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Gastric Cancer

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Gastric cancer is one of the common malignant diseases. As in other parts of the Western world, the age-standardized incidence has been steadily decreasing in Germany, Austria, and Switzerland over the past decades. Men are affected twice as often as women. A group of patients has a hereditary risk. Acquired risk factors include Helicobacter pylori infection of the gastric mucosa. Population-based endoscopic screening for the detection of early gastric cancer is currently not recommended for Germany.

The prognosis of the patient is mainly determined by the stage, but also by histology, general condition and comorbidity. In early and localized stages, the therapeutic approach is curative, in metastatic stages it is palliative. Therapeutic modalities are mainly surgery and systemic drug treatment. Despite some progress in the last 10 years, cancer-specific mortality is very high at 70%.

This guideline refers to adenocarcinoma of the stomach. Recommendations for tumors of the esophago-gastric junction can be found at Onkopedia Esophageal Cancer. Recommendations for therapy of adenocarcinomas of the esophago-gastric junction and esophagus are largely the same as those for gastric cancer. Recommendations for rarer, non-epithelial tumors of the stomach can be found in Onkopedia Gastrointestinal Stromal Tumors (GIST) *(German Version)* or Onkopedia Extranodal Marginal Zone Lymphomas *(German Version).*

2 Basics

2.1 Definition and basic information

Gastric adenocarcinomas arise in the proximal portions of the stomach (subcardiac), in the middle third (fundus and corpus), and in the distal stomach (antrum). Proximal gastric cancers often have an anatomic relationship to the esophago-gastric junction and are then also referred to as adenocarcinomas of the esophago-gastric junction type III (according to Siewert).

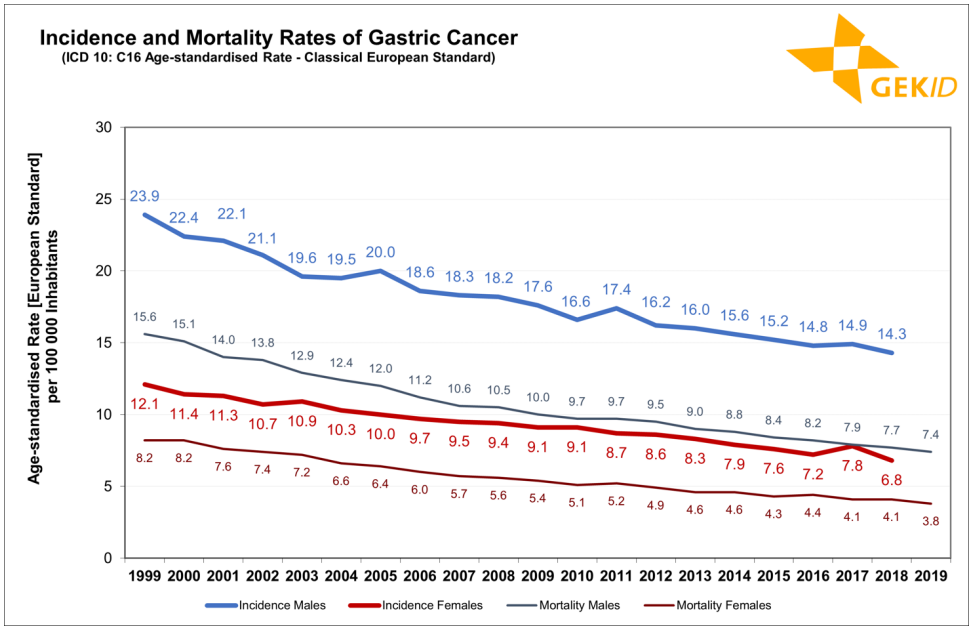
The guideline presented here refers to gastric cancers according to the current 8th edition of the TNM/UICC classification. The special features of adenocarcinomas of the esophago-gastric junction type I and type II according to Siewert, which are categorized as esophageal carcinomas according to the current TNM/UICC classification, are addressed here only in a cursory manner, as their clinical algorithms are distinct from gastric cancer.

2.2 Epidemiology

Annually, approximately 9,500 new cases of gastric cancer are diagnosed in men and approximately 6,000 new cases in women in Germany. This makes gastric cancer the tenth most common cancer in men, accounting for about 3.5% of all malignant tumor cases, and the ninth most common cancer in women, accounting for about 2.4%. In terms of cancer-related mortality, the relevance of gastric cancer is even higher. Gastric cancer accounts for about 3.5% of all cancer deaths in women and 4.2% in men. The median age of onset, 71 for men and 76 for women, is higher than that of cancer overall (70 years for men, 69 years for women). The median age at death is 74 years (men) and 78 years (women) (cancer total: 75 and 77 years). It can be assumed that there are about 33,000 patients in Germany whose diagnosis was made no more than five years ago, and 52,000 patients with a diagnosis in the last 10 years.

