# Thesis

# Treatment patterns in metastatic and locally advanced gastroesophageal cancer: a real-world single-center cohort study

submitted by

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Graz, May 4, 2023

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*Graz, May 4, 2023* *Martin Halbherr m.p.*

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# Zusammenfassung


## Einleitung

Obwohl kürzlich in einer Untergruppe von PatientInnen mit fortgeschrittenen gastroösophagealen Adenokarzinomen bei der Verwendung von Immuncheckpoint-Inhibitoren ein verbessertes Behandlungsergebnis nachgewiesen werden konnte, sind die Therapiemöglichkeiten in dieser Situation nach wie vor limitiert und die Prognose bleibt bescheiden. Wir wollten untersuchen, wie sich die Behandlungsschemata von gastroösophagealen Adenokarzinomen in der palliativen Erst-, Zweit- und Drittlinientherapie in den letzten 15 Jahren, vor Einführung der Immuntherapie, verändert haben und ob sich diese Veränderungen in einem besseren Behandlungsergebnis niederschlagen.

## Material und Methoden

In diese monozentrisch, retrospektiv durchgeführte Kohortenstudie schlossen wir 382 PatientInnen mit lokal fortgeschrittenen inoperablen oder metastasierten Speiseröhrenkarzinom, Magenkarzinom sowie Karzinomen des gastroösophagealen Überganges ein, welche zwischen 2006 und 2020 eine palliative systemische Therapie an der Abteilung für Onkologie der Medizinischen Universität Graz erhalten haben. Anhand eines Stichtages, gewählt nach Behandlungszeitraum am 1. Jänner 2013, wurden die PatientInnen zwei annähernd gleich großen Gruppen zugewiesen: Kohorte A (2006-2012) und Kohorte B (2013-2020). Der primäre Endpunkt der Studie war das Gesamtüberleben ab Start der palliativen Erstlinientherapie (OS1). Weitere sekundäre Endpunkte waren das progressionsfreie Überleben in der palliativen Erstlinientherapie (PFS1) und das Gesamtüberleben sowie progressionsfreie Überleben in der palliativen Zweit- und Drittlinientherapie (OS2, OS3, PFS2, PFS3).

## Ergebnisse

Signifikante Unterschiede hinsichtlich Behandlungsschemata und -intensität wurden zwischen der Kohorte A (n=175; 45,8%) und Kohorte B (n=207; 54.2%). festgestellt. Insgesamt wurden PatientInnen in der Kohorte B intensiver

therapiert, was sich sowohl im höheren Anteil jener PatientInnen zeigte, die in der palliativen Erstlinientherapie eine 3-fach Kombinationstherapie erhalten hat (Kohorte A 12,0% vs. Kohorte B 23,7%, p=0.001), als auch im größeren Anteil an PatientInnen, welche in weiterer Folge eine Zweit- (Kohorte A 43,4% vs. Kohorte B 53,6%, p=0.005) und Drittlinientherapie (Kohorte A 13,1% vs. Kohorte B 25,1%, p=0.738) erhalten hat. Bezüglich unseres primären Endpunktes konnte für die Kohorte B nur eine nicht signifikante Verbesserung des OS1 ab Start der palliativen Erstlinie nachgewiesen werden. Das mediane Gesamtüberleben der palliativen Erstlinientherapie lag bei 8,0 Monaten in der Kohorte A und bei 9,7 Monaten in der Kohorte B (Log-Rank p=0.055). Nach multivariabler Bereinigung von potenziellen Störfaktoren in der Cox-Regressionsanalyse schwächte sich der Einfluss des Behandlungszeitraumes weiter ab (Hazard ratio (HR): 0,9; 95% CI: 0,7-1,3; p=0,706). Die einzigen unabhängigen Prädiktoren für ein ungünstigeres Gesamtüberleben in der palliativen Erstlinientherapie waren ein höherer ECOG-Status (HR für ECOG 1 vs. ECOG 0: 1,9; 95% CI: 1,4-2,5), ein jüngeres Alter (HR pro Erhöhung um 10 Jahre: HR 0,8; 95% CI: 0,7-1,0) und ein höherer CRP-Ausgangswert (HR pro CRP-Verdopplung: HR 0,6; 95% CI: 0,3-1,0). Hinsichtlich der Analyse der sekundären Endpunkte konnten in der palliativen Zweit- (4,7 vs. 7,0 Monate, p=0.006) und Drittlinientherapie (3,2 vs. 5,0 Monate; p=0.031) in der Kohorte B ein signifikant besseres Gesamtüberleben nachgewiesen werden, wohingegen das progressionsfreie Überleben zwischen den Kohorten über alle Therapielinien sehr ähnlich war.

**Conclusio**

Obwohl sich die Behandlungsmuster der palliativen systemischen Therapie des fortgeschrittenen gastroösophagealen Adenokarzinoms in den letzten 15 Jahren geändert haben, zeigt unsere Studie, dass diese Änderungen in der Behandlung zu keiner signifikanten Verbesserung des Gesamtüberlebens geführt haben.

# Abstract

## Introduction

Although immune checkpoint inhibition has been recently shown to improve the outcome in a subset of patients with advanced gastroesophageal adenocarcinoma, treatment options in this setting are still limited and the prognosis remains modest. We aimed to evaluate how treatment patterns in the palliative first-, second- and third-line treatment of gastroesophageal adenocarcinoma have changed over the last 15 years before the introduction of immunotherapy and whether these treatment changes translated into an improved outcome.

## Material and methods

In this single-center retrospective cohort study we included 382 patients with locally advanced unresectable or metastatic esophageal, gastric or gastroesophageal junction cancer, who underwent palliative systemic treatment at the Department of Oncology at the Medical University of Graz between 2006 and 2020. Based on a cut-off date set on January 1, 2013, patients were assigned to two nearly equally sized treatment era groups: Cohort A (2006-2012) and Cohort B (2013-2020). Primary endpoint of this study was the overall survival from start of palliative first-line (OS1) therapy. Co-secondary endpoints were the progression-free survival of palliative first-line (PFS1) and the OS and PFS in palliative second- and third-line (OS2, OS3, PFS2, PFS3).

## Results

Significant differences in terms of treatment patterns and intensity were observed between Cohort A (n=175, 45.8%) and Cohort B (n=207, 54.2%). Overall, patients in Cohort B were treated more intensely, which is underlined by a higher proportion of patients undergoing triplet therapies in the first-line setting (Cohort A 12.0% vs. Cohort B 23.7%, p=0.001), as well a higher proportion of patients who received subsequent second- (Cohort A 43.4% vs. Cohort B 53.6%, p=0.005), and third-line treatment (Cohort A 13.1% vs. Cohort B 25.1%, p=0.738). In terms of our primary endpoint analysis, only a non-significant improvement of OS1 from start of palliative first-line could be observed for Cohort B. The median OS1 was 8.0 months in Cohort A vs. 9.7 months in Cohort B. (logrank p=0.055).

After multivariable adjusting for potential confounders in Cox regression analysis, the impact of treatment era on OS1 further weakened (Hazard ratio (HR): 0.9, 95% CI: 0.7-1.3, p=0.706). The only independent predictors of adverse OS1 were higher ECOG performance status (HR for ECOG 1 vs ECOG 0: 1.9, 95% CI: 1.4-2.5), lower age (HR per 10-year increase: HR 0.8, 95% CI: 0.7-1.0) and increased baseline CRP (HR per doubling of CRP: HR 0.6, 95% CI: 0.3-1.0). In terms of the secondary endpoint analysis, significantly superior OS2 (4.7 vs. 7.0 months, p=0.006) and OS3 (3.2 vs 5.0 months; p=0.031) were shown for Cohort B, whereas the PFS was highly similar between the study cohorts across all three therapy lines.

**Conclusion**

Although treatment patterns of palliative systematic therapy in advanced gastroesophageal adenocarcinoma have changed over the last 15 years, our study indicates that these treatment changes did not translate into a significant overall improvement of survival.

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# Abbreviations

5-fu ..... *5-fluorouracil*

AEG ..... Adenocarcinoma of the esophagogastric junction

AFP ..... *Alpha-1-fetoprotein*

AJCC ..... *American Joint Committee on Cancer*

BMI ..... *Body Mass Index*

CA 19-9 ..... *carbohydrate antigen 19-9*

CCI ..... *Charlson Comorbidity Index*

CEA ..... *Carcinoembryonal antigen*

CHD1 ..... Chromodomain-Helicase DNA-binding 1

CPT-11 ..... *Irinotecan*

CRP ..... *C-reactive protein*

CRT ..... Chemoradiotherapy

CT ..... *Computed tomography*

CTX ..... *Chemotherapy*

DCR ..... *Disease control rate*

dMMR ..... *Mismatch repair deficiency*

DNA ..... *Desoxyribonucleic acid*

EBV ..... *Epstein-Barr virus*

ECOG ..... Eastern Cooperative Oncology Group

EMA ..... European Medicines Agency

EMR ..... *Endoscopic mucosal resection*

ESMO ..... *European Society for Medical Oncology*

EUS ..... *Endoscopic ultrasound*

FDA ..... Food and Drug Administration

FIGC ..... *Familial intestinal gastric cancer*

FLOT ..... 5-fluorouracil, folinic acid, oxaliplatin, docetaxel

FOLFIRI ..... Folinic acid, 5-fluorouracil, irinotecan

FOLFOX ..... Folinic acid, 5-fluorouracil, oxaliplatin

GAPPS ..... *Gastric adenocarcinoma and proximal polyposis of the stomach*

HDGC ..... *Hereditary diffuse gastric cancer*

HER2-receptor ..... *Human epidermal growth factor receptor-2*

IHC ..... *Immunohistochemistry*

LDH ..... *Lactate dehydrogenase*

NCCN ..... *National Comprehensive Cancer Network*

ORR ..... *Objective response rate*

OS ..... *Overall survival*

PD-1 ..... *programmed cell death-1 membrane receptor*

PET ..... *Positron emission tomography*

PFS ..... *Progression-free survival*

REDCap ..... *Research Electronic Data Capture*

RNA ..... *Ribonucleic acid*

RTX ..... *Radiotherapy*

SN-38 ..... 7-Ethyl-10-hydroxycamptothecin

TNM ..... *Tumor, nodes, metastases*

UICC ..... *Union for International Cancer Control*

VEGFR-2 ..... *Vascular endothelial growth factor recetpor-2*

WHO ..... World Health Organization

XELOX ..... Capecitabine, oxaliplatin

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# Introduction

## Epidemiology

Due to rising case numbers, cancer is a significant health problem and therefore poses an increasing challenge to medicine. A growing population and an aging society are two reasons for an increase in numbers. For gastric cancer, in 2020 over a million new cases occurred worldwide what corresponds to 8% of all cancer diagnoses made in 2020. Gastric cancer marks fifth in the ranking of the most common cancer diagnoses and is responsible for nearly 800,000 deaths in 2020. This makes gastric cancer the fourth leading cause of cancer-related deaths. (2) Although gastric cancer is a global health issue, striking differences in incidences can be found in different regions of the world. Some high-incidence regions like East Asia or South America face regions like Europe, Africa, or North America where numbers are lower. The reason for this contrast can mainly be found in different demographic characteristics as well as cultural aspects like eating and drinking habits of the respective society and the associated presence of relevant risk factors like smoking or alcohol consumption. (3)

Despite a decreasing incidence the absolute number of newly diagnosed cases is expected to rise in the future. Especially in individuals aged 50 years and younger growing numbers are expected to arise. Even though men are affected twice as often as women, decreasing incidences will be more present in the male population. (2, 4)

In Austria, equivalent to those of other low-incidence country decreasing incidences have been observed over the past years. Compared to 1.800 new cases in 1998 only 1.121 diagnosis were made in 2018. (5)

## Prognosis

The prognosis of gastric cancer mainly depends on an early detection of the disease, the stage of disease at the time of diagnosis as well as other factors like the primary tumor location or histological aspects.

Patients with stage I disease show a very good prognosis with a 5-year survival rate of over 90% whereas patients with stage IV diagnosed stomach tumor have a very poor prognosis with a 5-year survival rate of 5% to 20%. (6) This underlines the importance of an early detection. Japanese patients are less frequently

diagnosed with stage IV tumors leading to a better survival of Japanese patients due to established early detection programs. (7) The 2021 published paper by the American Cancer Society reports a 5-year survival rate of 70% for localized tumors, and 6% for tumors that have already spread combining to a survival rate of 32% for all stages. (8)

Wanebo et al. examined the differences in stage-dependent 5-year survival between resected Japanese and American patients and concluded the following results: (9)

| | Japanese cohort | American cohort |
|---|---|---|
| **Number of patients** | 12,535 | 10,237 |
| **Stage I** | 95.6% | 50.0% |
| **Stage II** | 70.1% | 29.0% |
| **Stage III** | 36.3% | 13.0% |
| **Stage IV** | 23.1% | 3.0% |
| **Overall survival** | **56.3%** | **19.0%** |

*Table 1: Stage related 5-year survival cohort comparison (9)*

## Etiology, pathogenesis and risk factors

Depending on the location of the primary tumor, a distinction is made between carcinomas which are located near the cardia and those which are off the cardia. The specific type of carcinoma typically comes along with the presence of various risk factors. (10) While obesity and gastroesophageal reflux disease are associated with the cardia-related type, a Helicobacter pylori infection or dietary factors seem to cause non-cardia-related gastric cancer. (11)

**Sex**

Incidence rates show that men are twice more likely to develop gastric cancer than women. (2) There seems to be a connection between dietary habits and the occurrence of gastric cancer as well as protective hormonal influences. Comparing incidences by age it is notable that incidence rates align when women enter menopause. Therefore, there appears to be a link between estrogen levels and the occurrence of gastric cancer. (12)

**Helicobacter pylori infection**

An infection with Helicobacter pylori, a bacterium which colonizes 50% of the global population is strongly linked with the potential development of gastric cancer. There is a common sense that a H. pylori infection is the most important risk factor of developing gastric cancer. (13) A large Japanese trial concluded that 3% of infected people developed a carcinoma within a follow-up period of 11 years. (14)

A Helicobacter pylori eradication should be performed in patients suffering from (15):

- Peptic ulcer disease
- MALT lymphoma
- Morbus Ménétrier
- Idiopathic Thrombocytopenic Purpura

Studies have shown a reduction in the risk of developing gastric carcinoma and could prove a positive effect of antibiotic eradication therapy. (16, 17)

**Dietary factors, smoking and alcohol**

A diet rich of salted food poses a risk of gastric cancer as it is thought to damage the mucosa and cause inflammation. This also applies to red meat and pickled food which is often consumed in the east Asian cuisine. In contrast to that, the intake of fruit and vegetables containing high levels of vitamin C has been shown to be protective due to its antioxidant effects. (18) However, this does not apply to coffee consumption. No association could be shown here. (19)

The association between smoking and an increased risk of gastric cancer has been proven in several studies. A large meta-analysis conducted by Ladeiras-

Lopes et al. pointed out that in the group of current smokers vs. non-smokers, smokers have a 1.62-fold higher risk of getting cancer. In comparison to former smokers, current smokers still have a 1.34-fold higher risk. Interestingly the negative effect of smoking is more noticeable in men than in women. (20)

