, 2014, 2006–2018), and ESMO/ECCO conferences (2009, 2013, 2015). Presenters were last abstract authors in E-2011-12, E-2012-7, E-2013-11, and E-2013-14, and therefore, presenter's and last abstract author's sex are similar. For papers published in 2019, journal impact factors of 2018 were used. Abbreviations: ECCO, European Cancer Organization; ESMO, European Society for Medical Oncology; F, female; IF, impact factor; M, male; N, negative; N/A, not applicable; no., number; N/P, outcome did not reach significance or endpoint, but did show improvement/benefit or reached some of the outcomes; P, positive. References of ESMO abstract can be found online.

Abstract authors

Figure 1 shows the overall proportion of female presenters and abstract authors. Of all authors of the presented abstracts (n = 2,425), 679 (28%) were female, 1,728 (71%) were male and sex was unknown in 19 (1%) authors. The distribution of sex of abstract authors differed statistically significantly over the years (p = 0.046), and a positive trend was observed in contribution of female authors over time (p = 0.007). The number of female authors was higher in abstracts with a female presenter (34%) compared to abstracts with a male presenter (26%; p = 0.001).

Overall, contribution of women to last abstract authorship was 20% (n = 33). Last abstracts' authors were female in 9/35 (26%) of the studies presented by a woman and in 23/131 (18%) of studies presented by a male researcher (p = 0.277).

Sex of the last abstract author was not associated with study outcomes (p = 0.433).

Subsequently published papers

 The majority of the 166 presented abstracts were subsequently published in an international journal (n = 156, 94%). In 56 (36%) of these 156 papers, either the first or last author was a woman. Female researchers were involved as first author in 29 (19%) and last author in 32 (21%) articles.

A total of 30/35 (86%) abstracts presented by a woman were published as article, which was statistically significantly less than the 126/131 (96%) abstracts with a male presenter that resulted in a paper (p = 0.021). In 4/30 (13%) articles, the female presenter of the abstract was not involved as first, second or last author, and the first authors of these papers were all males (A-2017-1, E-2011-4, E-2013-8 and E-2015-10; Tables 1 and 2). In 3/126 (2%) published papers with a male abstract presenter, the presenter was not first, second or last author of the article, and all the first authors were other males (E-2010-2, E-2011-1, E-2017-1; Table 2).

Median IF of journals of papers with a female first author was 20.3 (interquartile range [IQR], 8.4, 53.4), which was lower than of papers with a male first author (median IF 35.4 [IQR, 20.5, 59.1]; p = 0.046). Sex of the presenter, last abstract author, or last author of the manuscript were not associated with IF of journals of subsequently published papers (p = 0.101, p = 0.864 and p = 0.922, respectively).

ASCO vs. ESMO

Figure 2 shows the sex distribution of abstract presenters in both ASCO and ESMO conferences. The distribution of sex of presenters did not differ between ASCO and ESMO (p = 0.756), but the proportion of female authors in ASCO abstracts (32%) was significantly higher compared to those of ESMO (27%; p = 0.048).

When analyzing the meetings separately, we found a statistically significant positive trend in female contribution observed in ESMO abstract authors (p = 0.014), which was not found in ASCO abstract authors (p = 0.544). This trend over time in female contribution was not identified in ASCO and ESMO presenters (p = 0.350 and p = 0.656).

Figure 2. Distribution of sex in both American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) abstract presenters and authors.