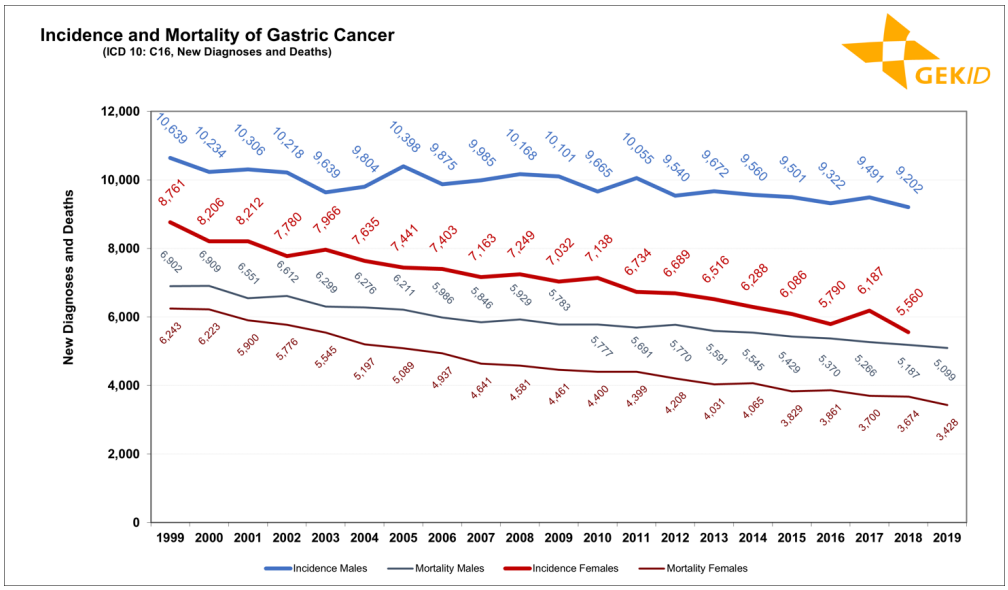
The age-standardized incidence rates, as well as the age-standardized mortality rates, have been decreasing for years in both sexes, see Figure 1. The age-standardized incidence rate in men has decreased by an average of 2.2% per year in the past 16 years - the mortality rate even by an average of 3.4% per year. The incidence rate in women has decreased by an average of 2.7% per year over the past 16 years, and the mortality rate by an average of 3.7% per year. Case rates and (crude) rates for males are about 60% higher than for females.

Figure 1: Estimated incidence and mortality rates of gastric cancer (ICD 10: C16) in Germany - age-standardized rates (old European standard) [1]



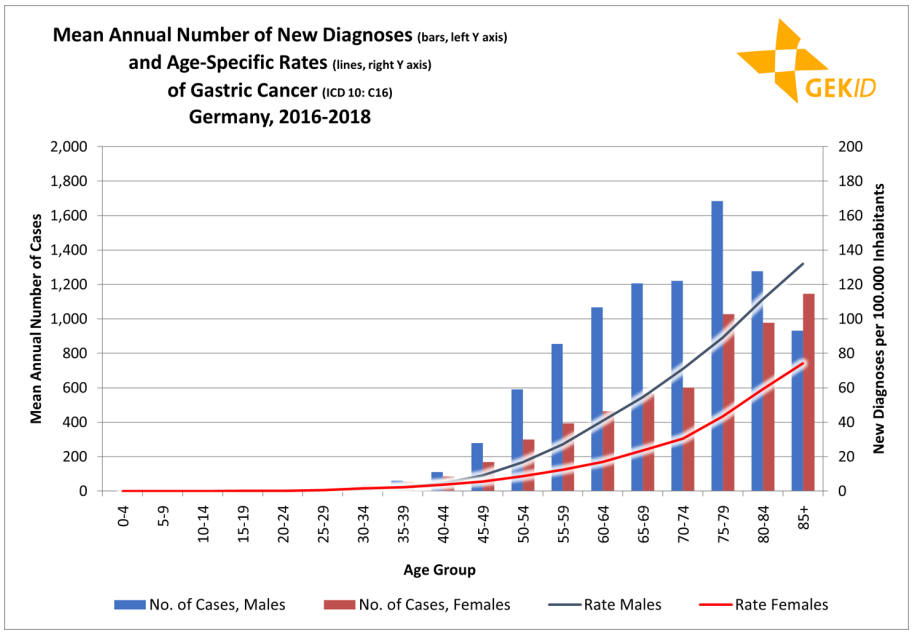
While age-standardized new case rates are a measure of disease probability and are largely independent of the population structure, the number of new cases reflects age structure and population size in addition to disease probability. Due to the shift in the age structure toward an older society and the reaching of the age cohorts of the baby boomers who are most likely to develop the disease, the courses of new cases and deaths differ from the courses of the rates. This shift is particularly evident in men. The number of cases of the disease is falling, but only by an average of 0.2% per year, despite a significant long-term decline in disease rates. The situation is similar for the number of deaths. Here, the number of men affected falls by an average of 1.2% per year, i.e., also less than the decline in mortality rates (3.4%). For women, too, the decline in the number of new cases (2.1% per year) or deaths (2.7% per year) is smaller than that of the corresponding rates. However, the difference is not quite as large (Figure 2).

Figure 2: Estimated incidence and mortality of gastric cancer (ICD 10: C16) in Germany - number of cases [1]



Most gastric cancers are diagnosed in men between 75 to 79 years of age, see Figure 3 (bars). From the age of 40 up to the age of 80, the number of new cases increases steadily. After that, it drops significantly. In women, the number increases almost continuously up to the highest age group. The highest risk of disease - i.e., the number of cases in relation to the underlying population per age group, see Figure 3 (lines) - is found in both sexes in the highest age group of 85 years and older. Case numbers and incidence rates of males exceed those of females in all age groups.

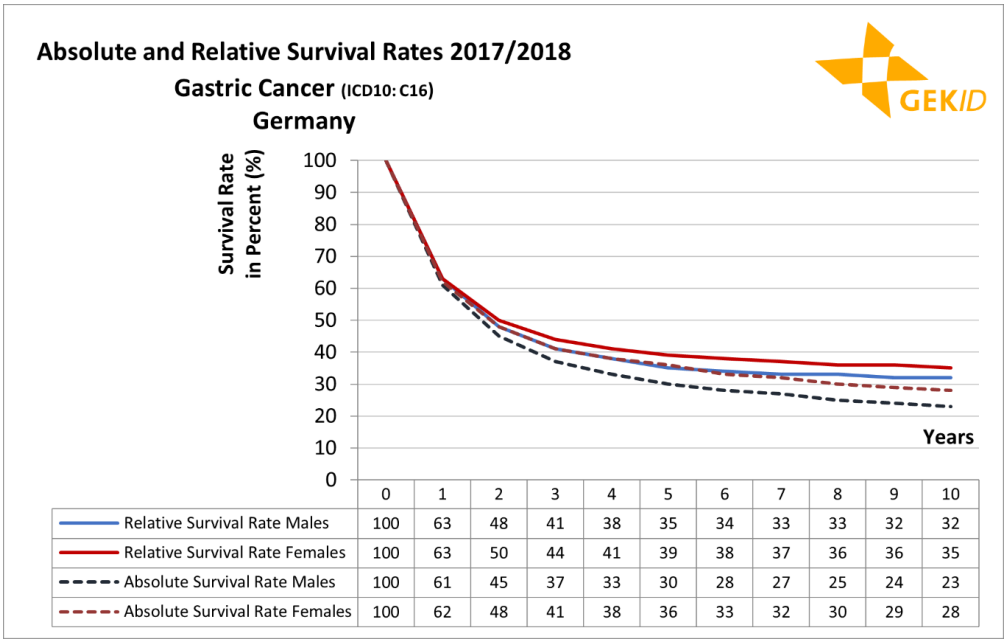
Figure 3: Age distribution of gastric cancer incidence (ICD 10: C16) - age-specific case numbers and rates [1]