Alcohol as a risk factor has been discussed in many contradictory ways. Numerous studies have investigated the association of alcohol consumption and gastric cancer risk. Tramacere et al. showed that the negative properties mainly depend on the amount of alcohol consumption. For heavy drinking a clear positive correlation was observed whereas moderate drinking does not come along with a higher risk. (21)

**Hereditary and genetic factors**

Familiar clustering occurs in 10 to 15% of all gastric cancer cases. (22, 23) Inherited syndromes are even rarer which account for approximately 1 to 3%. (23) The most common diseases are:

Hereditary diffuse gastric cancer (HDGC)

HDGC is an autosomal dominant inherited disease. Within the group of inherited syndromes HDGS is the most commonly seen condition leading to gastric cancer. It is caused by a germline mutation of the CHD1-gene coding for the protein E-Cadherin. Moreover, HDGC also raises the risk of developing other malignant diseases like breast cancer or prostate cancer. (23, 24) Considering a lifetime risk of 70% for developing gastric cancer Guilford and colleagues suggest a prophylactic gastrectomy for individuals with HDGC. (24, 25)

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

GAPPS is another autosomal-dominant inherited syndrome associated with an increased gastric cancer risk. First described in 2012 by Worthley et al. this syndrome is characterized by a polyposis of the fundic glands and dysplasia leading to a high risk of developing gastric cancer. The more probable occurrence of other malignancies except gastric cancer has not been described yet in relation to this disease. (24, 26, 27)

Familial intestinal gastric cancer (FIGC)

FIGC represents a rare hereditary form of gastric cancer, and its path of inheritance has not been well understood so far. Diagnostic criteria such as familial accumulation, intestinal subtype gastric adenocarcinoma as well as the absence of polyposis were proposed. (28, 29)

Other syndromes leading to an increased risk of disease are Li-Fraumeni syndrome, Peutz-Jeghers syndrome and familial adenomatous polyposis. (30)

**EBV infection**

Epstein-Barr Virus is closely associated with several malignancies and there is scientific consensus on the role of EBV in the development of cancer. In a large meta-analysis Murphy et al. investigated the importance of EBV as a risk factor for gastric cancer. 8.7% of all gastric cancer cases are EBV positive. Notable gender differences show a 2-fold higher EBV positivity in males than in females (11.1% vs. 5.2%). There is also a difference in tumor location and EBV positivity. Tumors localized in the cardia and corpus are two times more likely to be EBV positive than those in the antrum of the stomach. (31)

## Pathology and histology

Gastric carcinomas are very heterogeneous and there is a wide variation in their characteristics. These differences concern the architecture, molecular pathological aspects, and cell differentiation. From a histological point of view, the majority of gastric cancers are adenocarcinomas. (32)

A special subtype are signet ring cell carcinomas. The World Health Organization describes signet ring carcinomas as poorly cohesive with cells that typically produce mucin. Their nucleus is crescent shaped. (33) In recent years, the worldwide overall incidence of gastric cancer has decreased, while numbers for the subtype of signet ring carcinoma have increased. Signet ring cell carcinoma show different epidemiological, histological, and pathogenic aspects. One difference from non-signet ring cell carcinoma is that their response to chemotherapy is worse. In addition, advanced signet ring cell carcinomas have significantly worse outcome as indicated by decreased OS. (34)

**Histological subtypes**

Two major classification systems are commonly used in the diagnosis of gastric cancer. These two are the Laurèn classification and the classification provided by the World Health Organization. Latest studies underline that combining traditional classification systems with additional molecular pathological features might be favorable as there seems to exist a correlation between the occurrence of some histological subtypes and the presence of different molecular pathological properties. (35) Other classification systems that play a minor role are the Goseki or the Ming classification. (36)

World Health Organization Classification (WHO)

The WHO classification differentiates between a tubular, papillary, poorly cohesive, mucinous and mixed type to classify gastric adenocarcinoma. Tubular and papillary cancers can be further graded. On the one hand there are low grade tumors which can be well or moderately differentiated and on the other hand there are neoplasms which are classified as high-grade tumors implicating that they are poorly differentiated. The fourth WHO classification update published in 2010 was the first version claiming that signet ring cell carcinoma is part of the poorly cohesive subtype. As the WHO allows to classify gastric cancer in a very detailed way there can be found some rarer subtypes, too. (33, 37) The latest edition available since 2019 brought some minor changes to the rarer subtypes and added a molecular pathological classification for the first time. (38)

Laurèn classification

The second widely used classification is based on a paper published by Laurèn in 1965. Since then, this classification has been still one of the most important systems to histologically categorize gastric adenocarcinoma. The three subgroups of intestinal (well-differentiated), diffuse (undifferentiated) and indeterminate stomach cancer were defined. In the Laurèn classification signet ring cell carcinoma belongs to the diffuse type. (36, 39, 40)

As the Laurèn classification has been known for many years and has proven itself in clinical practice, there have been many investigations on its prognostic importance on the one hand and how disease-related characteristics correlate with different subtypes on the other hand.

The diffuse type which is more frequent in high-risk areas than the intestinal subtype comes along with poorer prognosis and is more likely to occur in females and younger patients whereas the intestinal type is associated with EBV-infections. Moreover, intestinal stomach cancer is found more frequently in high incidence areas. (39) So, it can be concluded that dependent on the tumor histology significant differences concerning epidemiological and etiological aspects can be observed. Further, different oncogenic pathways in the development of gastric cancer can be derived based on histological properties. (36, 41, 42)

In terms of the prognostic value of those classification systems studies showed conflicting results. While some studies found a correlation, others did not. (36, 43, 44)

**Localization**

The exact anatomic location of the tumor varies greatly with respect to demographic and epidemiologic variables. Tumors close to the cardia are found most frequently. (45) Crew et al. has shown that incidence rates of gastric cancer have differed over time with respect to tumor location. (9, 40) An increase was observed especially in those tumors that are located in the proximal part of the stomach and those close to the cardia. (45, 46)

In terms of prognosis, tumors located at the cardia and the gastroesophageal junctions are associated with worse outcome. (47)

A major change concerning the classification of tumors located at the esophagogastric junction can be found in the updated UICC/AJCC cancer classification. The border was redrawn. Esophagogastric junction tumors that are centered in the first two centimeters of the proximal stomach should be classified and treated according to the esophageal scheme. Exceeding this 2 cm border the gastric cancer classification should be used even if also the esophagogastric junction is involved. (48, 49)

**Staging**

The UICC and AJCC cancer classification provides a standardized globally acknowledged method to classify malignant diseases. For this purpose, the TNM system is used. Gastric cancer is classified depending on the infiltration depth of the primary tumor (T), the lymph node status (N) and the existence of distant metastases (M). TNM classification is a powerful method not only for staging of malignant tumors at diagnosis but also for planning further treatment or as a prognostic tool. The latest update published in 2017 provides even more precise possibilities in handling different malignant diseases. A clinical pre-treatment TNM is distinguished from a pathological post-treatment TNM. Based on the TNM classification five different stages can be determined: (49)

Stage 0 describes intraepithelial lesions which do not reach the lamina propria and present with neither regional lymph node metastases nor distant metastases.

Stage I classifies tumors that invade the mucosa but stay within the border to the subserosa. A maximum of 2 affected lymph nodes can be present to be categorized as stage I.

Stage II tumors exceed at least the mucosa and can reach but not penetrate the subserosa. Up to 15 regional lymph nodes may be affected.

The third stage is characterized by tumors which invade all layers of the stomach and already reaches adjacent structures. In contrast to stage IV the tumor has not disseminated to other organs yet.

**Gastric cancer**

| Classification | | Tumor |
|---|---|---|
| **T** | | **Primary tumor** |
| | **TX** | Primary tumor cannot be assessed |
| | **T0** | No evidence of primary tumor |
| | **Tis** | Carcinoma in situ |
| | **T1** | Tumor invades mucosa |
| | **T1a** | Tumor invades lamina propria or muscularis propriae |
| | **T1b** | Tumor invades submucosa |
| | **T2** | Tumor invades muscularis propria |

| | | |
|---|---|---|
| | **T3** | Tumor invades subserosa (without penetration of the visceral peritoneum) |
| | **T4** | Tumor perforates serosa (visceral peritoneum) or invades adjacent structures |
| | **T4a** | Tumor penetrates serosa |
| | **T4b** | Tumor invades adjacent structures |
| **N** | | **Regional lymph nodes** |
| | **NX** | Regional lymph nodes cannot be assessed |
| | **N0** | No regional lymph nodes |
| | **N1** | Metastases in 1-2 regional lymph nodes |
| | **N2** | Metastases in 3-6 regional lymph nodes |
| | **N3a** | Metastases in 7-15 regional lymph nodes |
| | **N3b** | Metastases in 16 or more regional lymph nodes |
| **M** | | **Distant metastases** |
| | **MX** | Distant metastases cannot be assessed |
| | **M0** | No distant metastases |
| | **M1** | Distant metastases or positive peritoneal cytology |

*Table 2: UICC-TNM classification - gastric cancer (49)*

| UICC stage | Primary tumor | Lymph nodes | Distant metastases |
|---|---|---|---|
| **0** | Tis | N0 | M0 |
| **IA** | T1 | N0 | M0 |
| **IB** | T2<br>T1 | N0<br>N1 | M0<br>M0 |
| **IIA** | T3<br>T2<br>T1 | N0<br>N1<br>N2 | M0<br>M0<br>M0 |
| **IIB** | T4a<br>T3<br>T2<br>T1 | N0<br>N1<br>N2<br>N3a | M0<br>M0<br>M0<br>M0 |
| **IIIA** | T4b | N0 | M0 |

| | | | |
|---|---|---|---|
| | T4a | N2 | M0 |
| | T4a | N1 | M0 |
| | T3 | N2 | M0 |
| | T2 | N3a | M0 |
| **IIIB** | T4b | N2 | M0 |
| | T4b | N1 | M0 |
| | T4a | N3a | M0 |
| | T3 | N3a | M0 |
| | T2 | N3b | M0 |
| | T1 | N3b | M0 |
| **IIIC** | T4b | N3b | M0 |
| | T4b | N3a | M0 |
| | T4a | N3b | M0 |
| | T3 | N3b | M0 |
| **IV** | Any T | Any N | M1 |

*Table 3: AJCC/UICC 8th edition staging system - gastric cancer (49)*

**Esophageal cancer**

| Classification | | Tumor |
|---|---|---|
| **T** | | **Primary tumor** |
| | **TX** | Primary tumor cannot be assessed |
| | **T0** | No evidence of primary tumor |
| | **Tis** | Carcinoma in situ/high grade dysplasia |
| | **T1** | Tumor invades lamina propria, muscularis mucosae or submucosa |
| | **T1a** | Tumor invades lamina propria or muscularis mucosae |
| | **T1b** | Tumor invades submucosa |
| | **T2** | Tumor invades muscularis propria |
| | **T3** | Tumor invades adventitia |
| | **T4** | Tumor invades adjacent structures |
| | **T4a** | Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum |

| | | |
|---|---|---|
| | **T4b** | Tumor invades other adjacent structures such as aorta, vertebral body, or trachea |
| **N** | | **Regional lymph nodes** |
| | **NX** | Regional lymph nodes cannot be assessed |
| | **N0** | No regional lymph node metastases |
| | **N1** | Metastases in 1 to 2 regional lymph nodes |
| | **N2** | Metastases in 3 to 6 regional lymph nodes |
| | **N3** | Metastases in 7 or more regional lymph nodes |
| **M** | | **Distant metastases** |
| | **MX** | Distant metastases cannot be assessed |
| | **M0** | No distant metastases |
| | **M1** | Distant metastases |

*Table 4: UICC-TNM classification - esophageal cancer (49)*

| UICC stage | Primary tumor | Lymph nodes | Distant metastases |
|---|---|---|---|
| **0** | Tis | N0 | M0 |
| **IA** | T1a | N0 | M0 |
| **IB** | T1b | N0 | M0 |
| **IIA** | T2 | N0 | M0 |
| **IIB** | T3<br>T1 | N0<br>N1 | M0<br>M0 |
| **IIIA** | T2<br>T1 | N1<br>N2 | M0<br>M0 |
| **IIIB** | T4a<br>T3<br>T2 | N0, N1<br>N1, N2<br>N2 | M0<br>M0<br>M0 |
| **IVA** | Any T<br>T4b<br>T4a | N3<br>Any N<br>N2 | M0<br>M0<br>M0 |
| **IV** | Any T | Any N | M1 |

*Table 5: AJCC/UICC 8th edition staging system - esophageal cancer (49)*

In countries without mass screening, patients more often present with advanced disease stages. In a large cohort study of gastric cancer patients in the United States of America Wanebo et al. could show that two thirds of the patients get diagnosed with a stage III or IV disease. (9) In contrast to that, Japanese studies show the effect of well-established cross-population screening. Nearly 60% of gastric cancer patients have a stage I or II disease at diagnosis. (50)

Even 50% of all patients have regional lymph node metastases when receiving their diagnosis. The presence of lymph node metastases is an important prognostic marker and comes along with an expected 5-year survival rate of less than 30%. (51) The depth of infiltration of the primary tumor is associated with the presence of lymph node metastases and varies depending on the stage between 5 and 64%. (52)

**Metastases**

Thirty-nine percent of all gastric cancer patients present with distant metastases at the time of diagnosis. The number of patients who already have metastases in more than one site accumulates to 13%. (53)

The location of distant metastases differs depending on clinicopathological factors including tumor histology, age, gender, and tumor location. However, the most frequent sites in which tumor dissemination takes place are the liver (48%), the peritoneum (32%), the lungs (15%) and the bones (12%) in descending order. The occurrence of peritoneal metastases is associated with a younger age and non-cardia tumors. The same applies to lymph node metastases. In contrast to that, liver or lung metastases occur more likely in older patients. (53)

Signet ring cell carcinoma tend to spread in the peritoneum, bones and ovaries. A metastatic spread to the lungs and liver is less likely.