SEX DISTRIBUTION OF ESMO PRESENTERS
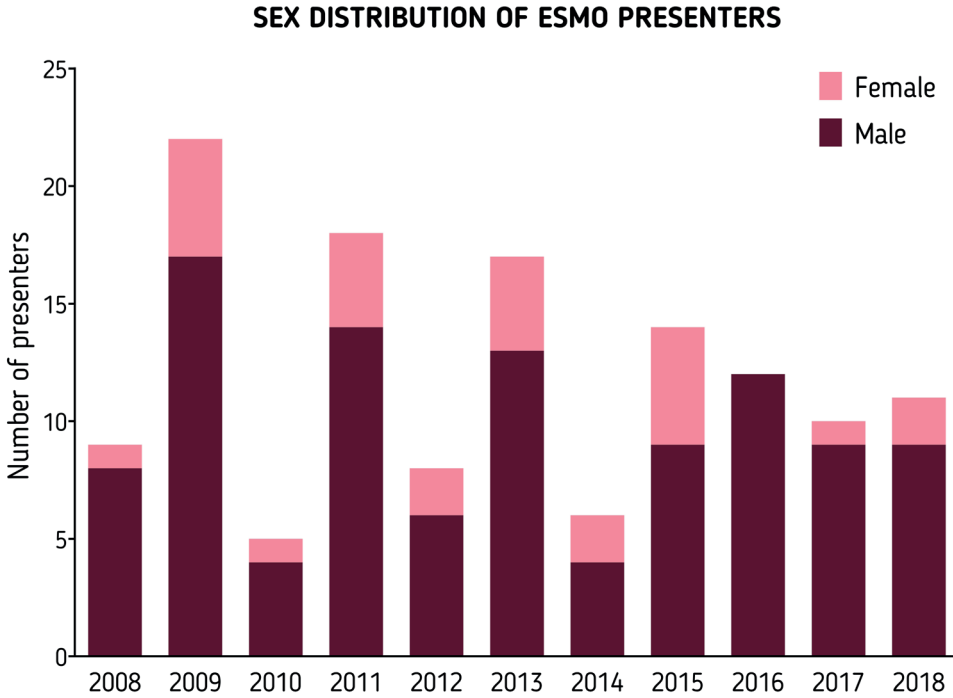
DISCUSSION

Although gender differences have been acknowledged in medical research,[1,2,5,6,8,9] this is the first study to describe the gender gap in contribution to research presentations at the two largest oncological conferences in the world. Of all oncological studies presented at the main sessions of the past 8 ASCO Annual Meetings and 12 ESMO Congresses, the number of female presenters did not reach a quarter. In subsequently published papers, the share of female first and last authors was even smaller. The gender gap appears to be more prominent in oncological research than in clinical practice, because nearly half of the hematology–oncology fellowship trainees in the United States,[19,20] more than half of medical oncologists in several European countries21 and 37% of ASCO and 41% of ESMO members are female.[22] Moreover, we found an association between sex of first author of subsequently published manuscripts and the journal's IF. Although IFs of these journals were all relatively high, which is not surprising given that these studies were presented at the most important sessions of the conferences, this corresponds with findings about the underrepresentation of female authors in high-impact journals.[23,24]

The lack of women presenting at oncological conferences is in line with the trend of gender differences in other research areas, where males numerically outweigh females, despite an increase in women entering scientific careers.[1,2,9,25,26] The number of publications by male researchers remains significantly higher than those by females, as is also seen in authorships of oncological publications.[10,12] In our study, we found an overall female contribution to abstract authorships of 27–31%, with an increase of female contribution as abstract authors over time.

However, this rise was not observed among female presenters at both conferences. Although it was not a statistically significant trend, the proportion of female presenters since 2015 appears to be shrinking rather than increasing and is therefore worrisome (Fig. 1). Over the span of their academic career, publication productivity of women increases at a later stage of their career compared to men.[4,27] While the publication productivity of female researchers exceeded those of male researchers toward the end of their careers, that is, after 27 years of service, most leadership appointments occurred before the 20th year of service.[4] Because productivity is an important factor in the selection of leaders, this could be one of the causes for the underrepresentation of women in leading positions. As not only the content of the abstract, but also past productivity and leadership positions may influence the selection of presenters for the most important sessions of ASCO and ESMO conferences, this could partly explain the underrepresentation of female presenters in these sessions as well.

Interpretation of data on gender disparities, including our data, may be hindered by a Simpson's paradox, as described earlier.[28,29] This paradox implies that an apparent association can actually be a result of a third dependent factor. For example, a finding that female researchers received requested grants less often than men was biased because women applied more often for grants in more competitive research fields.[28] More specifically, our findings could be the result of self-selection, in case that less women chose to submit an abstract to ASCO and ESMO or indicated they wanted to give a poster presentation rather than an oral presentation. In other scientific fields, gender differences in presentations at a congress have been identified as a result of self-selection.[14,17,30] For example, in biology women were asked less often as an invited speaker, even when adjusted for career stage, but also declined invitations more often than men.[17] Similarly, at an anthropology conference, women appeared to ask for oral presentations less frequently than men, resulting in significantly more poster and less oral presentations than male reseachers.[30] At an conference on evolutionary biology, women presented for relatively shorter duration compared to men despite a fifty-fifty attendance, mainly because men requested longer presentations more often.[14] Unfortunately, we did not have information about the number of submitted abstracts to ASCO and ESMO or whether the persons who submitted the abstracts requested a presentation or a poster. However, the findings in other fields highlight the possibility of self-selection as a cause for the gender differences that we found and emphasize the need for women to increase their assertiveness in order to narrow the gender gap.