The prognosis in gastric cancer is relatively unfavorable, especially in the first two years after diagnosis. Approximately 40% of patients die in the first year after diagnosis. The small difference between the absolute survival rate - that is, the percentage of patients who survive for a given time - and the relative survival rate – i.e., the ratio of absolute survival to expected survival in the general population - shows the excess mortality due to the cancer. From the fifth year after diagnosis, the gap between absolute and relative survival increases and, at the same time, relative survival is largely constant. This means that after about five years, there are no

or hardly any additional cancer-related deaths. Figure 4 presents the absolute and relative survival rates for the first 10 years after diagnosis. There is little difference between the sexes in terms of survival.

Figure 4: Absolute and relative survival rates in gastric cancer (ICD 10: C16) [1]



	0	1	2	3	4	5	6	7	8	9	10
Relative Survival Rate Males	100	63	48	41	38	35	34	33	33	32	32
Relative Survival Rate Females	100	63	50	44	41	39	38	37	36	36	35
Absolute Survival Rate Males	100	61	45	37	33	30	28	27	25	24	23
Absolute Survival Rate Females	100	62	48	41	38	36	33	32	30	29	28

If the current incidence of disease and the 14th coordinated population projection of the Federal Statistical Office (Statistisches Bundesamt) of Germany (G2L2W2, moderate development) are taken as a basis, an increase in the number of cases by about 30% to about 20,000 new cases (2050) can be expected in the next 30 years due to the shift in age structures of the population. In reality, however, the increase is likely to be smaller because of declining disease rates.

2.3 Pathogenesis

Gastric cancers - in analogy to carcinomas of the rest of the digestive tract - develop sequentially in multistage processes via precancerous intermediate stages and histologically defined lesions [2]. Unlike for Laurén's diffuse type, this stepwise process is well characterized for the intestinal type [3]. The clinical observation that gastric cancers are histologically heterogeneous in up to 30%, i.e., have both intestinal and diffuse components, underscores the importance of local factors of cellular microenvironment and genetic or epigenetic heterogeneity. Generally accepted, histologically graspable components of the sequential development of gastric cancer are: Helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, intraepithelial neoplasia (low- and high-grade), and gastric adenoma, which is rare in the Western Hemisphere.

2.4 Risk factors

The risk of developing gastric cancer is associated with the presence of the following risk factors [4]:

- Genetic
  - Hereditary colorectal carcinoma without polyposis (HNPCC, Lynch syndrome) [5]
  - Hereditary diffuse gastric carcinoma (HDGC) with mutations in the cadherin 1- (CDH-1) or catenin-alpha-1 (CTNNA1) gene [6, 7]
  - Peutz-Jeghers syndrome (mutation in the serine-threonine kinase gene [STK11]).

    - First-degree relatives with gastric cancer
    - Male gender (incidence males:females about 2:1)
    - Blood group A
- Acquired
    - Helicobacter pylori infection of the gastric mucosa
    - Epstein-Barr virus infection of the gastric mucosa
    - Inhalative tobacco use
    - Atrophic gastritis
    - Partial gastrectomy
    - Ménétrier's disease

Risk factors differ for the different anatomic locations. Distal gastric carcinomas are frequently found associated with Helicobacter pylori infection of the gastric mucosa, high-salt and low fruit and vegetable intake. Carcinomas of the esophago-gastric junction are more commonly associated with obesity and gastroesophageal acid reflux.

3 Prevention and early detection

3.1 Prevention

Helicobacter pylori eradication with the aim of gastric cancer prophylaxis is recommended in high-risk individuals, see also chapter 3.2.2. Currently, it is assumed that the timing of treatment is crucial for the efficiency of Helicobacter pylori eradication for the prevention of gastric cancer. This should occur before preneoplastic changes have not yet developed [8]. Data from randomized intervention trials are not available.

There is currently insufficient evidence for chemoprevention of gastric cancer, e.g., with nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, or acetylsalicylic acid [9].

3.2 Early detection

3.2.1 Population

Since Germany/Austria/Switzerland are no high-incidence regions for gastric cancer, it seems unlikely that population-based screening would be cost-effective. However, a study explicitly testing cost-effectiveness under conditions in German-speaking Central Europe has not yet been conducted. Population-based endoscopic screening for the detection of early gastric cancer is currently not recommended in the countries mentioned.

3.2.2 Persons at risk

If more than one first-degree relative has gastric cancer, the risk is increased approximately 10-fold [10]. Nevertheless, a scientifically sound recommendation for screening endoscopy in individuals with a positive family history cannot be given. There is currently no scientific evidence for a benefit of specific preventive measures in close relatives of patients with gastric cancer [11]. However, H. pylori eradication in first-degree relatives of gastric cancer patients is recommended [12].

Individuals with evidence of pathogenic CDH1 gene mutations should be offered prophylactic gastrectomy, if they have a positive family history of hereditary diffuse gastric carcinoma [11]. Current knowledge on the penetrance of pathogenic CTNNA1 mutations is still limited, so that a clear recommendation for prophylactic gastrectomy cannot be given at present. At least, close endoscopic surveillance should be advised. Individual consultation in a specialized center is recommended [13, 14].