## Clinical management

The late onset of characteristic symptoms leading to medical examination is a big issue in the diagnosis of gastric cancer. Approximately 25% of patients are diagnosed in a disease stage in which curation can be aimed. Those early-stage diagnosis are mostly incidental findings. (54)

### Clinical presentation

Ordinary gastrointestinal symptoms such as dyspepsia often do not suggest a diagnosis of gastric cancer, as they also occur in other more common disorders of the digestive system. Symptoms such as loss of weight, dysphagia or acute or chronic gastrointestinal bleeding usually occur at a later time. (55)

The most common symptoms at diagnosis are: (9)

- Weight loss (61.6%)
- Abdominal pain (51.6%)
- Nausea (34.3%)
- Dysphagia (26.1%)

Dysphagia is more likely to be a warning symptom in tumors involving the cardia or the gastroesophageal junction. (55)

According to the German S3-guideline published by the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften endoscopic examination should be performed at presence of one or more red flag symptoms including dysphagia, recurrent vomiting, inappetence, unintentional weight loss, gastrointestinal bleeding, or iron deficiency anemia. (56)

The today's average time delay between the onset of the first symptoms and diagnosis is 3.5 months and is now shorter than 10 years ago. (57) Time delay can be shortened in countries where mass screening programs are established, and endoscopy is widely available. (58, 59)

### Diagnostic tools

Early detection of gastric cancer is crucial to follow a potential curative approach ultimately resulting in beneficial outcome and better survival. Except of countries with national mass screening programs like Japan or South Korea, gastric cancer is mostly diagnosed in advanced stages. However, mass screening is only

beneficial and efficient in countries with high incidences. Modern diagnostic tools and innovative approaches in the way of diagnosing stomach cancer have led to a significant improvement regarding the earliest possible detection of the disease. (60)

First of all, the patient should undergo a physical examination as well as lab tests, like a complete blood count test (assessment for anemia), liver and kidney function tests (evaluation of suitable treatment options) and coagulation tests. (61, 62) The gold standard for the detection of gastric cancer is endoscopy. It offers an advantageous combination of imaging techniques and the accuracy of histological processing. Obtaining tissue by upper gastrointestinal endoscopy followed by a histological workup is indispensable. (54) Nevertheless, in early stages it is difficult to detect suspicious lesions as they might appear as benign. If histology is negative and malignancy is still suspected, the biopsy should be repeated. (56) It is essential to obtain multiple biopsy specimens as this approach increases the chance of detecting malignant lesions. Graham et al. proved that using 7 specimens instead of one increased the accuracy of diagnosis from 70% to more than 98%. (63) Taking samples by brush cytology is an alternative especially in cases where complications due to bleeding can be expected. (64)

Endoscopic ultrasound plays an important role for staging purposes. EUS has a high accuracy to assess the infiltration depth of gastric cancer and to detect affected regional lymph nodes. (65) Because of the excellent possibility to evaluate the T stage National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines suggest applying EUS when there is no evidence of distant metastases, and a surgical tumor resection is planned. (62) However, United Kingdom-guidelines do not generally suggest performing endosonography, but only in case that the T stage impacts the treatment plan. (66)

For pre-treatment staging purposes imaging techniques like X-ray, ultrasound, CT scans and PET-scans are used to receive additional information regarding the primary tumor, lymph node status and a possible tumor dissemination. The European Society for Medical Oncology guidelines recommend the use of CT-scans, EUS and PET-scans, when available, for each patient. (62) It is also

recommended that a contrast-enhanced CT-scan of the thorax, abdomen and pelvis should be carried out in all patients. (54) When a patient is eligible for curative surgery, a pre-operative staging laparoscopy for exclusion of peritoneal carcinomatosis should be performed. If beneficial for further treatment decisions a PET-CT scan can be performed in a suspected metastatic setting. (56, 66) Especially in case of >T2N0 disease, and no evidence of distant metastases in CT scan a PET-CT scan should be performed to rule out distant metastases. (54)

There is no evidence that a routine use of serologic markers like CEA, CA 19-9, AFP, and pepsinogen helps in treatment decision making or improves the prognosis. Despite a relatively low sensitivity and specificity of serologic markers a few studies have shown that there is a correlation between serologic markers and OS. (56, 67)

## Treatment options

The treatment options mainly depend on pre-treatment staging, the patient's condition and on possible comorbidities. A multidisciplinary planning of the treatment involving different disciplines like surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, and other health care professions should be pursued. (62)

Depending on stage a distinction is made between early gastric cancer, locoregional diseases and locally advanced unresectable or metastatic gastric cancer. Stage I to III tumors can be considered as potentially curable whereas in most cases stage IV disease implies a palliative treatment intent. (54)

An early detection of potentially curable diseases is crucial but unfortunately due to the delay between the onset of symptoms and the diagnosis only performed in patients with either incidental findings or those with a fast clarification of suspicious symptoms. In early-stage gastric cancer surgical tumor resection is essential for enabling long-term survival. For patients with small lesions and superficial infiltration of the wall endoscopic mucosal resection alone can be the preferred therapy approach to achieve cure. EMR is a gentle way to remove the tumor in early stages in a minimal invasive way. (68) In tumors >T1N a multimodal approach with a combination of surgery and peri-operative chemotherapy is

superior in terms of disease-free survival and OS compared to surgery alone, since pre-operative chemotherapy reduces the size of the tumor and therefore enables a less invasive operation, while adjuvant chemotherapy is thought to eliminate micrometastases and thus reducing the recurrence risk. (69)

**Surgery**

Resection of the carcinoma including resection of adjacent lymph nodes should be performed with curative intent. A tumor is considered to be unresectable if it has spread to other organs, infiltrates the aorta or occludes the hepatic artery or splenic artery. (70) A palliative gastrectomy can be performed to relieve symptoms and shows a benefit in OS at presence of at maximum one metastasis. (71) A gastrectomy can be performed either way as a total gastrectomy when the whole stomach is removed or a partial gastrectomy in which just a part of the stomach is resected. Total gastrectomy is most commonly used when the upper part of the stomach is involved where on the other hand partial gastrectomy is performed with involvement of the distal two thirds of the stomach. (70) A partial gastrectomy is favorable in terms of symptomatic outcome in comparison to a more invasive total gastrectomy. (72)

The resection of lymph nodes plays another important role following a curative approach. Depending on which lymph nodes are resected the lymphadenectomy can be more or less radical. Even if there is consensus that a lymphadenectomy with histological examination of at least 15 lymph nodes leads to a better outcome, the extent of lymphadenectomy is controversially discussed. (73) Large meta-analyses reported that it is not automatically beneficial choosing a more aggressive and radical approach. (74, 75, 76)

Generally, only tumors classified as stage IA should be endoscopically resected. Higher graded tumors with stage IB-III should receive a combination of peri-operative therapy and radical surgery. Ideally a D2-resection of the tumor is performed in specialized tumor centers with high case numbers and the available expertise. (1) A D2-resection is defined as an operation with removal of additionally level 2 lymph nodes in comparison to a D1-resection with extirpation of level 1 lymph nodes alone. (77)

**Systemic treatment**

Systemic treatment with chemotherapy, targeted therapy and immunotherapy is the second important pillar on which gastric cancer treatment is based, besides the possibility of surgery. Frequently used drugs include:

5-fluorouracil

5-fluorouracil is an antineoplastic agent known for over 60 years and is still part of many chemotherapy regimens in the treatment of gastric cancer and many other tumor types. 5-fu belongs to the group of fluoropyrimidines, and its efficacy is based on two properties. Firstly, it has the potential to inhibit thymidylate synthase which is needed to synthesize thymidine which in turn is part of the desoxyribonucleic acid. Secondly, its metabolites are incorporated into the ribonucleic acid which has toxic effects to the RNA. The addition of leucovorin, a folate analog optimizes and boosts the cytotoxic effect of 5-fu and thereby increases the response rates. (78)

Frequently observed side effects are: (79)

- Diarrhea
- Mucositis
- Nausea
- Bone marrow suppression
- Cardiotoxicity

Capecitabine

Because of its oral intake, capecitabine offers the possibility of decentralized treatment outside of a clinical setting. The enzyme thymidine phosphorylase catalyzes the reaction to fluorouracil, the active metabolite of capecitabine. Trials comparing 5-fu plus leucovorin to capecitabine showed a similar efficacy and side effects were tolerable. Capecitabine is used for several types of cancer like breast cancer, prostate cancer, ovarian cancer, and those affecting the gastrointestinal tract.

Applied under the trade name Xeloda® the following adverse effects are commonly reported: (80, 81)

- Hand-foot-syndrome
- Hyperbilirubinemia
- Neutropenia
- Stomatitis
- Diarrhea

Cisplatin/oxaliplatin

Although cisplatin has been known for over 170 years its cytotoxic properties in many types of cancer were discovered in the 60s of the last century. Since then, it has been widely used in cancer treatment of solid malignancies, most commonly combined with other agents. Its effect is based on causing damage to the DNA, triggering tumor cell apoptosis and intervening DNA repair mechanisms. As cisplatin has a relatively wide toxicity profile other platinum-based substances like oxaliplatin or carboplatin represent alternatives. In the treatment of gastric cancer, today oxaliplatin represents the backbone of chemotherapy regiments including FOLFOX and FLOT. Most important toxicities of platinum agents are: (82)

- Neuropathy
- Ototoxicity
- Nephrotoxicity
- Allergic reactions
- Hematotoxicity

Irinotecan

Irinotecan, also known as CPT-11 is a topoisomerase I inhibitor. By inhibiting topoisomerase I it impacts the cell cycle and therefore has a cytotoxic effect. It is administered as a prodrug and converted to its active metabolite SN-38. (83) Due to its cytotoxic effect and a well tolerable and manageable side effect profile, irinotecan is used for colorectal cancer, pancreatic cancer, and lung cancer, too.

Common side effects are: (84)

- Neutropenia
- Diarrhea
- Nausea
- Alopecia
- Fatigue

Paclitaxel

As part of a palliative second-line chemotherapy option paclitaxel, which belongs to the taxane family, is either used as monotherapy or in combination with the monoclonal antibody ramucirumab. It prevents the correct assembly of the spindle and thus disturbs the cell cycle. Adverse effects that may occur as a result of paclitaxel therapy are: (85):

- Allergic reactions
- Neuropathy
- Neutropenia
- Myalgia
- Bradycardia

Docetaxel

Docetaxel is a cytotoxic substance which is widely used in peri-operative chemotherapy. Its cytotoxic effect is based on triggering the polymerization of the microtubules which leads to an intervention in the cell cycle and results in apoptotic cell death. Observed side effects include: (86, 87)

- Neutropenia
- Alopecia
- Dermatologic side effects (e.g., pruritus, erythema)
- Nausea
- Diarrhea

Epirubicin

Epirubicin was an integral part of many older chemotherapies but has been progressively replaced by other substances and no longer plays a central role in modern chemotherapy of gastric cancer. Its cytotoxic effect is based on the accumulation between the DNA strands and the associated disruption of DNA replication. Known side effects that may occur during the course of administration are: (88)

- Nausea
- Alopecia
- Fever
- Diarrhea

Trifluridine/tipiracil

The TAGS-trial reported a new standard third-line chemotherapy alternative in advanced gastric cancer. The two-drug combination of trifluridine, which is built into the DNA and tipiracil, which enhances the trifluridine bioavailability by blocking the thymidine phosphorylase was shown to be superior compared to placebo in terms of OS (5.7 months vs. 3.6 months), PFS (2.0 months vs. 1.8 months) and quality of life. Important adverse effects occurred while administration were: (89)

- Nausea
- Anemia
- Diarrhea
- Fatigue
- Neutropenia

Frequently used treatment regimens in gastric cancer combining these chemotherapy agents are:

FOLFOX

- Folinic acid (leucovorin)
- 5-fu
- Oxaliplatin

XELOX

- Capecitabine (Xeloda®)
- Oxaliplatin

FLOT

- 5-fu
- Folinic acid (leucovorin)
- Oxaliplatin
- Docetaxel

FOLFIRI

- Folinic acid (leucovorin)
- 5-fu
- Irinotecan (CPT-11)

Based on a better understanding of molecular pathological pathways of gastric cancer in recent years modern therapy approaches have been developed enabling a targeted treatment approach. The growing understanding that the surfaces of tumor cells differ in the type and extent of expression of tumor-specific antigens led to the idea of making targeted use of this in cancer therapy. Being able to exploit this directly or indirectly by using antibodies revolutionized cancer therapy. New therapies that are being applied as a result of this progress are: (90)

Ramucirumab

Ramucirumab is a monoclonal antibody and VEGFR-2 inhibitor and was the first biologic agent used for second-line therapy in advanced gastric cancer patients. Ramucirumab monotherapy resulted in a 1.4 month longer OS compared to placebo. (91) In the RAINBOW trial, a double-blind, randomized phase 3 study, a combined use of ramucirumab plus paclitaxel showed an even better effect with a survival benefit of 9.6 month compared to 7.4 month with placebo plus paclitaxel therapy.

Observed side effects were: (92)

- Neutropenia
- Leucopenia
- Hypertension
- Fatigue
- Anemia

Trastuzumab

The humanized monoclonal antibody trastuzumab targets the HER2-receptor which is overexpressed in about 20% of all gastric cancer cases. An overexpression is defined as 3+ in immunohistochemistry or as at least 2+ in immunohistochemistry and a confirmation of HER2-amplification in fluorescence in situ hybridization. Initially only used for the treatment of breast cancer with HER2-positivity, in 2010 trastuzumab also received an approval for the treatment of HER2-positive metastatic adenocarcinoma of the stomach and gastroesophageal junction. This approval was based on the multicenter, phase 3 ToGA trial. In the ToGA trial palliative first-line treatment with trastuzumab in combination with chemotherapy was compared to chemotherapy alone. Importantly, trastuzumab plus chemotherapy resulted in longer OS and PFS (OS 13.8 vs. 11.1 months and PFS 6.7 vs. 5.5 months) making this combination the new standard of care treatment of HER2-positive gastric and gastroesophageal junction cancer. Most common side effects of trastuzumab are: (93, 94)

- Nausea and Vomiting
- Diarrhea
- Neutropenia
- Anorexia

A novel treatment approach for gastric cancer that has recently come into focus is the use of immunotherapy. The immune system recognizes cancer cells either via tumor-specific antigens or tumor-associated antigens of the cancer cell. Immunotherapy makes use of these mechanisms, thus achieving a high selectivity. Immune checkpoint inhibitors block checkpoint receptors that can be

modified by the tumor and thus trigger a T cell-specific immune response. (95) Agents that are used for the treatment of gastric cancer are:

Nivolumab

Nivolumab is a monoclonal antibody and programmed cell death-1 (PD-1) membrane receptor inhibitor. It prevents programmed death-1 from binding to the programmed cell death-1 ligand (PD-L1), which without this inhibition would cause a downregulation of lymphocyte activation. By preventing binding to the ligand, this downregulation is stopped and at the same time T cells are reactivated, which enables a specific reaction of the immune system against tumor cells. (96)

Kang et al. were first to report a beneficial effect of nivolumab in the treatment of gastric cancer. In the setting of metastatic gastric cancer patients who have already received two previous palliative therapy lines, nivolumab led to a marginal but statistically significant OS benefit of 5.25 vs 4.14 months. Although not approved in this setting, these results have promoted further investigations of Nivolumab in the treatment of gastric cancer. (97)

Recently, the Checkmate 649 trial, a randomized, open-label, phase 3 trial evaluating the benefit of nivolumab plus chemotherapy in untreated HER2-negative advanced or metastatic gastric, gastroesophageal junction or esophageal adenocarcinoma demonstrated a statically significant OS benefit for a combination of nivolumab plus chemotherapy versus chemotherapy alone. The beneficial effect of nivolumab was strongest in the subgroup of patients with a combined positive score (CPS) ≥ 5. The CPS indicates the relative ratio of PD-L1 positive tumor cells compared to all tumor cells multiplied by 100. (98) This has led to a European Medicines Agency (EMA) and Food and Drug Administration (FDA) approval of nivolumab in this setting. Common treatment related side effects of nivolumab are:

- Pruritus
- Diarrhea
- Rash
- Fatigue
- Nausea

Pembrolizumab

Pembrolizumab is a monoclonal antibody and PD1-antagonist used as a therapeutic option in the first-line treatment of metastatic or locally advanced unresectable esophageal cancer or HER2-conegative adenocarcinoma of the gastroesophageal junction if CPS is 10 or higher. This approval by the European Medicines Agency is based on the KEYNOTE-590 study, a randomized, placebo-controlled, phase 3 trial, conducted by Sun et al. The study showed that the combination of pembrolizumab plus chemotherapy resulted in an improvement in OS (12.4 vs. 9.8 months) and PFS (6.3 vs. 5.8 months). Frequently observed side effects include: (99, 100)