Gender, in contrast to sex, is a social construct of characteristics as norms and roles of and between women and men, instead of a "biological given" that is beyond our control.[31,32] To open up avenues for change, possible consequences of gender and its behavior-based cause must be underlined.[33] This starts with recognizing the gender gap[34] and efforts to change perceptions of inequality associated with gender, for example, on competence[32,35]

and meritocracy.[24,27,35] Possible solutions beside acknowledgement of these biases that could bridge the gap in (oncological) research and level the playing field for both sexes may include encouragement of self-promotion in female researchers, and implementation of guidelines that concern gender equality.[33] For example, this could start with involving more women in the organizing committees of conferences, because this has been positively associated with female representation at conferences.[13,30] Second, the abstract assessment process could be changed by appraising the abstracts without information on the presenter's or authors' sexes or names. Moreover, female presenters could inspire and encourage female young researchers to follow their example. Finally, because all the female presenters came from the USA or Europe in our study, there should be greater awareness of the gender gap among researchers originating from other parts of the world.

Not only do gender gaps potentially disadvantage women, they could also impair patients outcomes and science.[1] In oncological research, for example, several sex-based differences in the treatment and outcomes of cancer patients have been explored and revealed important issues in, for example, drug responses and toxicity.[36–38] The presence of a female author in a study has been positively associated with the likelihood of the exploration and analysis of these sex-based differences.[39,40] Diversity in sex of researchers could therefore also contribute to a more diverse perception of science, possibly contributing to favorable outcomes for patients in the end, especially in the light of recent findings in sex-based differences in oncology.[36]

Our study has some limitations. We only included abstracts presented at the most important sessions of two main oncological conferences in the world, therefore we do not know the gender balance in abstracts presented in other sessions or at other conferences. Moreover, a considerable part of the abstracts presented in 2018 were not yet published, which could have resulted in a bias. Lastly, we did not have data on the sex distribution of attendees at the conferences, or the proportion of females that participate in oncological research worldwide to compare this to the share of female presenters and abstract authors.

In conclusion, the share of female presenters at the main sessions of ASCO Annual Meetings and ESMO Congresses is only 21%, and 28% in authorships of these presented abstracts. Greater visibility of women at these large oncological conferences should be encouraged to allow acknowledgement for their research and opportunities for their academic career, as well as positively drive heterogeneity in research through diversity in sex of researches.

Conflict of interest
Antonio Calles reports honorary/consulting fees from AstraZeneca, Boehringer-Ingelheim,

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Wan-Ling Tan	Department of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

LIST OF PUBLICATIONS INCLUDED IN THIS THESIS

Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, Van Voorthuizen T, Creemers GJ, Van Oijen MGH, Van Laarhoven HWM. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: a real-world evidence study. *Intl J Cancer,* 2019;146(7):1889-1901. DOI: 10.1002/ijc.32580.

Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, Van Voorthuizen T, Creemers GJ, Van Oijen MGH, Van Laarhoven HWM. Increased assessment of HER2 in metastatic gastroesophageal cancer patients: a nationwide population-based cohort study. *Gastric Cancer,* 2020 23(4):579-590. DOI: 10.1007/s10120-020-01039-7.

Dijksterhuis WPM, Verhoeven RHA, Pape M, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, Van Voorthuizen T, Creemers GJ, Lemmens VEPP, Van Oijen MGH, Van Laarhoven HWM. Hospital volume and beyond first-line palliative systemic treatment in metastatic esophagogastric adenocarcinoma: a population-based study. *Eur J Cancer,* 2020;139:108-117. DOI: 10.1016/j.ejca.2020.08.010.

Dijksterhuis WPM*, Kroese TE*, Verhoeven RHA, Van Rossum PSN, Mook S, Haj Mohammad N, Hulshof MCCM, Gisbertz SS, Ruurda JP, Van Oijen MGH, Van Hillegersberg R*, Van Laarhoven HWM*. Management and outcomes of gastric cancer patients with interval distant metastases in clinical practice. *Submitted. *Share first/senior authorship.*

Kroese TE*, Dijksterhuis WPM*, Van Rossum PSN, Verhoeven RHA, Mook S, Haj Mohammad N, Hulshof MCCM, Van Berge Henegouwen MI, Van Oijen MGH, Ruurda JP, Van Laarhoven HWM*, Van Hillegersberg R*. Management and prognosis of interval distant metastases in esophageal or junction cancer patients. *Ann Thorac Surg,* 2021. *Share first/senior authorship.*

Dijksterhuis WPM, Pruijt MJ, van der Woude SO, Klaassen R, Kurk SA, van Oijen, MGH, Van Laarhoven HWM. Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. *J Cachexia Sarcopenia Muscle,* 2019;10:199-206. DOI: 10.1002/jcsm.12371.