4 Clinical characteristics

4.1 Symptoms

Early gastric carcinomas are generally asymptomatic. The following symptoms may be observed in locally advanced or metastatic carcinomas [15]:

- Dysphagia
- Dyspepsia
- Recurrent vomiting
- Loss of appetite
- Early feeling of satiety
- Weight loss
- Signs of gastrointestinal bleeding
- Epigastric pain
- Symptoms from metastatically affected organs (such liver capsule pain or ileus symptoms in peritoneal carcinomatosis)

Gastric cancer may present with various paraneoplastic syndromes, with cutaneous manifestations being observed more frequently than others [16].

5 Diagnosis

5.2 Diagnosis

5.2.1 Initial diagnosis

Endoscopy is considered the most sensitive and specific diagnostic method. Using high-resolution video-assisted endoscopy, it is possible to detect even discrete changes in color, mucosal surface, and architecture of the gastric mucosa. Endoscopic detection of early lesions can be improved by chromoendoscopy.

The aims of further diagnostics are to determine the stage of the disease and to guide therapy, see Table 1.

Table 1: Diagnostic procedures and staging in gastric cancer

Investigation	Note
Physical examination	
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation
Endoscopy upper gastrointestinal tract	Optional addition of chromoendoscopy
Endoscopic ultrasound examination (EUS) [1]	For therapy planning in case of localized disease
Computed tomography of thorax, abdomen and pelvis with oral and intravenous contrast media	For visualization of locoregional and distant tumor spread
Abdominal ultrasound	Complementary to computed tomography
Laparoscopy, if indicated plus cytology[2]	In cT2/cT3/cT4 without evidence of other distant metastases, to detect/exclude peritoneal metastasis

Legend:
[1] see Chapter 5.2.3.1
[2] Laparoscopy with cytologic examination of the lavage samples helps to detect clinically occult metastasis to the peritoneum in locally resectable tumors. The detection of macroscopic peritoneal metastasis has immediate implications for treatment planning [17]. Cytologic evidence of malignant cells in the lavage samples is an unfavorable prognostic factor, but - outside of clinical studies - has no definite impact on treatment recommendation to date. Laparoscopically abnormal findings are more frequently found in T3/T4 classified tumors [18]

5.2.2 Histology and subtypes

Histologic diagnosis of gastric cancer should be made from a biopsy, which is evaluated by two experienced pathologists [11].

5.2.2.1 Laurén classification

Histologically, gastric cancer is characterized by a strong heterogeneity, as several different histological features may be present in one tumor. Over the past decades, histologic classification has been based on the Laurén classification [19]:

- Intestinal type, approximately 54%
- Diffuse type, approx. 32
- Indeterminant, approx. 15%

The diffuse subtype is found more in women and people of younger age, while the intestinal type is more common in men and people of older age and is associated with intestinal metaplasia and Helicobacter pylori infection [20].

5.2.2.2 World Health Organization (WHO) classification of gastric cancer

The World Health Organization (WHO) classification distinguishes four definitive types of gastric cancer [21]:

- Tubular
- Papillary
- Mucinous
- Poorly cohesive (including signet ring cell carcinoma).

The classification is based on the predominant histologic pattern of the carcinoma, which often coexists with less dominant features or other histologic patterns.

5.2.2.3 The Cancer Genome Atlas (TCGA) Classification

Molecular genetic studies divide gastric cancer into molecular subtypes based on studies of the genome, transcriptome, epigenome, and proteome. The most popular molecular subtyping according to TCGA distinguishes four subtypes [22]:

- Chromosomal instability - CIN
- Epstein-Barr virus-associated - EBV
- Microsatellite instability - MSI
- Genomically stable - GS

This classification currently has limited impact on treatment selection.

5.2.3 Stages and staging

5.2.3.1 TNM Staging

The classification of the extent of the primary tumor and metastasis is based on the UICC/AJCC TNM criteria [19, 21, 23]. Since January 1, 2017, the 8th edition has been used in Europe [21]. The TNM criteria are summarized in Table 2, and the staging is summarized in Table 3.

Table 2: UICC-TNM classification of gastric cancer [21]

Classification	Tumor
T	**Primary tumor**
T1	Superficial infiltrating tumor
T1a	Tumor infiltrating lamina propria or muscularis mucosae
T1b	Tumor infiltrating submucosa
T2	Tumor infiltrating muscularis propria
T3	Tumor infiltrating subserosa without invasion of visceral peritoneum
T4a	Tumor penetrating subserosa (visceral peritoneum)
T4b	Tumor infiltrating adjacent structures
N	**Regional lymph nodes**
N0	No regional lymph node metastases
N1	Metastases in 1 - 2 lymph nodes
N2	Metastases in 3 - 6 lymph nodes
N3a	Metastases in 7 - 15 lymph nodes
N3b	Metastases in 16 or more lymph nodes
M	**Distant metastases**
M0	No distant metastases
M1	Distant metastases or positive peritoneal cytology

Table 3: Classification of tumor stages [21]

UICC stage	Primary tumor	Lymph nodes	Distant metastases
0	Tis	N0	M0
IA	T1a T1b	N0 N0	M0 M0
IB	T2 T1	N0 N1	M0 M0
IIA	T3 T2 T1	N0 N1 N2	M0 M0 M0
IIB	T4a T3 T2 T1	N0 N1 N2 N3	M0 M0 M0 M0
IIIA	T4a T3 T2	N1 N2 N3	M0 M0 M0
IIIB	T4b T4a T3	N0/1 N2 N3	M0 M0 M0
IIIC	T4b T4a	N2/3 N3	M0 M0
IV	Any T	Any N	M1

Endosonography (EUS) is particularly suitable for determining the clinical T category, as it can best visualize the different layers of the gastric wall. EUS should therefore be part of primary staging in a patient with a curative therapeutic approach.