- Nausea
- Decreased appetite
- Anemia
- Fatigue

## Curative treatment setting

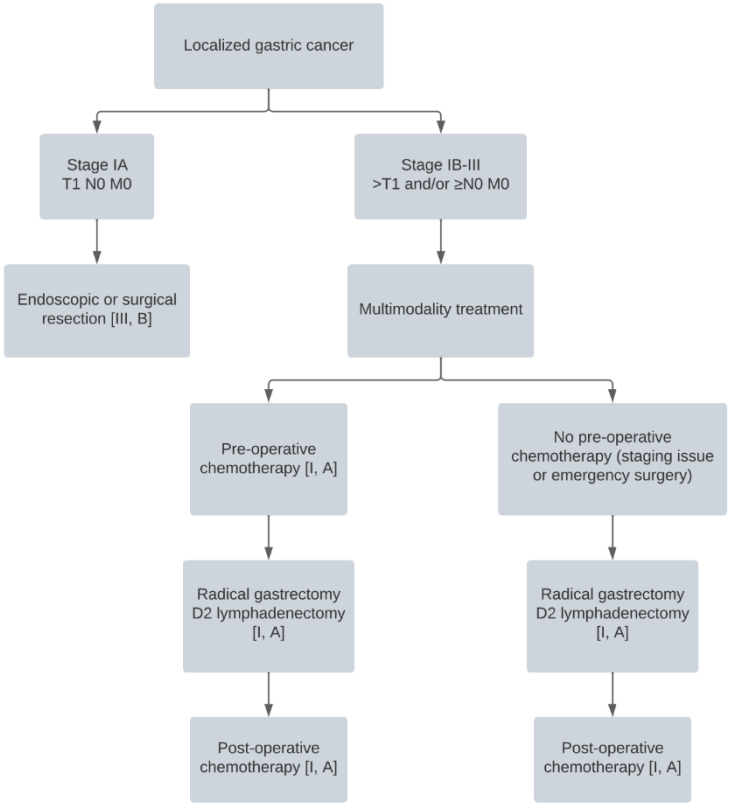


*Figure 1: Curative therapy treatment options in gastric cancer (1)*

As pointed out previously, in patients with resectable gastric cancer with stage >T1/N0 a multimodal treatment approach combining surgery, chemotherapy and/or radiotherapy is recommended. Neoadjuvant therapy is administered with the intent to downsize the tumor to enable a less invasive operation, whereas adjuvant therapy shall eliminate micrometastases and thereby reduce the risk of disease recurrence. According to the current ESMO guidelines, in patients who are able to tolerate a triplet cytotoxic drug regimen, a peri-operative treatment combining neoadjuvant and adjuvant chemotherapy with FLOT (5-fu, folinic acid, oxaliplatin and docetaxel) is the standard of care. This recommendation is based on the FLOT4 trial by Al-Batran et al. in which the superiority of the above-described drug combination over conventionally used regimes like ECF (epirubicin, cisplatin, 5-fu) could be shown in patients with locally advanced, resectable gastric or gastroesophageal adenocarcinoma. FLOT4 was a randomized, open-label phase 2/3 study in which the authors concluded an improvement of OS (HR 0.77) when FLOT was administered instead of ECF (MAGIC trial). (69, 101)

Alternatively, a doublet chemotherapy combination (e.g., FOLFOX) of a fluoropyrimidine with a platinum agent like oxaliplatin or cisplatin is recommended for patients with notable comorbidities who are unfit for triplet chemotherapy. (102) For patients who have already undergone surgery without prior neoadjuvant chemotherapy an adjuvant treatment approach is indicated. (103)

The exact role of radiotherapy in the treatment of gastric cancer is still controversial. Adjuvant chemotherapy seems equivalent to adjuvant chemoradiotherapy (CRT) according to the CRITICS trial, an open-label, randomized phase 3 trial. (104) Whether an additional application of pre-operative radiotherapy is advantageous compared to a peri-operative chemotherapy alone is currently under investigation. (1) The Korean studies ARTIST-I and ARTIST-II showed that there is no evidence that the addition of radiotherapy to adjuvant chemotherapy brings survival advantages in patients with previously performed D2-resection. (105, 106)

There is no indication for adjuvant radiotherapy if a R0-resection or a peri-operative chemotherapy was performed. If not so, a CRT following surgery should be discussed. (107, 108)

In case of a locally advanced inoperable disease without distant metastases the best approach has not been determined yet. An induction chemotherapy aiming for maximal downsizing of the tumor might be useful for patients with good physical health. Regarding the choice of therapy, the same regimes are used as for metastatic disease. (109)

Ongoing trials could bring some major innovations in terms of the optimal regimen for patients with HER2-positive gastric cancer in the peri-operative treatment setting. The ongoing prospective, randomized, open-label phase 2 INNOVATION trial investigates whether an additional use of chemotherapy plus trastuzumab, or chemotherapy plus trastuzumab plus pertuzumab is superior to chemotherapy alone. The study includes patients with HER2-positive gastric or gastroesophageal adenocarcinoma. Primary endpoint is a tumor regression with less than 10% vital tumor cells after administration of therapy according to a tumor regression classification of Becker et al. (110, 111) Final results regarding the same question are provided by the PETRARCA study, a prospective, multicenter, randomized phase II/III trial in which patients with HER2-positive resectable tumors of the esophagogastric junction were included. A complete remission could be reached significantly more often (35% vs. 12%) when trastuzumab and pertuzumab were added to a FLOT regimen. (112)

## Palliative treatment setting

In an inoperable or metastatic setting in which curation cannot be achieved palliative antineoplastic therapy is the standard of care as best supportive care alone shows significantly worse results in terms of OS. Moreover, by combining antineoplastic drugs, prognosis can be further improved. (113) Undoubtedly, locally advanced inoperable or metastatic gastric cancer is associated with a poor prognosis and an estimated OS of less than a year in Western populations. (114) The palliative treatment is mainly aiming for a relief of symptoms, improvement of quality of life and a prolonged survival. To maximize the treatment benefit and

outcome a nutritional and psychological assessment and care should also be integrated. (115)

The optimal treatment strategy is individual and depends on tumor related factors and on patient-related characteristics. Relevant tumor related factors include the HER2 and PD-L1 expression status as well as the presence or absence of a mismatch repair deficiency (dMMR). In addition, the patient´s age, relevant comorbidities and the performance status have to be considered. (1, 116)

**Palliative first-line therapy**

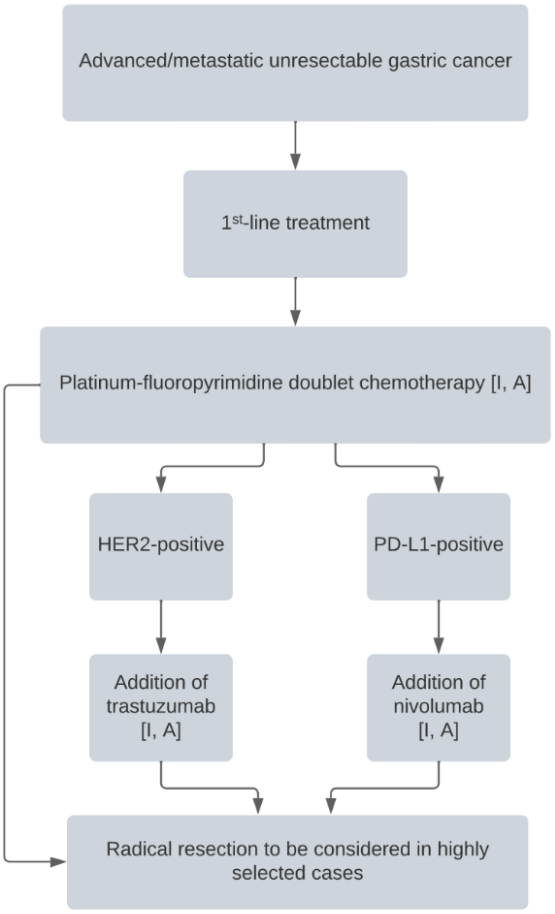


*Figure 2: Palliative first-line therapy treatment options in gastric cancer (1)*

Biomarker negative treatment options

A doublet therapy based on a platinum and fluoropyrimidine combination is considered to be the standard approach in palliative first-line therapy of gastric cancer. Platinum containing drugs typically include cisplatin or oxaliplatin which can be equally used because of their very similar effectiveness. (1) In patients aged 65 or older oxaliplatin seems to have superior safety characteristics. (117) From the group of fluoropyrimidines, mainly 5-fu or as an oral alternative capecitabine are used. Only applied in Asian countries, S-1 can be considered as a third fluoropyrimidine alternative. (118) In case of a reduced performance status or the presence of relevant comorbidities there are several alternatives available. One is the FOLFIRI regimen which contains the agents 5-fu, folinic acid and irinotecan. Alternatively, the monotherapeutical infusional administration of 5-fu represents an option. (119, 120)

An additional use of taxanes in palliative first-line therapy has already been under investigation. Van Cutsem et al. conducted a phase 3 study on this question and has demonstrated improved OS but at the cost of increased toxicity of the therapy. (121) A large Japanese phase 3, open label, randomized controlled study by Yamada et al. could not prove benefits in terms of OS and therefore the use of taxanes in this therapy setting is no therapeutical standard. (122)

Triplets with epirubicin (EOX, ECF, ECX) are no longer recommended as they come along with substantial toxicity. (116, 123)

Palliative treatment in gastric cancer with a CPS ≥ 5

The randomized phase 3 CheckMate-649 trial, including patients with HER2-negative advanced or metastatic gastric, gastroesophageal junction or esophageal adenocarcinoma could demonstrate that the additional use of the PD-1 inhibitor nivolumab in combination with standard chemotherapy results in a significant improvement of OS and PFS. Although the OS benefit was also shown in the overall cohort, the effect was strongest in the subgroup of patients with a CPS ≥ 5. Detailed results are shown in Table 6.

| OS (in months) | Nivolumab plus chemotherapy | Chemotherapy alone |
|---|---|---|
| **CPS ≥ 5** | 14.4 | 11.1 |
| **CPS ≥ 1** | 14.0 | 11.3 |
| **All patients included** | 13.8 | 11.6 |
| | | |
| **PFS (in months)** | | |
| **CPS ≥ 5** | 7.7 | 6.0 |
| **CPS ≥ 1** | 7.5 | 6.9 |
| **All patients included** | 7.7 | 6.9 |

*Table 6: Results of Checkmate-649 (98)*

These results have led to an EMA approval of nivolumab in previously untreated patients with HER2-negative advanced gastric, gastroesophageal junction or esophageal adenocarcinoma and a CPS ≥ 5. (98)

Similar studies on this topic are the Keynote-062 and the Asian ATTRACTION-4 study. The Keynote-062 study, a global, randomized, controlled, phase 3 study that included 763 untreated patients with advanced, non-resectable or metastatic gastric or gastroesophageal cancer with a CPS of at least ≥ 1, evaluated both the addition of pembrolizumab to palliative first-line chemotherapy and the difference of single agent pembrolizumab vs. chemotherapy. Patients with a CPS ≥ 10 had the greatest benefit of using pembrolizumab monotherapy compared to standard chemotherapy (OS 17.4 vs. 10.8 months), which however was not statistically tested. Regarding the combination of pembrolizumab plus chemotherapy vs. chemotherapy, no significant benefit in terms of OS was demonstrated in patients with CPS ≥ 10 (12.3 vs. 10.8 months), but an improvement in ORR was recorded. (124) An update published in 2022 underlined the preliminary results. (125)

The ATTRACTION-4 study supports the additional use of nivolumab in palliative first-line chemotherapy in advanced, unresectable HER2-negative gastric or gastroesophageal cancer patients as PFS was shown to be prolonged (10.5 vs. 8.3 months) by additionally using nivolumab to standard chemotherapy. However, no improvement in OS could be demonstrated in this study. (126)

The reasons for the different results of these 3 studies can probably be explained by the different study designs and the inconsistent conditions regarding cohorts, demographic aspects, and the chemotherapy backbone. (98)

HER2-positive treatment

Approximately 20% of gastric cancers show a HER2 overexpression and/or amplification. (127) This offers the possibility of a targeted therapy with the monoclonal antibody trastuzumab according to the findings of the ToGA trial. The ToGA trial published by Bang et al. is an open-label phase 3, randomized controlled trial, which demonstrated a significant improvement of OS and PFS in patients with HER2-positive gastric cancer when trastuzumab was added to a standard chemotherapy with either capecitabine plus cisplatin or fluorouracil plus cisplatin. Overall, 584 patients with advanced gastric or gastroesophageal junction cancer were included in this study. The primary endpoint was the OS. In detail the median OS was 13.8 months in the trastuzumab plus chemotherapy arm and 11.1 months in the control arm. In terms of toxicity no significant differences were observed between the two treatment arms. (93)

The lately published interim results of the KEYNOTE-811 trial, an ongoing randomized, placebo-controlled, double-blind, phase 3 study further suggests adding the PD-1-inhibitor pembrolizumab to trastuzumab plus chemotherapy in patients with HER2-positive gastric cancer. Patients suffering from non-resectable, or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma were included in this multicenter trial either to efficacy or placebo group. Primary endpoints of this study were OS and PFS, the secondary endpoint was the ORR. Results show that adding pembrolizumab is beneficial in terms of tumor size reduction and regarding the aforementioned endpoints. However, promising results of the interims analysis still need to be supported by further investigations. (128)

**Palliative second-line therapy**

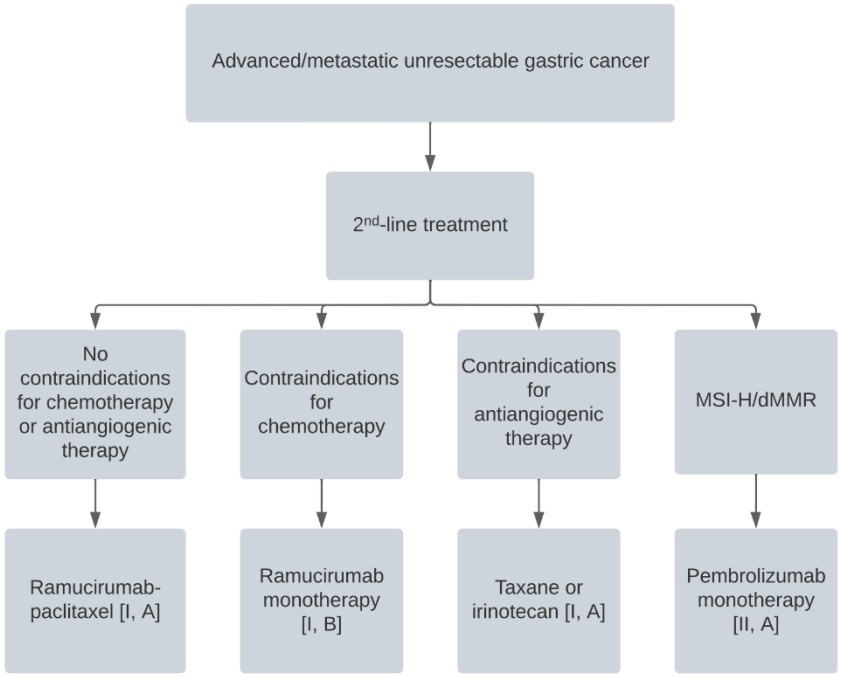


*Figure 3: Palliative second-line therapy treatment options in gastric cancer (1)*