Dijksterhuis WPM, Latenstein AEJ, Van Kleef JJ, Verhoeven RHA, De Vries JHM, Slingerland M, Steenhagen E, Heisterkamp J, Timmermans LM, De van der Schueren MAE, Van Oijen MGH, Beijer S*, Van Laarhoven HWM*. Cachexia and dietetic interventions in esophagogastric cancer patients: a population-based study. *JNCCN, 2020.* DOI: 10.6004/jnccn.2020.7615. *Share senior authorship.*

Van Kleef JJ, Dijksterhuis WPM, Van den Boorn HG, Prins M, Verhoeven RHA, Van Oijen MGH, Sprangers MAG, Van Laarhoven HWM. Prognostic value of patient-reported quality of life for survival in esophagogastric cancer: a population-based study. *Submitted.*

Dijksterhuis WPM, Kalff MC, Wagner AD, Verhoeven RHA, Lemmens VEPP, Van Oijen MGH, Gisbertz SS, Van Berge Henegouwen MI, Van Laarhoven HWM. Gender Differences in Treatment Allocation and Survival of Advanced Gastroesophageal Cancer: a Population-Based Study. *J Natl Cancer Inst,* 2021.

Dijksterhuis WPM, Stroes CI, Tan WL, Ithimakin S, Calles A, Van Oijen MGH, Verhoeven RHA, Barriuso J, Oosting SF, Kolarivic Ivankovic D, Furness AJS, Bozovic-Spasojevic I, Gomez-Roca C, Van Laarhoven HWM. From presentation to paper: gender disparities in oncological research. *Int J Cancer,* 2020 Jun 1;146(11):3011-3021. DOI: 10.1002/ijc.32660.

LIST OF PUBLICATIONS NOT INCLUDED IN THESIS

Van den Boorn HG*, Dijksterhuis WPM*, Van der Geest LGM, De Vos-Geelen J, Besselink MG, Wilmink JW, Van Oijen MGH, Van Laarhoven HWM. SOURCE-PANC: a prediction model for patients with metastatic pancreatic ductal adenocarcinoma based on nationwide population-based data. *JNCCN,* 2021. *Share first authorship.*

Beukinga RJ, Wang D, Karrenbeld A, Dijksterhuis WPM, Faber H, Burgerhof JGM, Mul VEM, Slart RHJA, Coppes RP, Plukker JTM. Addition of HER2 and CD44 to 18F-FDG PET-based clinico-radiomic models enhances prediction of neoadjuvant chemoradiotherapy response in esophageal cancer. *Eur Radiol,* 2020. DOI: 10.1007/s00330-020-07439-8.

Latenstein AEJ*, Dijksterhuis WPM*, Mackay TM, Beijer S, Van Eijck CHJ, De Hingh IHJT, Molenaar IQ, Van Oijen MGH, Van Santvoort HC, De van der Schueren MAE, De Vos-Geelen J, De Vries JHM, Wilmink JW, Besselink MG, Van Laarhoven HWM. Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: a multicenter cohort study. *Cancer Medicine,* 2020;9(24):9385-9395. DOI: 10.1002/cam4.3556. *Share first authorship.*

Van de Water LF, Van Kleef JJ, Dijksterhuis WPM, Henselmans I, Van den Boorn HG, Vaarzon Morel NM, Schut KF, Daams JG, Smets EMA, Van Laarhoven HWM. Communicating treatment risks and benefits to cancer patients: a systematic review of communication methods. *Quality of Life Research,* 2020;29(7):1747-1766. DOI: 10.1007/s11136-020-02503-8.

Dijksterhuis WPM, Hulshoff JB, Van Dullemen HM, Kats-Ugurlu G, Burgerhof JGM, Korteweg T, Mul VEM, Hospers GAP, Plukker JTM. Reliability of clinical nodal status regarding response to neoadjuvant chemoradiotherapy compared with surgery alone and prognosis in esophageal cancer patients. *Acta Oncol,* 2019;58:1640-1647. DOI: 10.1080/0284186X.2019.1648865.