The following characteristics serve to identify malignant lymph nodes on CT slice imaging [24]:

- Diameter ≥ 6-8 mm (shorter axis) in perigastric lymph nodes
- Round shape
- Central necrosis
- Loss of the fat hilus
- Heterogeneous or enhanced contrast agent uptake

The sensitivity of CT for lymph node staging is variably estimated at 62.5-91.9% in systematic reviews [25].

EUS improves the accurate determination of the T and N categories and can help determine the proximal and distal margins of the tumor. EUS is less accurate for tumors of the antrum. EUS is considered more accurate than CT in diagnosing malignant lymph nodes.

Signs of malignancy on EUS include [26]:

- Hypoechoic
- Round shape
- Blurred demarcation from the surrounding area
- Size in the longest diameter > 1cm

6 Therapy

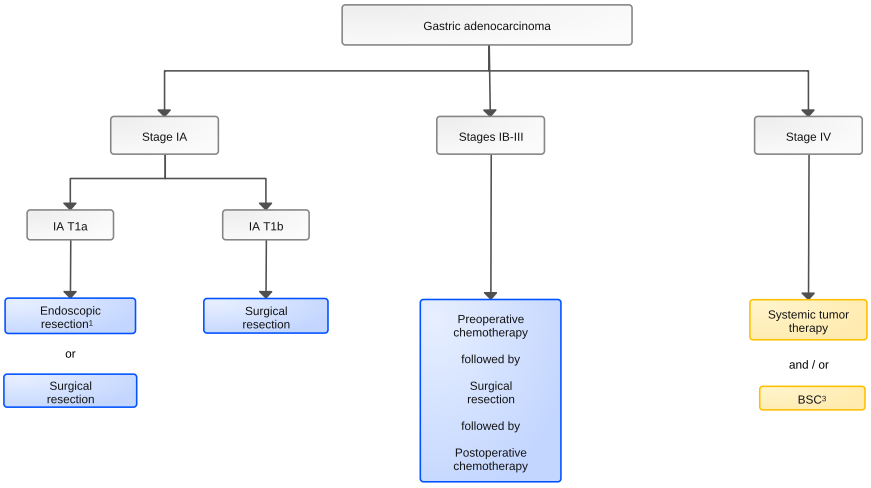
6.1 Therapy structure

Multidisciplinary planning is required for any initial treatment recommendation. It should be developed in a qualified multidisciplinary tumor board.

Core members of the multidisciplinary board include the following disciplines: Visceral Surgery, Medical Oncology, Radiation Oncology, Gastroenterology, Radiology and Pathology. Whenever possible, patients should be treated in clinical trials.

Therapy is stage-adapted. A treatment algorithm for first-line therapy is shown in Figure 5.

Figure 5: Algorithm for first-line therapy of gastric adenocarcinoma



Legend:
curative intended therapy; non-curative intended therapy;
[1] see Table 4
[2] Best Supportive Care

6.1.1 Stage IA - T1a (early carcinoma)

Since the probability of lymph node metastasis in mucosal gastric cancer (T1a) is very low, endoscopic resection (ER) may be sufficient [27]. If histopathologic workup after endoscopic resection reveals that tumor infiltration extends into the submucosa (T1b), surgical resection with systematic lymphadenectomy should be performed, as lymph node metastases may already be present in up to 30% of cases.

Gastric cancers classified as pT1a cN0 cM0 should be treated with endoscopic resection, considering the adapted Japanese criteria, if the following criteria are met [11, 28], see Table 4.

Table 4: Criteria for endoscopic resection in stage IA T1a [11, 107]

- Lesions ≤ 2 cm in elevated types
- Lesions ≤ 1 cm in flat types
- Histological degree of differentiation good or intermediate (G1/G2)
- No macroscopic ulceration
- Invasion limited to the mucosa
- No residual tumor after endoscopic resection

Early gastric cancers with a maximum of one "extended criterion" can also be curatively resected endoscopically [11]. Endoscopic submucosal dissection (ESD) should be used for

resection. If more than one extended criterion is present, oncologic surgical resection should be performed. The extended criteria are defined as:

- Differentiated mucosal carcinoma (G1/G2) without ulceration and size > 2cm
- Differentiated mucosal carcinoma (G1/G2) with ulceration and size < 3cm
- Well-differentiated carcinomas (G1/G2) with submucosal invasion < 500µm and size < 3cm
- Poorly differentiated mucosal carcinoma (G3/G4) < 2cm in diameter (unless there is histological evidence of tumor cells at a distance ≤ 1cm [11]).

ER of early gastric cancer is performed as an en-bloc resection. It allows complete histological assessment of the lateral and basal margins. The recommended endoscopic control intervals are 3 months in the first and 6 months in the second year of follow-up. Thereafter, controls should be performed annually. Local recurrences after ER of early gastric cancer can be treated endoscopically if relapse is confined to the mucosal (rT1a cN0 cM0). A (limited) surgical approach is an alternative.

6.1.2 Stage IA - T1b

For stage IA gastric cancer with infiltration of the submucosa, the risk of lymph node metastases is 25-28%. The 5-year survival rate is 70.8% for all stage IA in the SEER database [29], and the cancer-specific survival rate at 10 years is 93% in the Italian IRGGC analysis. Therapy of choice in stage I (T1b category) is radical surgical resection (subtotal, total, or transhiatal extended gastrectomy). Limited resection can be recommended only in exceptional cases due to the imprecise accuracy of pretherapeutic staging.

A benefit from perioperative or adjuvant chemotherapy has not been established for stage IA (T1b) patients.

6.1.3 Stage IB - III

In stage IB - III, resection should consist of radical resection (subtotal, total, or transhiatal extended gastrectomy) in combination with D2- lymphadenectomy. Subtotal gastrectomy can be performed if safe free tumor margins can be achieved. The previously recommended tumor-free margins of 5 and 8 cm for intestinal and diffuse tumor growth types, respectively, are no longer accepted. The scientific evidence for definitve recommendations is low. A negative oral margin in the intraoperative frozen section is crucial.