Several regimens have the potential to prolong life, increase quality of life and relieve symptoms as palliative second-line treatment. Depending on individual therapy goals and performance status, it should be discussed which therapy is most promising. However, it has been shown that the administration of a second-line chemotherapy in the setting of advanced or metastatic gastric cancer comes along with a significant reduction in the risk of death and thus a better OS. (129)

If a patient is fit enough, the current guidelines recommend the use of ramucirumab, and paclitaxel combination based on the RAINBOW trial. In this randomized, double-blind, phase 3 study the above-mentioned combination has proven its effectiveness in second-line chemotherapy of advanced or metastatic gastric or gastroesophageal adenocarcinoma. Overall, 600 patients who had previously progressed on a platinum and fluoropyrimidine based first-line treatment, were included. OS and PFS was significantly longer in patients who were assigned to the ramucirumab plus paclitaxel group compared to the placebo group. The median OS was 9.6 months in the intervention group vs. 7.4 months in the placebo group. (92)

Alternatively, the REGARD trial suggests using the VEGFR2-inhibitor ramucirumab as a monotherapy. The randomized, placebo-controlled phase 3 study could show that monotherapy with ramucirumab resulted in a significantly improved OS compared to placebo. The median OS was 5.2 months in the intervention group and 3.8 months in the control group. (91)

Other single agent treatment options include paclitaxel or irinotecan monotherapy, which show similar efficacy. (130) The use of docetaxel may be considered equivalent but is associated with greater toxicity. (113)

**Palliative third-line therapy**

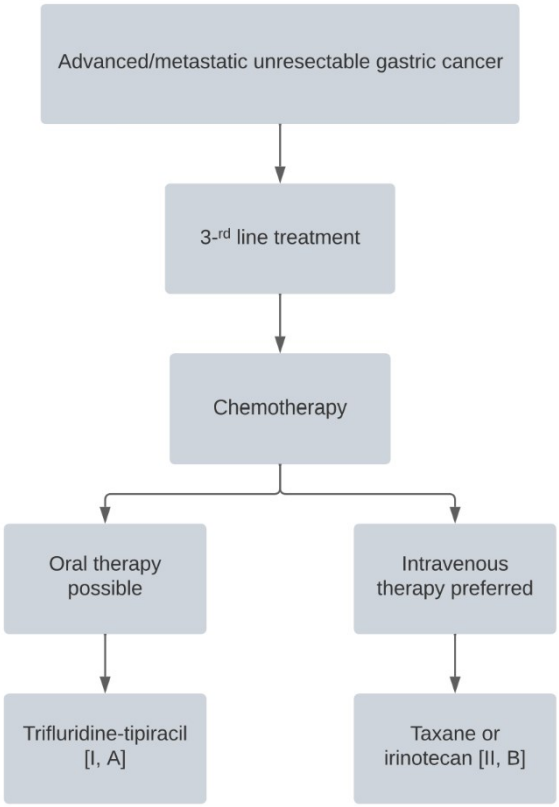


*Figure 4: Palliative third-line therapy treatment options in gastric cancer (1)*

Available options are limited in this setting, but the TAGS study and the ATTRACTION-2 trial provides a basis for further treatment possibilities after progression under second-line therapy. (114)

A clinically meaningful prolongation of the OS could be proved in the TAGS trial when trifluridine/tipiracil was administered in a later line setting of advanced non-operable or metastatic gastric or gastroesophageal adenocarcinoma. In this randomized, double-blind, placebo-controlled, phase 3 trial the OS was 5.7 in the trifluridine/tipiracil group and 3.6 months in the placebo group. The results of this study now represent a new treatment alternative when there has been progression after at least two chemotherapy lines. The safety profile of trifluridine/tipiracil was favorable as side effects were tolerable and manageable. (89)

# Material and methods

## Study aim

The aim of this single-center retrospective cohort study was to investigate how treatment patterns of palliative first-, second- and third-line in patients with advanced gastroesophageal adenocarcinomas have changed over time and whether these treatment changes have translated into an improved outcome. For this purpose, the medical records of all patients with unresectable or metastatic adenocarcinoma of the esophagus, stomach or gastroesophageal junction who underwent palliative systematic treatment at the Division of Oncology, Medical University of Graz in the period from January 1, 2006, to December 31, 2020, were thoroughly searched to ascertain all relevant data.

## Data acquisition & documentation

For the purpose of data collection, the in-house electronic healthcare databases as well as the in-house pharmacy prescription program was used. The medical records of each patient were now studied in detail and recorded in an online database using the software REDCap.

Overall, 767 data points were queried per case. These included demographic information such as age and sex, tumor-specific data including tumor location, tumor histology and tumor biology as well treatment and outcome related data including information on treatment response and progression dates. For the sake of clarity, 7 subforms were defined to allow a structured approach. These were: Baseline characteristics, curative treatment, surgery, palliative treatment, palliative supportive care, complications, and BSC/death.

## Study cohort

The overall REDCap database comprised all patients with esophageal squamous cell carcinoma, esophageal adenocarcinoma, adenocarcinoma of the gastroesophageal junction and gastric adenocarcinoma in any disease stages who were treated at the Department of Oncology at the Medical University of Graz between 2006 and 2020. For the present study only patients who had histologically confirmed locally advanced, metastatic and/or non-resectable adenocarcinoma of the esophagus, stomach or gastroesophageal junction and

had received at least one cycle of palliative systematic treatment between January 1, 2006, and December 31, 2020, were considered.

Figure 5 illustrates the flow chart of the study cohort. In total the REDCap database covered 951 patients of whom 767 patients had an adenocarcinoma and 174 patients had squamous cell carcinoma. 371 patients were not eligible for the present study, as they did not receive palliative therapy. Data were missing for a further 14 patients, so finally 382 (40.2%) patients met the inclusion criteria and were enrolled in the study as they had locally advanced unresectable or metastatic disease and received at least one cycle of palliative systemic treatment. To determine time dependent differences of treatment patterns and outcome the cohort was split into two nearly equally sized cohorts according to the start date of palliative first-line therapy, which represented the study baseline. As a cut-off date January 1, 2013, was chosen.

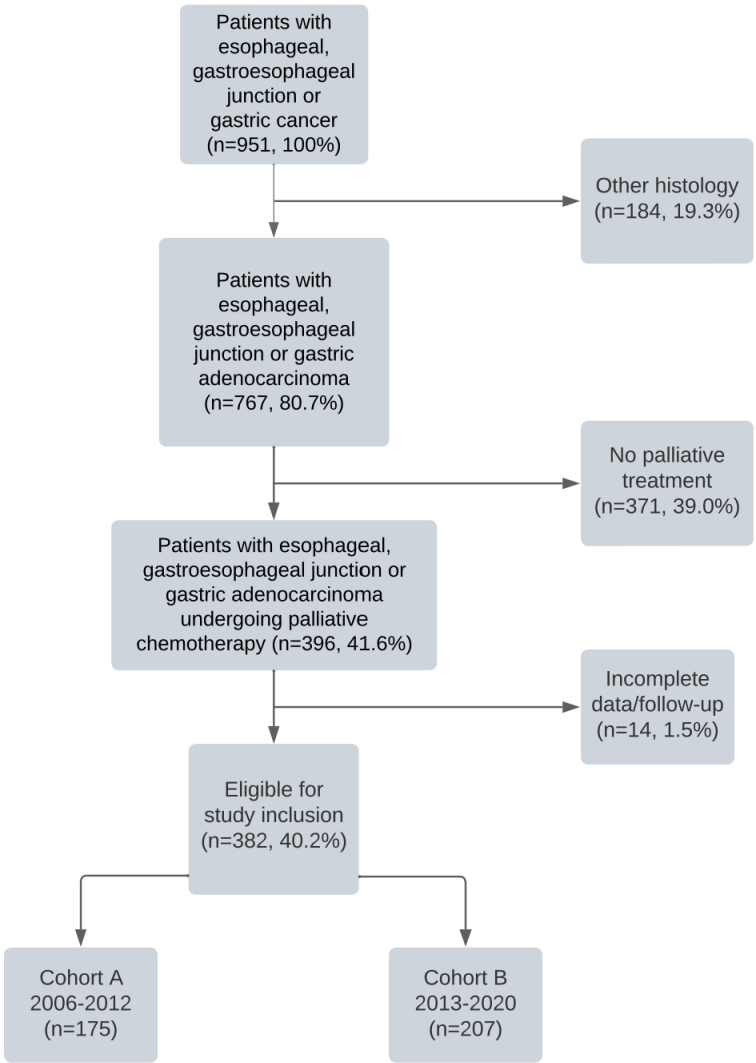


*Figure 5: Flow chart study enrollment*

## Endpoints

The primary endpoint of this study was the OS measured from the date of initiation of palliative first-line until death or last day alive. Co-secondary endpoints were the PFS from the start of palliative first-line (PFS1) and the OS and PFS from the start of palliative second- and third-line (OS2, OS3, PFS2, PFS3). The PFS was defined as the time from start of therapy until radiological disease progression, clinical progression, or death, whatever came first. The radiographic objective response rate (ORR) was defined as a composite of complete or partial remission according to the assessment of the investigating radiologist.

## Ethics statement

Before data collection and patient related analysis this study was approved by the local institutional review board (Ethics Committee of the Medical University of Graz, Austria; EK-number 33-380 ex 20/21). All investigations and analyses were carried out in strict compliance with local, national, and international guidelines for ethical conduct in medical research involving human subjects.

## Statistical analysis

All statistical analyses were conducted with Stata 17.0 (Stata Corp., Houston, TX, USA). The start date of palliative first-line therapy was defined as the study baseline. Patients´ baseline characteristics were described for the overall cohort and separately for the two treatment era cohorts, Cohort A (2006-2012) and Cohort B (2013-2020). Continuous variables were summarized as medians [25th-75th percentile], whereas categorical variables were reported as absolute counts (%). Numbers of missing data were reported as absolute counts (%). To determine potential differences of baseline characteristics and treatment patterns between the two study groups t-tests and rank-sum tests were performed for continuous data and Chi-square and Fisher-exact tests were performed for categorical data as appropriate. Graphical methods and the Shapiro–Wilk test were used to test for normality. The median follow-up was assessed with the reverse Kaplan-Meier estimator according to Schemper & Smith. Survival times were estimated with the Kaplan-Meier method and truncated at 24 months of follow-up. Log-rank tests were used to test for survival differences between the two study groups. The association between clinicopathologic parameters and the

primary outcome of OS1 was assessed with uni- and multivariable Cox proportional hazards models. All variables which showed a significant association with OS1 in the univariable model at a significance level of 5% and had a maximum of 25% missing data, were included in the multivariable model. The proportional hazards assumption for treatment era was assessed using Schoenfeld tests.

# Results

## Cohort analysis at baseline

A total of 382 patients with a median age of 63 years were included in the study. Among them were 69.9% male patients and 30.1% women (Table 7). A relative majority of 45.8% had at least one comorbidity as well as 51.9% had an ECOG worse than 0. Slightly more than 40% had a positive smoking history and 76.4% of all patients suffered from gastric cancer representing the most common tumor site. Signet ring carcinoma was present in approximately one-third of the total cohort. HER2-positive tumors were diagnosed in 26.9% of all cases. Higher grade malignancy defined as grade 3-4 was present in 68% of the patients. Metastases in at least one site, were evident in 54.2% of the patients. The most common localization of metastases was the peritoneum followed by liver and lung metastases. Of the 382 patients identified, 147 received prior curative treatment, corresponding to 38.5%. One third of the patients underwent prior curative surgery. Overall, clinicopathologic characteristics were highly similar between the two study groups. Cohort-specific differences were evident in terms of previous treatment. In Cohort B a significantly higher proportion of patients has received prior chemotherapy and radiotherapy. In addition, patients in Cohort B had significantly lower levels of baseline albumin **(Table 7)**.

| **Variable** | **n (% miss.)** | **Overall (n=382)** | **Cohort A 2006-2012 (n=175)** | **Cohort B 2013-2020 (n=207)** | **p** |
|---|---|---|---|---|---|
| **Demographics at baseline** | | | | | |
| Age | 382 (0%) | 63 [54-70] | 62 [52-70] | 63 [55-71] | 0.272 |
| Female gender | 115 (0%) | 115 (30.1%) | 53 (30.3%) | 62 (30.0%) | 0.943 |
| Male gender | 267 (0%) | 267 (69.9%) | 122 (69.7%) | 145 (70.0%) | 0.943 |
| Weight (kg) | 345 (10%) | 69 [60-80] | 70 [60-80] | 68 [59-80] | 0.620 |
| BMI | 334 (12.6%) | 23.1 [20.5-26.6] | 22.9 [20.8-26.3] | 23.2 [20.3-26.9] | 0.683 |

| | | | | | |
|---|---|---|---|---|---|
| Charlson Comorbidity Index | 382 (0%) | | | | |
| CCI 0 | / | 50 (13.1%) | 25 (14.3%) | 25 (12.1%) | 0.560 |
| CCI 1 and 2 | / | 175 (45.8%) | 83 (47.4%) | 92 (44.4%) | |
| CCI ≥ 3 | / | 157 | 67 (38.3%) | 90 43.5%) | |
| Performance status | 293 (23.3%) | | | | |
| ECOG 0 | / | 141 (48.1%) | 58 (45.7%) | 83 (50.0%) | 0.056 |
| ECOG 1 | / | 142 (48.5%) | 61 (48.0%) | 81 (48.8%) | |
| ECOG ≥ 2 | / | 10 (3.4%) | 8 (6.3%) | 2 (1.2%) | |
| Smoking history yes | 122 (21.9%) | 122 (40.4%) | 50 (36.5%) | 72 (43.6%) | 0.208 |
| **Tumor variables** | | | | | |
| Tumor location | 381 (0.3%) | | | | |
| Esophagus | / | 65 (17.1%) | 29 (16.6%) | 36 (17.5%) | 0.551 |
| Stomach | / | 291 (76.4%) | 137 (78.3%) | 154 (74.8%) | |
| AEG | / | 25 (6.6%) | 9 (5.1%) | 16 (7.8%) | |
| Signet ring carcinoma yes | 116 (0%) | 116 (30.4%) | 45 (25.7%) | 71 (34.3%) | 0.069 |
| HER2-status positive | 72 (29.8%) | 72 (26.9%) | 23 (26.7%) | 49 (26.9%) | 0.975 |
| Tumor grade 3-4 | 246 (5.8%) | 246 (68.3%) | 119 (70.8%) | 127 (66.2%) | 0.340 |
| Laurèn classification | 251 (34.3%) | | | | |
| Diffuse type | / | 116 (46.2%) | 53 (47.8%) | 63 (45.0%) | 0.888 |
| Intestinal type | / | 80 (31.9%) | 35 (31.5%) | 45 (32.1%) | |
| Indeterminate type | / | 55 (21.9%) | 23 (20.7%) | 32 (22.9%) | |
| **Disease extent** | | | | | |
| Tumor burden | 382 (0%) | | | | |
| Locally advanced | 382 (0%) | 35 (9.2%) | 14 (8.0%) | 21 (10.1%) | 0.143 |
| Metast. in 1 site | 382 (0%) | 207 (54.2%) | 87 (49.7%) | 120 (58.0%) | |