Mokadem I, Dijksterhuis WPM, Van Putten M, Heuthorst L, De Vos-Geelen J, Haj Mohammad N, Nieuwenhuijzen GAP, Van Laarhoven HWM, Verhoeven RHA. Recurrence after preoperative chemotherapy and surgery for gastric adenocarcinoma: a multicenter study. *Gastric Cancer,* 2019;22(6):1263-1273. DOI: 10.1007/s10120-019-00956-6.

Faiz Z*, Dijksterhuis WPM*, Burgerhof JGM, Muijs CT, Mul VEM, Wijnhoven BPL, Smit JK, Plukker JTM. A meta-analysis on salvage surgery as a potentially curative procedure in patients with isolated local recurrent or persistent esophageal cancer after chemoradiotherapy. *Eur J Surg Oncol*, 2019:45(6):931-940. DOI: 10.1016/j.ejso.2018.11.002. *Share first authorship.*

Pijnappel EN, Dijksterhuis WPM, Van der Geest LGM, De Vos-Geelen J, De Groot JWB, Ten Tije AJ, Homs MYV, Creemers GJ, Haj Mohammad N, Besselink MG, Van Laarhoven HWM, Wilmink JW. First and second-line palliative systemic treatment outcomes in a real-world metastatic pancreatic cancer cohort. *JNCCN,* 2021.

Van Velzen M, Pape M, Dijksterhuis WPM, Haj Mohammad N, Verhoeven RHA, Van Laarhoven HWM. Efficacy of first first-line treatment as a predictive factor for outcome of second-line treatment in gastroesophageal cancer. *Submitted.*

Hamers PAH, Vink GR, Elferink MAG, Stellato RK, Dijksterhuis WPM, Punt CJA, Koopman M, May AM, on behalf of the Qualitas study group. Quality of life and survival of metastatic colorectal cancer patients treated with trifluridine-tipiracil (QUALITAS). *Submitted.*

Mackay TM, Dijksterhuis WPM, Latenstein AEJ, Van der Geest LG, Sprangers MAG, Van Eijck CHJ, Homs MYV, Luelmo SAC, Molenaar IQ, Van Santvoort H, Schreinemakers JMJ, Wilmink JW, Bessl. ink MG, Van Laarhoven HWM*, Van Oijen MGH*, on behalf of the Dutch Pancreatic Cancer Group. Quality of life in patients with pancreatic or periampullary cancer with and without cancer treatment: a propensity score matched analysis. *Submitted. *Share last authorship.*

Kalff MC, Dijksterhuis WPM, Wagner AD, Verhoeven RHA, Lemmens VEPP, Van Laarhoven HWM, Gisbertz SS, Van Berge Henegouwen MI. Gender differences in treatment allocation and survival rated of curable gastro-esophageal cancer, results of a population-based study. *Submitted.*

Pijnappel EN, Dijksterhuis WPM, Sprangers MAG, Van de Poll-Franse LV, De Vos-Geelen J, Van Santvoort HV, De Hingh IHJT, Molenaar IQ, Busch OR, Besselink MG, Wilmink JW, Van Laarhoven HWM. The fear of cancer progression and recurrence in patients with pancreatic cancer. *Submitted.*

PhD PORTFOLIO

Name PhD student: W.P.M. Dijksterhuis (Willemieke)
PhD period: 2017-2021
Promotor: Prof. dr. H.W.M. van Laarhoven
Copromotors: Dr. M.G.H. van Oijen & dr. R.H.A. Verhoeven

Courses	Year	Workload, hours (ECTS)
Practical biostatistics – AMC	2017	40 (1.4)
Clinical Epidemiology: Observational Epidemiology – AMC	2018	16 (0.6)
Clinical Epidemiology: Evaluation of Medical Tests – AMC	2018	26 (0.9)
Clinical Epidemiology: Systematic Reviews – AMC	2019	20 (0.7)
Clinical Epidemiology: Randomized Clinical Trials – AMC	2019	16 (0.6)
Didactic skills – AMC	2018	10 (0.4)
Medical Literature: Citation Analysis and Impact Factors – AMC	2018	2.5 (0.1)
Oral presentation in English – AMC	2019	10 (0.4)
Epidemiology and Evidence Based Practice: concepts – UvA	2019	280 (10)
Epidemiology and Evidence Based Practice: design – UvA	2020	336 (12)
Genetic Epidemiology – AMC	2020	30 (1.1)
eBROK® course – NFU	2020	42 (1.5)
Clinimetrics – UvA	2021	252 (9)
Health Economics – UvA	2021	168 (6)