Perioperative chemotherapy with a platinum derivative, a fluoropyrimidine, and an anthracycline significantly prolonged overall survival in patients with resectable gastric cancer in the MAGIC trial [30]. In the French FNCLCC / FFCD multicenter study, perioperative chemotherapy with a platinum derivative and a fluoropyrimidine without anthracycline showed a comparable effect size on improving survival [31]. Currently, neither chemotherapy regimen is the first choice.

Treatment according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) further improved progression-free survival (hazard ratio, HR 0.75) and overall survival (HR 0.77) in patients with stage ≥ cT2 and/or cN+ compared with therapy analogous to MAGIC; see also chapter 6.2.3.1 The relatively higher efficacy of FLOT was shown to be consistent across relevant subgroup analyses such as age, histology, and tumor location. The rate of perioperative complications was comparable [32].

For patients with gastric cancer ≥ stage IB who received resection without prior chemotherapy (e.g., due to misdiagnosed tumor stage prior to surgery), adjuvant chemotherapy may be recommended, see chapter 6.2.3.1.

In HER2-positive tumors, a benefit from combining perioperative chemotherapy with a HER2 antibody in the perioperative setting in terms of overall survival has not been proven and therefore cannot be recommended outside of clinical trials. The AIO-PETRARCA phase 2 study showed a higher histopathologic remission rate when FLOT chemotherapy was combined with trastuzumab + pertuzumab and a trend in favor of better progression-free and overall survival [121]. These data require validation in larger and independent cohorts.

In microsatellite instability (MSI-H) localized gastric carcinoma, the efficacy of perioperative chemotherapy, based on retrospective data analyses [35], has been controversially discussed. However, more recent data from the DANTE trial show that complete and subtotal tumor remissions can be achieved with FLOT chemotherapy even in MSI-H subtype gastric carcinomas [35, 36]. Thus, according to the current status, perioperative chemotherapy with the FLOT regimen remains indicated for MSI-H gastric cancers if tumor response is pursued. The FFCD-NEONIPIGA phase 2 study showed a high histopathologic remission rate after 12 weeks of therapy with nivolumab + ipilimumab without chemotherapy in resectable MSI-H cancers [122]. Data require validation in larger and independent patient cohorts.

After R1 resection, adjuvant radiochemotherapy may be considered, see chapter 6.2.2.1.

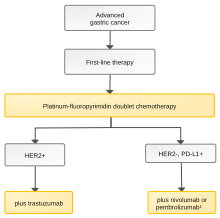
6.1.4 Stage IV

The aim of therapy is usually non-curative. The first priority is systemic drug therapy, supplemented in individual cases by local therapeutic measures. Active symptom control and supportive measures such as nutritional counseling, psychosocial support, and palliative care are an integral part of treatment. The prognosis of patients with locally advanced and irresectable or metastatic (pooled here as "advanced") gastric cancer is unfavorable. Studies evaluating the benefit from chemotherapy have shown a median survival of less than one year [35]. However, there is evidence that chemotherapy can prolong the survival of patients with advanced gastric cancer compared to best supportive therapy alone and maintain quality of life longer [36].

6.1.4.1 Systemic tumor therapy

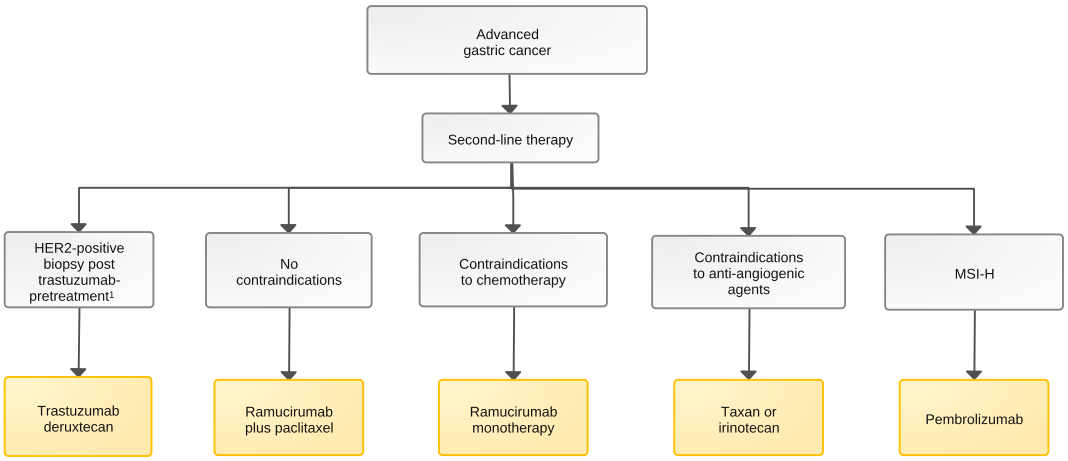
The current recommended algorithms for drug tumor therapy of patients with advanced gastric cancer are shown in Figure 6, Figure7, and Figure 8.