| | | | | | |
|---|---|---|---|---|---|
| Metast. in 2 sites | 382 (0%) | 107 (28.0%) | 59 (33.7%) | 48 (23.2%) | |
| Metast. in ≥ 3 sites | 382 (0%) | 33 (8.6%) | 15 (8.6%) | 18 (8.7%) | |
| Lung metast. | 382 (0%) | 49 (12.8%) | 22 (12.6%) | 27 (13.0%) | 0.891 |
| Liver metast. | 382 (0%) | 129 (33.8%) | 67 (38.3%) | 62 (30.0%) | 0.086 |
| Perit. metast. | 382 (0%) | 159 (41.6%) | 67 (38.3%) | 92 (44.4%) | 0.224 |
| Bone metast. | 382 (0%) | 41 (10.7%) | 18 (10.3%) | 23 (11.1%) | 0.795 |
| **Previous treatment** | | | | | |
| Curative treatment | 382 (0%) | 147 (38.5%) | 59 (33.7%) | 88 (42.5%) | 0.078 |
| Previous CTX | 382 (0%) | 72 (18.9%) | 18 (10.3%) | 54 (26.1%) | <0.001 |
| Previous RTX | 382 (0%) | 23 (6.0%) | 5 (2.9%) | 18 (8.7%) | 0.017 |
| Curative surgery | 382 (0%) | 131 (34.3%) | 52 (29.7%) | 79 (38.2%) | 0.083 |
| **Laboratory parameters at baseline** | | | | | |
| CRP (mg/L) | 329 (13.9%) | 11[3.3-34.6] | 13.5 [3.7-36.2] | 10 [3.2-32.2] | 0.356 |
| Leukocyte count (G/L) | 344 (10%) | 7.9 [6.3-9.7] | 8 [6.5-9.6] | 7.7 [6.1-9.9] | 0.826 |
| Neutrophil count (G/L) | 340 (11%) | 5.5 [4.1-6.9] | 5.6 [4.3-7.0] | 5.2 [4.0-6.7] | 0.292 |
| Albumin (g/dL) | 299 (21,7%) | 3.9 [3.5-4.2] | 4 [3.7-4.4] | 3.8 [3.5-4.2] | 0.005 |
| CEA (ng/mL) | 251 (34,3%) | 3.8 [1.4-24.2] | 3.2 [1.5-21.6] | 4.0 [1.4-27.6] | 0.940 |
| LDH (IU/L) | 324 (15,2%) | 190 [162-251.5] | 189 [158-256] | 190 [163-246] | 0.719 |

*Table 7: Baseline characteristics of the study cohort (n=382)*
*Distribution overall and by study cohorts. Data are medians [25$^{th}$-75$^{th}$ percentile] for continuous data and absolute frequencies (column %) for count data. n (%miss.) shows the number of patients with fully observed records for the respective variable (% missing).*

## Analysis of treatment patterns

### Palliative first-line therapy

All 382 included patients received palliative first-line therapy most commonly consisting of 2 substances (63.4%). Monotherapies and the combination of 3 drugs were administered with similar frequency of 17.8% and 18.3%. Cisplatin (37.4%) and oxaliplatin (23.3%) as well as 5-fu (62.3%) and capecitabine (30.4%) were the most frequently administered agents in palliative first-line therapy. The most

prevalent first-line combination regimens were cisplatin/5-fu (18.6%) and FOLFOX (16.2%), the most common monotherapy treatment was capecitabine. Treatment patterns were significantly different between the two study groups. Among others, patients in Cohort B were significantly more likely to undergo a three-agent treatment combination and to receive 5-fu, oxaliplatin, irinotecan and trastuzumab containing regimens. The three most common treatment regimens in descending order were cisplatin/fluorouracil, cisplatin/capecitabine and capecitabine monotherapy in Cohort A and FOLFOX, FOLFIRI and cisplatin/5-fu in Cohort B **(Table 8)**.

| **Variable** | **Overall cohort n (%)** | **Cohort A 2006-2012 n (%)** | **Cohort B 2013-2020 n (%)** | **p** |
|---|---|---|---|---|
| | | | | |
| **Palliative first-line therapy** | 382 (100.0%) | 175 (100.0%) | 207 (100.0%) | / |
| | | | | |
| **1st-line intensity** | | | | |
| Monotherapy | 68 (17.8%) | 41 (23.4%) | 27 (13.0%) | 0.001 |
| Combination of 2 substances | 242 (63.4%) | 113 (64.6%) | 129 (62.3%) | |
| Combination of 3 substances | 70 (18.3%) | 21 (12.0%) | 49 (23.7%) | |
| Combination of 4 substances | 2 (0.5%) | 0 (0.0%) | 2 (0.1%) | |
| | | | | |
| **Most frequently used substances** | | | | |
| 5-fu | 238 (62.3%) | 91 (52.0%) | 147 (71.0%) | <0.001 |
| Cisplatin | 143 (37.4%) | 95 (54.3%) | 48 (23.2%) | <0.001 |
| Capecitabine | 116 (30.4%) | 73 (41.7%) | 43 (20.8%) | <0.001 |
| Oxaliplatin | 89 (23.3%) | 7 (4.0%) | 82 (39.6%) | <0.001 |
| Trastuzumab | 47 (12.3%) | 12 (6.9%) | 35 (16.9%) | 0.003 |
| Carboplatin | 38 (10.0%) | 24 (13.7%) | 14 (6.8%) | 0.024 |
| Irinotecan | 38 (10.0%) | 6 (3.4%) | 32 (15.5%) | <0.001 |
| Docetaxel | 18 (4.7%) | 11 (6.3%) | 7 (3.4%) | 0.182 |
| Epirubicin | 16 (4.2%) | 3 (1.7%) | 13 (6.3%) | 0.038 |
| Paclitaxel | 9 (2.4%) | 1 (0.6%) | 8 (3.9%) | 0.043 |

| **Most frequently used regimens** | | | | |
|---|---|---|---|---|
| Cisplatin/5-fu | 71 (18.6%) | 51 (29.1%) | 20 (9.7%) | <0.001 |
| FOLFOX | 62 (16.2%) | 4 (2.3%) | 58 (28.0%) | <0.001 |
| Capecitabine mono | 36 (9.4%) | 25 (14.3%) | 11 (5.3%) | 0.003 |
| Cisplatin/Capecitabine | 32 (8.4%) | 24 (13.7%) | 8 (3.9%) | 0.001 |
| FOLFIRI | 32 (8.4%) | 4 (2.3%) | 28 (13.5%) | <0.001 |
| Cisplatin/5-fu/Trastuzumab | 17 (4.5%) | 4 (2.3%) | 13 (6.3%) | 0.080 |
| Epirubicin/Oxaliplatin | 14 (3.7%) | 2 (1.1%) | 12 (5.8%) | 0.016 |
| Carboplatin/Capecitabine | 14 (3.7%) | 13 (7.4%) | 1 (0.5%) | <0.001 |
| Carboplatin/5-fu | 13 (3.4%) | 9 (5.1%) | 4 (1.9%) | 0.096 |
| Cisplatin/Capecitabine/Trast. | 12 (3.1%) | 5 (2.9%) | 7 (3.4%) | 0.770 |

*Table 8: Therapy characteristics palliative first-line therapy*
*Distribution overall and by study cohorts. Data are absolute frequencies (column n (%)) for count data.*

**Palliative second-line therapy**

Nearly half of the patients included in the study received a palliative second-line therapy. Again, treatment patterns were significantly different between the two study cohorts. Patients in Cohort B had overall higher frequencies of receiving palliative second-line therapy and were more likely to undergo combination treatment. Among others, a higher proportion of patients in Cohort B received irinotecan, paclitaxel and ramucirumab containing regimens whereas patients in Cohort A were more likely to be treated with docetaxel. The most common second-line treatment regimens used were FOLFIRI and docetaxel monotherapy in Cohort A and FOLFIRI and paclitaxel/ramucirumab in Cohort B **(Table 9)**.

| Variable | Overall cohort n (%) | Cohort A 2006-2012 n (%) | Cohort B 2013-2020 n (%) | p |
|---|---|---|---|---|
| **Palliative second-line therapy** | 187 (49.0%) | 76 (43.4%) | 111 (53.6%) | 0.005 |
| | | | | |
| **2nd-line intensity** | | | | |
| Monotherapy | 70 (37.4%) | 39 (51.3%) | 31 (27.9%) | 0.005 |
| Combination of 2 substances | 106 (56.7%) | 35 (46.0%) | 71 (64.0%) | |
| Combination of 3 substances | 10 (5.4%) | 2 (2.6%) | 8 (7.2%) | |
| Combination of 4 substances | 1 (0.5%) | 0 (0.0%) | 1 (0.9%) | |
| | | | | |
| **Most frequently used substances** | | | | |
| 5-fu | 78 (41.7%) | 27 (35.5%) | 51 (46.0%) | 0.156 |
| Irinotecan | 72 (38.5%) | 27 (35.5%) | 45 (40.5%) | 0.004 |
| Paclitaxel | 42 (22.5%) | 9 (11.8%) | 33 (29.7%) | 0.001 |
| Ramucirumab | 34 (18.2%) | 2 (2.6%) | 32 (28.3%) | <0.001 |
| Docetaxel | 21 (11.2%) | 18 (23.7%) | 3 (2.7%) | <0.001 |
| Trastuzumab | 21 (11.2%) | 5 (6.6%) | 16 (14.4%) | 0.096 |
| Capecitabine | 19 (10.2%) | 10 (13.2%) | 9 (8.1%) | 0.262 |
| Oxaliplatin | 11 (5.9%) | 5 (6.6%) | 6 (5.4%) | 0.738 |
| Cisplatin | 5 (2.7%) | 2 (2.6%) | 3 (2.7%) | 1.000 |
| | | | | |
| **Most frequently used regimens** | | | | |
| FOLFIRI | 56 (30.0%) | 21 (27.6%) | 35 (31.5%) | 0.567 |
| Paclitaxel/Ramucirumab | 23 (12.3%) | 2 (2.6%) | 21 (18.9%) | 0.001 |
| Docetaxel mono | 18 (9.6%) | 17 (22.4%) | 1 (0.9%) | <0.001 |
| Paclitaxel mono | 16 (8.6%) | 6 (7.9%) | 10 (9.0%) | 0.789 |
| Capecitabine mono | 13 (7.0%) | 8 (10.5%) | 5 (4.5%) | 0.112 |
| Ramucirumab mono | 10 (5.4%) | 0 (0.0%) | 10 (9.0%) | 0.007 |
| Irinotecan mono | 8 (4.3%) | 5 (6.6%) | 3 (2.7%) | 0.198 |
| FOLFOX | 6 (3.2%) | 3 (4.0%) | 3 (2.7%) | 0.635 |

*Table 9: Therapy characteristics palliative second-line therapy*
*Distribution overall and by study cohorts. Data are absolute frequencies (column n (%)) for count data.*

**Palliative third-line therapy**

Only 20% of the entire cohort were suitable for palliative third-line therapy, with a higher proportion of patients undergoing palliative third-line in Cohort B. In both cohorts about 50% of the patients received a monotherapy. The most frequently used regimen was FOLFIRI in Cohort A and paclitaxel mono in Cohort B **(Table 10)**.

| **Variable** | **Overall cohort n (%)** | **Cohort A 2006-2012 n (%)** | **Cohort B 2013-2020 n (%)** | **p** |
|---|---|---|---|---|
| **Palliative third-line therapy** | 75 (19.6%) | 23 (13.1%) | 52 (25.1%) | 0.738 |
| | | | | |
| **3rd-line intensity** | | | | |
| Monotherapy | 39 (52.0%) | 11 (47.8%) | 28 (53.9%) | 0.738 |
| Combination of 2 substances | 35 (46.7%) | 12 (52.2%) | 23 (44.2%) | |
| Combination of 3 substances | 1 (1.3%) | 0 (0.0%) | 1 (1.9%) | |
| | | | | |
| **Most frequently used substances** | | | | |
| 5-fu | 18 (24.0%) | 11 (47.8%) | 7 (13.5%) | 0.001 |
| Irinotecan | 21 (28.0%) | 12 (52.2%) | 9 (17.3%) | 0.002 |
| Paclitaxel | 24 (32.0%) | 2 (8.7%) | 22 (42.3%) | 0.004 |
| Ramucirumab | 18 (24.0%) | 0 (0.0%) | 18 (34.6%) | 0.001 |
| Docetaxel | 7 (9.3%) | 3 (13.0%) | 4 (7.7%) | 0.669 |
| Trastuzumab | 5 (6.7%) | 1 (4.4%) | 4 (7.7%) | 1.000 |
| Trifluridine/Tipiracil | 4 (5.3%) | 0 (0.0%) | 4 (7.7%) | 0.306 |
| | | | | |
| **Most frequently used regimens** | | | | |
| FOLFIRI | 15 (20.0%) | 10 (43.5%) | 5 (9.6%) | 0.001 |
| Paclitaxel mono | 11 (14.7%) | 1 (4.4%) | 10 (19.2%) | 0.156 |
| Ramucirumab mono | 9 (12.0%) | 0 (0.0%) | 9 (17.3%) | 0.050 |
| Paclitaxel/Ramucirumab | 8 (10.7%) | 0 (0.0%) | 8 (15.4%) | 0.097 |
| Docetaxel mono | 7 (9.3%) | 3 (13.0%) | 4 (7.7%) | 0.669 |
| Irinotecan mono | 4 (5.3%) | 2 (8.7%) | 2 (3.9%) | 0.582 |
| Trifluridine/Tipiracil mono | 3 (4.0%) | 0 (0.0%) | 3 (5.8%) | 0.548 |

*Table 10: Therapy characteristics palliative third-line therapy*
*Distribution overall and by study cohorts. Data are absolute frequencies (column n (%)) for count data.*

**Primary endpoint analysis of OS1 in palliative first-line therapy**

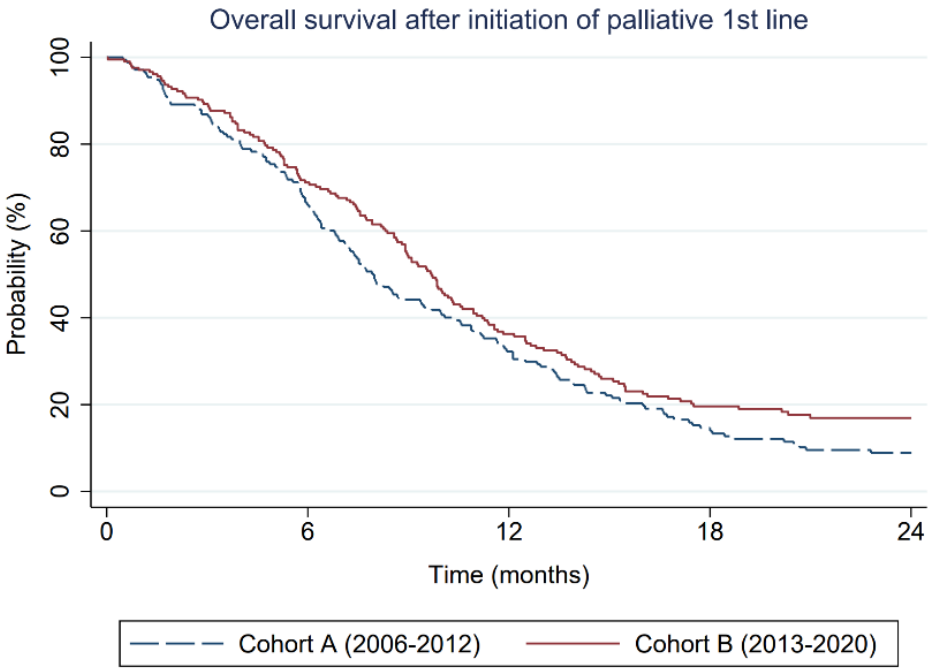


*Figure 6: OS after start of palliative 1st-line therapy*

The median OS in the overall cohort was of 8.9 (95% CI: 8.0-9.9) months. No significant difference was observed between group A and B. In detail, the median OS was 8.0 (95% CI: 6.9-9.5) months in Cohort A compared to a median OS of 9.7 (95% CI: 8.8-10.3) in Cohort B (p=0.055). **(Figure 6) (Table 11)**