Presentations		
Poster presentation ASCO Annual Meeting	2018	32 (1.1)
Poster presentation European Gastric Cancer Congress	2018	16 (0.6)
Poster presentation ASCO Annual Meeting	2019	32 (1.1)
Two poster presentations ESMO Congress	2019	32 (1.1)
Two poster presentations ESMO Virtual Congress	2020	32 (1.1)
Oral presentation DUCG study evening	2020	8 (0.3)
Oral presentation expert meeting on metastatic gastric cancer	2021	8 (0.3)

International conferences		
ASCO Annual Meeting, Chicago, USA	2018	32 (1.1)
European Gastric Cancer Congress, Leiden, the Netherlands	2018	16 (0.6)
ESMO Congress, München, Germany	2018	32 (1.1)
ESMO workshop: Gender medicine meets oncology, Lausanne, Switzerland	2018	16 (0.6)
ASCO Annual Meeting, Chicago, USA	2019	32 (1.1)
ESMO Congress, Barcelona, Spain	2019	32 (1.1)
ESMO Virtual Congress	2020	32 (1.1)

National conferences		
DUCG	2017	8 (0.3)
NCR	2017	8 (0.3)
5Ds Congress	2018	16 (0.6)
NCR	2018	8 (0.3)
DUCG	2019	8 (0.3)
NVMO Targeted Therapy	2019	8 (0.3)
NCR	2019	8 (0.3)
5Ds Congress	2020	16 (0.6)

Teaching		
Bachelor's thesis – B. Kiestra	2018	16 (0.6)
Lectures for registrars of IKNL	2018-2020	8 (0.3)

Grants	
ESMO Young Oncologist Travel Grant	2018

Committees	
ESMO Project group Line of Therapy (LoT)	2021

Other contributions

- Nog te veel variatie in eerste- en tweedelijnsbehandeling bij maag- en slokdarmcarcinoom. *Oncologie up-to-date*, december 2020. Available from: https://www.oncologie.nu/nieuws/nog-te-veel-variatie-eerste-en-tweedelijnsbehandeling-bij-maag-en-slokdarmcarcinoom/
- Meten van HER2 belangrijk bij slokdarm- en maagcarcinomen. *Oncologie up-to-date*, mei2020. Available from: https://www.oncologie.nu/nieuws/meten-van-her2-expressie-belangrijk-bij-slokdarm-en-maagcarcinomen/.
- Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, Van Voorthuizen T, Creemers GJ, Van Oijen MGH, Van Laarhoven HWM. Praktijkvariatie in de eerstelijns- systemische behandeling bij het gemetastaseerd oesofagus- en maagcarcinoom. *Ned Tijdschr Oncol* 2020;17:58−65.
- ASCO Presentations Illustrate Sexism and Bias Among Women in Oncology. *ASCO Daily News*, 19 July 2019. Available from: https://dailynews.ascopubs.org/do/10.1200/ADN.19.190372/full/.
- Sekseverschillen in kanker: nog veel onbekend. *Oncologie up-to-date*, maart 2019. Available from: https://www.oncologie.nu/nieuws/sekseverschillen-bij-kanker-nog-veel-onbekend/

CURRICULUM VITAE

Willemieke Dijksterhuis was born on January 16th, 1993 in Kampen. After she graduated cum laude from Gymnasium Celeanum in Zwolle, she studied Medicine at the University of Groningen between 2010 and 2017. In the final year of the study, she performed her master thesis at the department of surgical oncology at the University Medical Center Groningen, where she came in touch with cancer research for the first time and where her interest in esophagogastric cancer was aroused. Subsequently, she moved to Amsterdam to do her final internships at the departments of medical oncology and radiation oncology at the Academic Medical Center. In July 2017, she started her PhD project in medical oncology under supervision of Hanneke van Laarhoven. During this project, she was affiliated at the Amsterdam UMC and Netherlands Comprehensive Cancer Organisation (IKNL). The research was focused on the palliative treatment of esophagogastric cancer in daily clinical practice. During her PhD, she obtained a master´s degree in epidemiology. Currently, she is working as an internal medicine resident at Tergooi in Hilversum.