Figure 6: Algorithm for first-line therapy of advanced gastric cancer



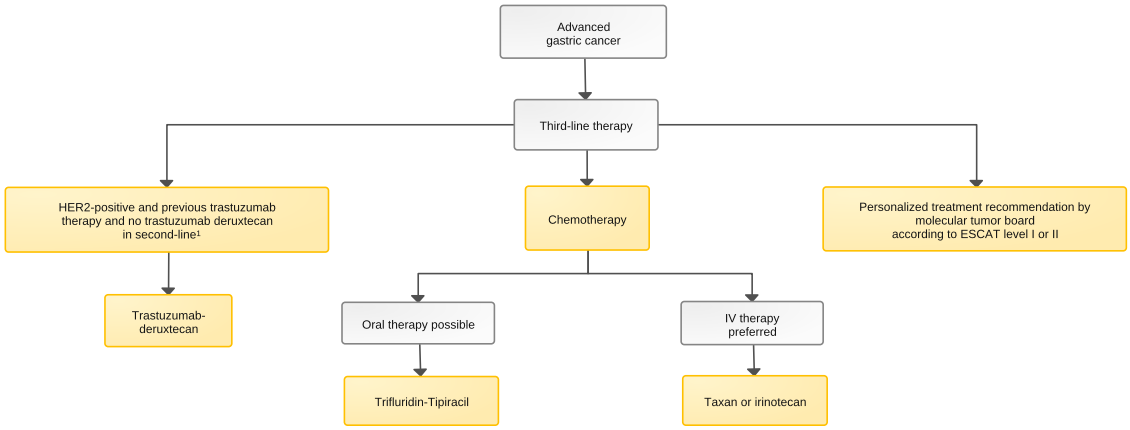
Legend:
[1] Nivolumab is approved in Europe for PD-L1 CPS ≥ 5 according to Checkmate-649; pembrolizumab is approved in Europe for adenocarcinoma of the esophagus and esophago-gastric junction for PD-L1 CPS ≥ 10 according to Keynote-590. Positive phase III trial results in patients with PD-L1 CPS-positive gastric cancer were also reported from Keynote-859

Figure 7: Algorithm for second-line therapy of advanced gastric cancer



Legend:
[1] Since many tumors lose HER2 overexpression after trastuzumab failure, reassessment of HER2 status using a fresh biopsy is recommended prior to second-line trastuzumab deruxtecan (T-DXd) therapy

Figure 8: Algorithm for third-line therapy of advanced gastric cancer



Legend:
[1] According to the Destiny Gastric 01 study, re-testing of HER2 status is not mandatory for third-line T-DXd therapy

6.1.4.1.1 First-line chemotherapy, molecular targeted therapy, and immunotherapy

6.1.4.1.1.1 Chemotherapy

The standard of care for first-line chemotherapy of advanced gastric cancer is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with a more favorable side effect profile for oxaliplatin. This may contribute to a trend toward better efficacy, especially in patients > 65 years [37, 23]. Fluoropyrimidines can be administered as infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparably effective to infused 5-FU [38, 41]. Capecitabine is approved in combination with a platinum derivative and has been studied with both cis- and oxaliplatin in European patients. S-1 is established as a standard of care in Japan and approved in Europe for palliative first-line therapy in combination with cisplatin. Infused 5-FU should be preferred over oral medications in patients with dysphagia or other feeding problems. In elderly or frail patients, results of the phase III GO-2 trial support a dose-reduced application of oxaliplatin-fluoropyrimidine chemotherapy (to 80% or 60% of the standard dose from the beginning), resulting in fewer side effects with comparable efficacy [42].

The addition of docetaxel to a platinum-fluoropyrimidine combination (three-weekly DCF regimen) improved radiographic response rates and prolonged overall survival in a historical phase III trial, but also resulted in significantly increased side effects [43]. Other phase II trials examined modified docetaxel-platinum-fluoropyrimidine triplets showed reduced toxicity compared with DCF in some cases [46, 49]. However, the higher response rate of a triplet (37% versus 25% [43] does not translate into prolonged survival in recent trials, which included effective second-line regimens. In the phase III JCOG1013 trial, patients with advanced gastric cancer received either cisplatin plus S-1 or cisplatin plus S-1 and docetaxel. There were no differences in radiographic response, progression-free survival, or overall survival [48]. Therefore, with increased toxicity and uncertain impact on overall survival, no recommendation can be made for first-line docetaxel-platinum-fluoropyrimidine therapy, so that a platinum-fluoropyrimidine doublet remains the standard approach. In individual cases, e.g., when fast tumor regression is urgently required, first-line therapy with a platinum-fluoropyrimidine-docetaxel triplet may be indicated.

Irinotecan-5-FU has been compared with cisplatin-5-FU and with epirubicin-cisplatin-capecitabine in randomized phase III trials and showed comparable survival with controllable side effects [49, 50]. Irinotecan-5-FU can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to scientific evidence, however, irinotecan has no approval in Europe for gastric cancer.

6.1.4.1.1.2 HER2-positive gastric cancer

HER2 positivity is defined in gastric cancer as the presence of protein expression with immunohistochemistry score [IHC] of 3+ or IHC 2+ and concomitant gene amplification on in situ hybridization [ISH], HER2/CEP17 ratio ≥ 2.0. HER2 diagnosis should be quality-controlled [51, 52]. Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer [36, 53]. The recommendation is based on data from the phase III ToGA trial, showing a higher response rate and prolonged survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy versus chemotherapy alone using the above selection criteria; the additional trastuzumab side effects are minor and controllable [53]. Combinations of trastuzumab and oxaliplatin plus fluoropyrimidine show comparable results to the historical cisplatin-containing ToGA regimen [54, 56].

6.1.4.1.1.3 Immunotherapy

The phase III CheckMate 649 trial evaluated the addition of nivolumab to chemotherapy (capecitabine-oxaliplatin or 5-FU/folinic acid-oxaliplatin) in patients with reviously untreated gastric, esophago-gastric junction, or esophageal adenocarcinoma [57]. The study included patients regardless of tumor PD-L1 status; the dual primary endpoints were overall survival and progression-free survival. Approximately 60% of the study population had tumors with a PD-L1 CPS ≥ 5. Nivolumab plus chemotherapy yielded a significant improvement over chemotherapy alone in overall survival (14.4 vs 11.1 months, HR 0.71 [98.4% CI 0.59-0.86]; p < 0.0001) and progression-free survival (7.7 vs. 6.0 months, HR 0.68 [98% CI 0.56-0.81]; p < 0.0001) in patients with a PD-L1 CPS ≥ 5.