**Secondary endpoint analysis**

**PFS1 in palliative first-line therapy**

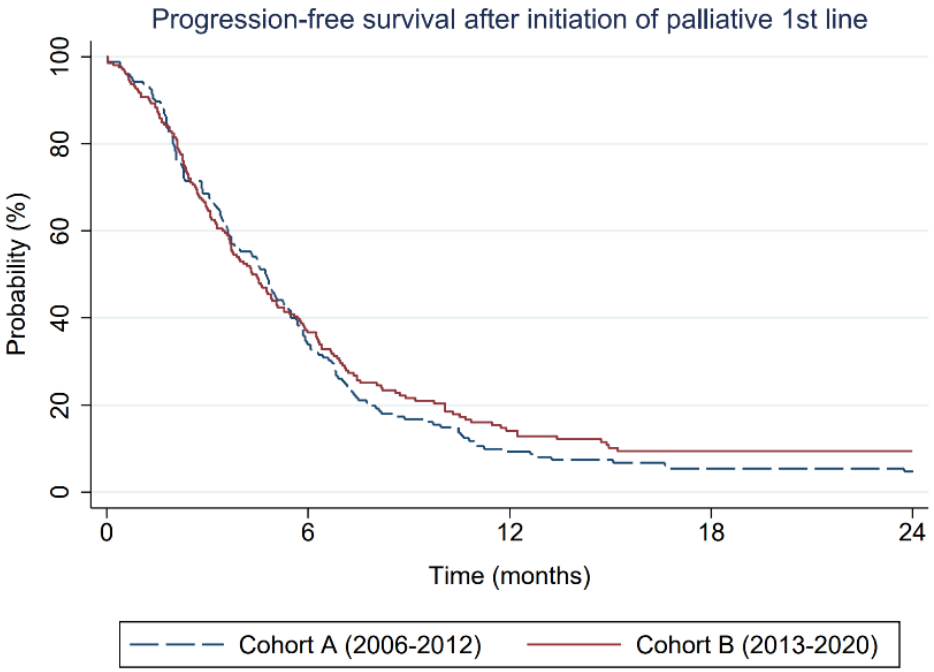


*Figure 7: PFS after start of palliative 1st-line therapy*

For PFS1 the difference between the two study cohorts was even smaller. The median PFS1 was 4.9 (95% CI: 4.3-5.5) months in Cohort A and of 5.1 (95% CI: 4.3-5.9) months in Cohort B (p=0.456).

The ORR of palliative first-line was 33.8% in the overall cohort with no significant difference between Cohort A (33.1%) and Cohort B (34.4%). The DCR was 74.8% and 74.0% in Cohorts A and B, respectively. **(Figure 7) (Table 11)**

**OS2 and PFS2 in palliative second-line therapy**

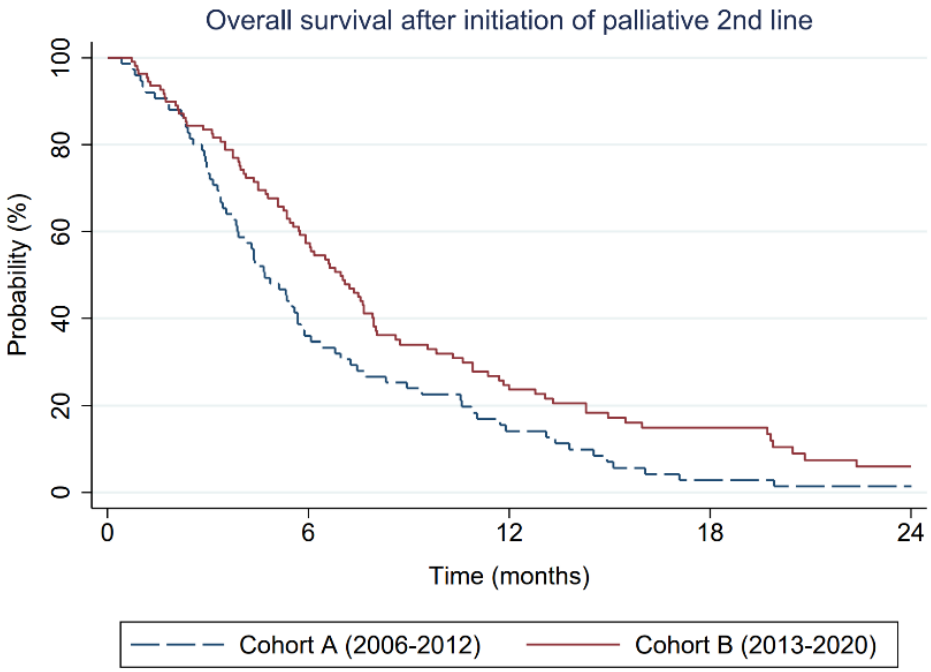


*Figure 8: OS after start of palliative 2nd-line therapy*

As anticipated, the median OS got shorter with each subsequent therapy line. In the subset of 187 patient who underwent palliative second-line treatment the median OS2 from start of palliative second-line was 5.9 (95% CI: 5.3-7.0) months. The OS2 was significantly longer in Cohort B with a median OS2 of 7.0 (95% CI: 5.7-7.9) months compared to a median OS of 4.7 (95% CI: 3.8-5.7) months in Cohort A (p=0.006). **(Figure 8) (Table 11)**

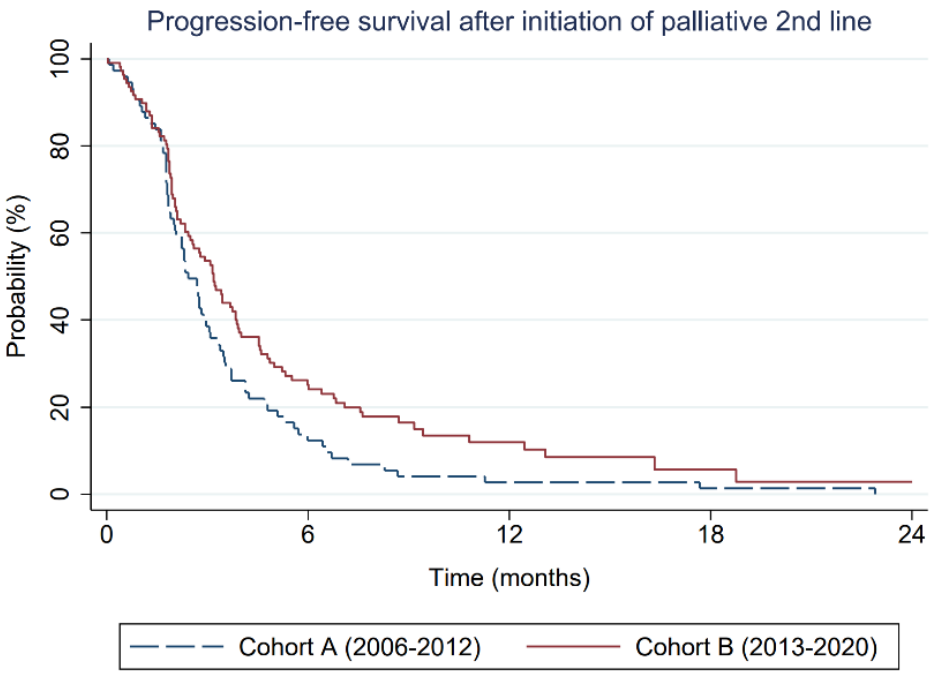


*Figure 9: PFS after start of palliative 2nd-line therapy*

For PFS2 only a non-significant difference was observed. The median PFS2 was 2.4 (95% CI: 2.0-3.1) months in Cohort A and 3.2 (95% CI: 2.3-3.7) months in Cohort B (p=0.083). The ORR2 and DCR2 in the overall cohort were 15% and 30%, respectively with no significant differences between the two study cohorts. **(Figure 9) (Table 11)**

### OS3 and PFS3 in palliative third-line therapy

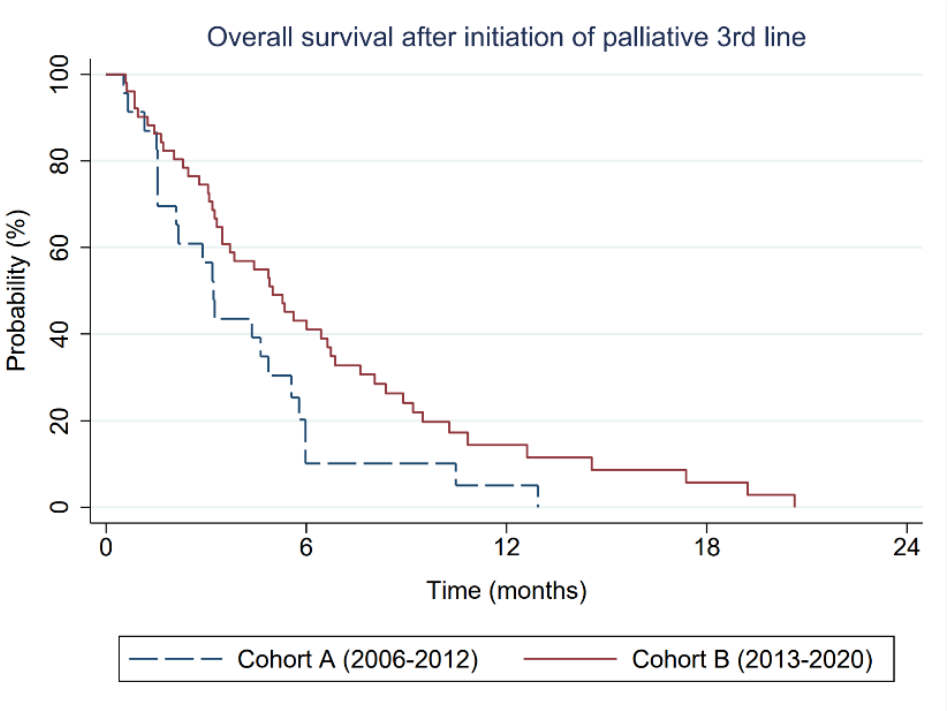


*Figure 10: OS after start of palliative 3rd-line therapy*

In palliative third-line the median OS3 was significantly longer in Cohort B than in Cohort A. In detail, the median OS3 was 5.0 (95% CI 3.3-6.6) months in Cohort B and 3.2 (95% CI: 1.5-4.9) in Cohort A (p=0.031). **(Figure 10) (Table 11)**

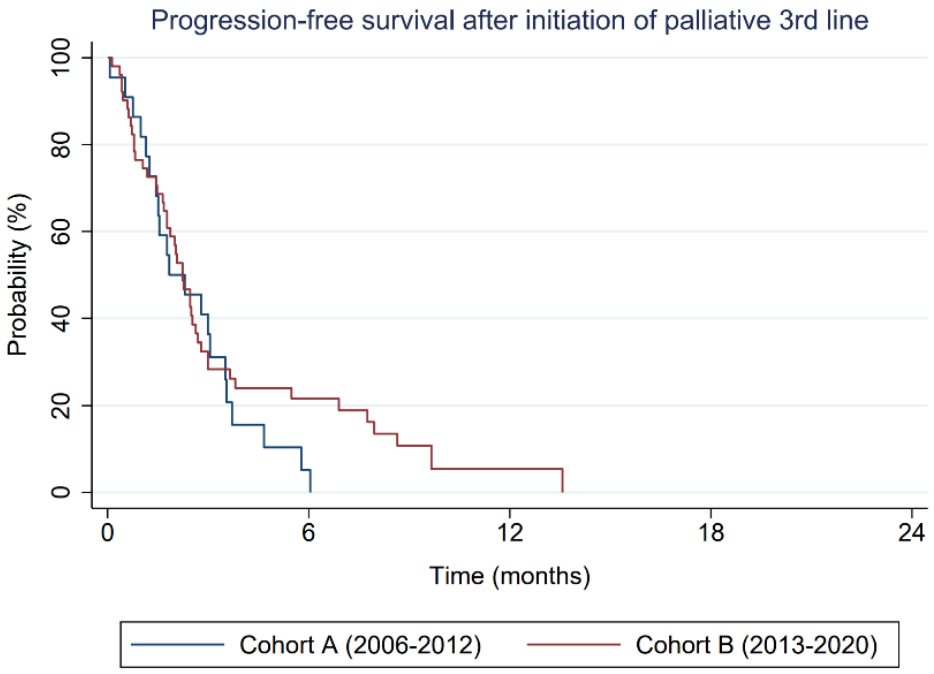


*Figure 11: PFS after start of palliative 3rd-line therapy*

The median PFS3 was very short with a weak trend for a longer PFS3 in Cohort B (2.2 months, 95% CI: 1.8-2.7) compared to Cohort A (1.8 months, 95% CI: 1.2-3.1). In line, the ORR and DCR were low with only 6.0% of patients experiencing a treatment response and 24% achieving a disease stabilization. **(Figure 11) (Table 11)**

| Pall. 1st-line therapy | | | | | |
|---|---|---|---|---|---|
| **Variable** | **n (% miss.)** | **Overall (n=382)** | **Cohort A 2006-2012 (n=175)** | **Cohort B 2013-2020 (n=207)** | **p** |
| ORR | 281 (26.4%) | 95 (33.8%) | 42 (33.1%) | 53 (34.4%) | 0.813 |
| DCR | 281 (26.4%) | 209 (74.4%) | 95 (74.8%) | 114 (74.0%) | 0.882 |
| Median PFS months [95% CI] | 382 (0.0%) | 4.9 [4.5-5.5] | 4.9 [4.3-5.5] | 5.1 [4.3-5.9] | 0.456 |
| Median OS months [95% CI] | 382 (0.0%) | 8.9 [8.0-9.9] | 8.0 [6.9-9.5] | 9.7 [8.8-10.3] | 0.055 |
| **Palliative 2nd-line therapy** | | | | | |
| **Variable** | **n (% miss.)** | **Overall (n=187)** | **Cohort A 2006-2012 (n=76)** | **Cohort B 2013-2020 (n=111)** | **p** |
| ORR | 134 (28.3%) | 20 (14.9%) | 8 (15.4%) | 12 (14.6%) | 0.905 |
| DCR | 134 (28.3%) | 64 (47.8%) | 20 (38.5%) | 44 (53.7%) | 0.086 |
| Median PFS months [95% CI] | 182 (2,7%) | 2.8 [2.3-3.2] | 2.4 [2.0-3.1] | 3.2 [2.3-3.7] | 0.083 |
| Median OS months [95% CI] | 184 (1,6%) | 5.9 [5.3-7.0] | 4.7 [3.8-5.7] | 7.0 [5.7-7.9] | 0.006 |
| **Palliative 3rd-line therapy** | | | | | |
| **Variable** | **n (% miss.)** | **Overall (n=75)** | **Cohort A 2006-2012 (n=23)** | **Cohort B 2013-2020 (n=52)** | **p** |
| ORR | 50 (33.3%) | 3 (6.0%) | 1 (7.1%) | 2 (5.6%) | 0.832 |
| DCR | 50 (33.3%) | 12 (24.0%) | 3 (21.4%) | 9 (25.0%) | 0.791 |
| Median PFS months [95% CI] | 73 (2.7%) | 2.2 [1.8-2.7] | 1.8 [1.2-3.1] | 2.2 [1.8-2.7] | 0.316 |
| Median OS months [95% CI] | 75 (0.0%) | 4.6 [3.3-5.6] | 3.2 [1.5-4.9] | 5.0 [3.3-6.6] | 0.031 |

*Table 11: Treatment outcomes*
*Distribution overall and by study cohorts. Data are absolute frequencies (column n (% miss.)) for Objective response rate and Disease control rate. 95%CI – 95% confidence interval, p25-p75 – 1st to 3rd quartile of the distribution of the respective variable, PFS – Progression-free survival, OS – Overall survival*

**Uni- and multivariable Cox regression analysis of OS in palliative first-line therapy**

To identify and account for potential confounders a uni- and multivariable Cox proportional hazards model for the primary outcome OS1 was performed. The following variables were considered: Treatment era, sex, ECOG performance status, signet ring histology, HER2-status, tumor location, Laurèn classification, smoking history, Charlson comorbidity index, prior curative treatment, tumor burden, BMI, laboratory values and treatment intensity.

In univariable Cox regression analysis age, ECOG 1 and ≥2, signet ring histology, HER2 status, presence of liver metastases, levels of CRP, albumin, leukocytes, neutrophils and LDH and treatment intensity of palliative first-line therapy were significantly associated with OS1 and were thus included in the multivariable model **(Table 12)**. After adjusting for these potential confounders, the impact of treatment era on OS1 further weakened (HR: 0.9 (95% CI: 0.7-1.3, p=0.706). The only independent predictors of increased risk of death were lower age (HR per 10 years increase: HR 0.8, 95% CI: 0.7-1.0, p=0.023), ECOG 1 (HR 1.9, 95% CI: 1.4-2.5, p=<0.001) and increased levels of baseline CRP (HR per doubling: HR 1.2, 95% CI: 1.1-1.4, p=<0.001). The one independent favorable factor was the application of a three-agent combination regimen as palliative first-line therapy (HR: 0.6, 95% CI: 0.3-1.0, p=0.041).

| **Variable** | **Univariable analysis** | | **Multivariable analysis** | |
|---|---|---|---|---|
| | **HR (CI 95%)** | **p** | **HR (CI 95%)** | **p** |
| **Treatment cohort** | | | | |
| Cohort A | 1 (reference) | | | |
| Cohort B | 0.8 (0.6-1.0) | 0.056 | 0.9 (0.7-1.3) | 0.706 |
| **Sex** | | | | |
| Male gender | 1 (reference) | | | |
| Female gender | 1.0 (0.8-1.3) | 0.749 | / | / |
| **Age (per 10 years increase)** | 0.9 (0.8-1.0) | 0.026 | 0.8 (0.7-1.0) | 0.023 |

| | | | | |
|---|---|---|---|---|
| **ECOG** | | | | |
| ECOG 0 | 1 (reference) | | | |
| ECOG 1 | 1.6 (1.2-2.1) | <0.001 | 1.9 (1.4-2.5) | <0.001 |
| ECOG ≥ 2 | 3.1 (1.6-6.1 | 0.001 | 1.3 (0.4-3.9) | 0.696 |
| **Signet ring carcinoma** | | | | |
| No | 1 (reference) | | | |
| Yes | 1.3 (1.1-1.7) | 0.015 | / | / |
| **HER2-status** | | | | |
| No | 1 (reference) | | | |
| Yes | 0.6 (0.5-0.8) | 0.003 | / | / |
| **Tumor location** | | | | |
| Esophagus | 1 (reference) | | | |
| Stomach | 1.1 (0.8-1.5) | 0.671 | / | / |
| AEG | 0.9 (0.5-1.5) | 0.689 | / | / |
| **Laurèn classification** | | | | |
| Intestinal type | 1 (reference) | | | |
| Diffuse type | 1.8 (1.3-2.4) | 0.001 | / | / |
| Indeterminate type | 1.7 (1.2-2.5) | 0.005 | / | / |
| **Smoking history** | | | | |
| Yes | 1 (reference) | | | |
| No | 1.0 (0.8-1.3) | 0.887 | / | / |
| **CCI** | | | | |
| CCI 0 | 1 (reference) | | | |
| CCI 1 and 2 | 1.1 (0.8-1.5) | 0.665 | / | / |
| CCI ≥ 3 | 0.8 (0.6-1.2) | 0.293 | / | / |
| **Prior curative treatment** | | | | |
| No | 1 (reference) | | | |
| Yes | 0.8 (0.6-1.0) | 0.060 | / | / |
| **Tumor burden** | | | | |
| Locally advanced | 1 (reference) | | | |
| Metast. in 1 site | 1.1 (0.7-1.7) | 0.624 | 0.9 (0.5-1.5) | 0.595 |
| Metast. in 2 sites | 1.5 (1.0-2.4) | 0.051 | 1.1 (0.6-2.0 | 0.717 |
| Metast. in ≥ 3 sites | 1.7 (1.0-2.8) | 0.053 | 1.3 (0.6-2.8) | 0.475 |

| | | | | |
|---|---|---|---|---|
| **Lung metast.** | | | | |
| No | 1 (reference) | | | |
| Yes | 0.9 (0.6-1.3) | 0.573 | / | / |
| **Liver metast.** | | | | |
| No | 1 (reference) | | | |
| Yes | 1.3 (1.0-1.6) | 0.049 | / | / |
| **Perit. metast.** | | | | |
| No | 1 (reference) | | | |
| Yes | 1.1 (0.9-1.4) | 0.436 | / | / |
| **Bone metast.** | | | | |
| No | 1 (reference) | | | |
| Yes | 1.2 (0.8-1.7) | 0.370 | / | / |
| **BMI (per 1 unit increase)** | 1.0 (0.9-1.0) | 0.054 | / | / |
| **Laboratory values** | | | | |
| CRP (per doubling) | 1.2 (1.2-1.3) | <0.001 | 1.2 (1.1-1.4) | <0.001 |
| Albumin (per g/dL increase) | 0.7 (0.5-0.8) | <0.001 | 0.9 (0.6-1.3) | 0.574 |
| Leukocyte count (per 1 G/L increase) | 1.0 (1.0-1.1) | 0.007 | 0.9 (0.7-1.1) | 0.152 |
| Neutrophil count (per 1 G/L increase) | 1.1 (1.0-1.1) | 0.001 | 1.1 (0.9-1.4) | 0.488 |
| LDH (per doubling) | 1.4 (1.2-1.7) | <0.001 | 1.2 (0.9-1.5) | 0.230 |
| CEA (per doubling) | 1.0 (1.0-1.1) | 0.103 | / | / |
| **Treatment intensity** | | | | |
| Monotherapy | 1 (reference) | | | |
| Combination of 2 substances | 0.7 (0.5-0.9) | 0.009 | 0.8 (0.5-1.3) | 0.378 |
| Combination of 3 substances | 0.6 (0.4-0.8) | 0.002 | 0.6 (0.3-1.0) | 0.041 |
| Combination of 4 substances | 0.3 (0.1-2.3) | 0.263 | 4.6 (0.5-38.5) | 0.162 |

*Table 12: Uni- and multivariable predictors of OS in palliative first-line*

# Discussion

Advanced gastroesophageal cancer is responsible for approximately 1.3 million cancer-related deaths worldwide per year and thus represents a severe global health issue. (2) In our retrospective cohort study, we demonstrated that despite significant changes of treatment patterns, the OS of patients with advanced gastroesophageal adenocarcinoma undergoing palliative therapy remains poor and has not significantly changed over the last 15 years. Only in later lines of palliative treatment a significant survival benefit could be shown. These results underline the aggressivity of advanced gastroesophageal adenocarcinoma and the challenge of making therapeutic decisions to positively impact patient survival.

**Treatment patterns**

Baseline characteristics in our study were well balanced between the two treatment era groups, which enabled a reliable inter-group comparison of survival outcomes. Unlike other first-line trials like the ToGA study, the patients in our investigation were a little older, but the performance status and tumor burden were quite similar. (93) Of the 382 patients who received palliative first-line therapy, 49.9% were suitable for second-line treatment after progression on first palliative therapy. This is a higher rate than reported before. (131, 132) Finally, only one fifth of the patients was treated with third-line therapy. These results are consistent with previous studies in this setting. (133) In palliative first-line therapy, treatment intensity has significantly changed, as in Cohort B a higher proportion of patients underwent triplet therapy. This may be related to the introduction of trastuzumab for the treatment of HER2-positive tumors according to the ToGA trial. (93) This finding was observed in the first- as well as in the second-line treatment. In contrast to that, in third-line therapy treatment intensity remained similar. The rate of patients undergoing a two-agent treatment combination as first-line treatment in our study (63.4%) was significantly lower compared to another published Korean study which promotes 93.2%. (134) This might be caused by a relatively high proportion of patients who had an ECOG performance status of 1 in our study.

Most patients who received first-line therapy were treated with platinum and fluoropyrimidine containing drugs according to established guidelines. (1) Interestingly, the use of platinum-containing drugs changed from cisplatin which was

the predominant drug use in Cohort A to oxaliplatin which has been used more frequently in Cohort B. This was likely prompted by the study findings of Yamada et al. who reported equal survival but a significantly better safety profile for oxaliplatin compared to cisplatin. (135)

Regarding second-line therapy it was evident that patients in Cohort B were treated more aggressively with a significantly higher proportion of patients receiving combination therapy than used in Cohort A. According to the findings of the RAINBOW and REGARD trial paclitaxel and ramucirumab have largely replaced older regimens in Cohort B. With the introduction of paclitaxel and ramucirumab, the use of monotherapies in the second-line generally decreased (Cohort A 51.3% vs. Cohort B 27.9%).

**Survival**

In concordance with previously published real-world data, the median OS from start of palliative first-line therapy was 8.9 months in the overall cohort. (136) Importantly, we could not observe a significant difference in OS between the two treatment era groups with an inter-group difference of median OS of 1.7 months (p=0.055). Reliable outcome data on OS in later lines is rare and previous studies have not investigated whether survival from start of second- and third-line therapy has changed over time. Kanagavel et al. for instance reported a median OS from start of second-line therapy of 5.3 months which is in line with our results (137). We could show that the OS has significantly improved over time in the second-line setting. This might be mainly related to the introduction of ramucirumab either given in combination with paclitaxel or as monotherapy according to the REGARD and RAINBOW trials. Our study thus provides real-world evidence that underlines the efficacy of ramucirumab in this setting. Moreover, we could demonstrate significant improvement in OS in the third-line as well (Cohort A 3.2 vs. Cohort B 5.0 months; p=0.031). An Asian study by Choi et al. shows better survival than our cohort in this setting, with a median OS of 6 months, but with limited comparability due to significant differences in terms of the study population. (138)

PFS improved in cohort comparison in all three lines of therapy but below the level of significance. First-line PFS was 4.9 months in the overall cohort, 2.8 months in the second-line treatment, and 2.2 months in the third-line therapy. Our data support

previously published results on PFS in the respective therapeutic lines. (132, 139, 140) As anticipated treatment response rates were rather low and decreased from 33.8% in palliative first-line analysis, to 14.9% in second-line treatment and only 6.0% in third-line therapy. These results are highly consistent with previous study findings. (132, 133, 141, 142)

Overall, these findings indicate that before the implementation of immune checkpoint inhibition (98) which is not covered by this study, significant advances in the treatment of advanced gastroesophageal adenocarcinoma over the last fifteen years were mainly made in later lines of palliative systemic treatment, whereas changes of treatment patterns in first-line did not result in an overall improvement of outcome.

**Prognostic markers**

Furthermore, we tried to determine prognostic markers for OS in palliative first-line therapy. We therefore set up a Cox regression model. In the univariable analysis we could determine several factors for predicting OS in palliative first-line therapy. After adjusting for potential confounders in the multivariable model we could demonstrate that the only independent predictors of increased risk of death were a lower age, higher ECOG performance status and increased levels of CRP. The one independent favorable factor was the application of a three-agent combination regimen as palliative first-line treatment. Surprisingly, patients with a younger age showed a worse OS. First, this seems conflicting as other studies published a consistent decline in survival in this advanced setting for gastric cancer with higher age. (53, 143, 144) Other studies, however, agree with our findings in this matter. (145, 146) One possible reason for this finding may be that tumors in younger patients have a more aggressive biology and a disproportionately higher incidence of diffuse type histology is present, which is associated with genetic disorder like mutations of the CDH1 gene and poorer survival. (147, 148, 149, 150) In our study, the proportion of patients with diffuse type carcinoma was 46.2%, which is comparable to other studies. (41) However, to evaluate reasons in detail, further investigation is required. In line with our findings, there is strong evidence that a worse performance status comes along with a decreased survival. (151, 152) Also increased levels of CRP have been consistently shown to be associated with worse

outcome in patients with advanced gastroesophageal cancer. (153, 154, 155, 156) An Italian study investigating the impact of treatment intensity on OS in third-line therapy reported a positive influence of a more aggressive therapy on OS and PFS. (157) We were able to report similar findings to these for the OS in palliative first-line therapy.

Finally, several limitations of our study must be discussed:

- Since our study was a retrospective cohort study, selection bias cannot be completely excluded.
- Our study was conducted as a single-center study without external validation. Thus, further studies must be conducted to validate our findings.
- Imaging data for radiological response assessment were not classified by central radiology review but by local investigators.
- Information on dose density of the respective therapy lines potentially influencing survival data were missing.

Strengths of our study are:

- The study includes a large single-center cohort of Western patients with gastroesophageal adenocarcinoma.
- The follow-up of the study was very long.
- The study population is very well characterized.
- Our study provides survival data not only for first-line treatment but also for later lines of therapy.

## Conclusion

This retrospective study provides robust data on treatment patterns and outcome in a large single-center cohort of Western patients with advanced gastroesophageal adenocarcinoma undergoing palliative systemic therapy before the widespread introduction of immunotherapy. Importantly, we could show that significant changes in terms of treatment intensity and treatment type over the last fifteen years did not translate into a significant improvement of OS from start of first-line therapy. In contrast, a significantly improved OS was shown for the subset of patients entering palliative second- and third-line therapy. Overall, the prognosis of patients with advanced gastroesophageal adenocarcinoma in need of palliative systemic therapy remains poor. Future real-world studies are necessary to investigate whether new therapy options including immune checkpoint inhibitors lead to improved outcome in an unselected study population.

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