The Asian phase II/III ATTRACTION-04 trial also showed a significant improvement in progression-free survival with nivolumab and first-line chemotherapy, but with no significant improvement in overall survival compared to first-line chemotherapy alone. The most likely reason for the lack of survival benefit (> 17 months in both arms) is that many patients received post-progression therapies including immunotherapy after first-line therapy [58].

The multinational randomized phase III Keynote 859 trial included 1589 patients with advanced incurable gastric cancer. Patients received either platinum-fluoropyrimidine plus pembrolizumab or the same chemotherapy plus placebo every 3 weeks. Overall survival was prolonged in the pembrolizumab group (HR 0.78 [95% CI 0.70-0.87], $p < 0.0001$). The effect was

most pronounced in the subgroup with a PD-L1 CPS ≥ 10 (HR 0.64), whereas efficacy was lower for CPS < 10 (HR 0.86) [123]. The results thus complement the positive trial data from the phase III Keynote 590 study, which led to EU approval of pembrolizumab in combination with platinum-fluoropyrimidine chemotherapy for adenocarcinoma of the esophagus and esophagogastric junction [124].

Positive phase III trial data were also presented on two immune checkpoint (PD-1) inhibitors not currently approved in Europe. Sintilimab in combination with oxaliplatin and capecitabine improved overall survival in the phase III ORIENT-16 trial [125]. In the phase III Rationale-305 study, tislelizumab prolonged overall survival in combination with platinum-fluoropyrimidine or platinum-investigator-choice chemotherapy in patients with a positive PD-L1 score. PD-L1 was evaluated according to a scoring system not yet established internationally (the so-called Tumor Area Proportion score, TAP) [126]. ORIENT-16 and Rationale-305 have not been fully published to date, but support the overall assessment that PD-1 immune checkpoint inhibitors can improve the efficacy of chemotherapy (depending on PD-L1 expression).

6.1.4.1.1.4 Claudin 18.2

Data from the multinational phase III Spotlight trial were recently presented. These show that in patients with advanced irresectable gastric cancer and tumor claudin18.2 expression in ≥ 75% of tumor cells, zolbetuximab, a chimeric monoclonal IgG1 antibody directed against claudin18.2, in combination with FOLFOX chemotherapy prolongs overall survival (median 18.23 vs. 15.54 months, HR 0.750, p = 0.0053). The main side effects of zolbetuximab are nausea and vomiting, especially during the first applications [127]. The results of the phase III Spotlight trial are largely confirmed by the multinational phase III GLOW trial, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab [128]. It remains to be seen whether the European Medicines Agency will grant approval to zolbetuximab in patients with claudin 18.2-positive metastatic and previously untreated gastric cancer.

6.1.4.1.2 Second-line and third-line therapy

6.1.4.1.2.1 Chemotherapy and anti-angiogenic therapy

Figure 7 and Figure 8 show the algorithm for second- and third-line therapy for patients with advanced gastric cancer. The evidence-based chemotherapy options in this setting are paclitaxel, docetaxel, and irinotecan, which have comparable efficacy with different specific toxicities [59, 62]. Irinotecan may be preferred in patients with preexisting neuropathy, however, there is no EU approval. 5-FU/folinic acid plus irinotecan (FOLFIRI) is also occasionally used, but the scientific evidence for its use in second- and third-line treatment is limited [63]. Ramucirumab plus paclitaxel is the recommended standard for second line therapy and is approved in the EU. The addition of the anti-vascular endothelial growth factor receptor-2 (VEGFR-2) antibody ramucirumab to paclitaxel increases tumor response rates and prolongs progression-free and overall survival according to the results of the phase III RAINBOW trial [64]. Already in the phase III REGARD trial, ramucirumab monotherapy showed prolonged survival compared to placebo, albeit with a low radiological response rate [65].

6.1.4.1.2.2 Immunotherapy in second- and third-line therapy

In the phase III KEYNOTE-061 trial, pembrolizumab monotherapy did not show prolonged overall survival compared with chemotherapy [64]. However, an exploratory subgroup analysis recognized a clear benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric cancer [67]. Therefore, PD-1 inhibition is recommended in advanced MSI-H carcinomas at the latest in second-line treatment. Pembrolizumab has European approval for this indication based on the

Keynote-061 and Keynote-158 trials [68]. Other biomarkers, particularly EBV and tumor mutation burden, are also discussed as predictive factors for PD-1 immune checkpoint inhibitor efficacy [69, 71]. However, the evidence to date is insufficient to support a positive recommendation for immunotherapy based upon the presence of these biomarkers.

6.1.4.1.2.3 HER2-targeted therapy

Studies evaluating trastuzumab, lapatinib, and trastuzumab emtansine for second-line treatment in patients with HER2-positive carcinomas were negative [72, 75]. Therefore, these drugs should not be used in gastric cancer outside of clinical trials. A randomized phase II trial showed an improvement in tumor response rate and overall survival for the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) compared with standard chemotherapy in patients with pretreated HER2-positive advanced gastric cancer [76].

Prerequisits for inclusion in the Destiny-GC-01 study were at least two prior lines of therapy, prior treatment with a platinum derivative, a fluoropyrimidine, and trastuzumab, and previously confirmed HER2 positivity. The study was recruited exclusively in East Asia. The results of Destiny-GC-01 were largely confirmed in the single-arm phase II Destiny-GC-02 trial, which included non-Asian patients in second-line therapy. Mandatory was platinum-fluoropyrimidine-trastuzumab pretreatment and confirmed HER2 positivity of the tumor in a recent re-biopsy before initiating T-DXd therapy [129].

The EU approval includes the following indication of T-DXd: monotherapy for the treatment of adult patients with advanced HER2-positive adenocarcinoma of the stomach or esophago-gastric junction who have received a prior trastuzumab-based regimen.

We recommend, according to the classically established HER2 diagnostic criteria, to check the HER2 status prior to therapy with T-DXd, especially if use in second-line therapy is planned, where a valid alternative with paclitaxel-ramucirumab is available. This recommendation is based on the inclusion criteria of the Destiny-GC-02 trial and the knowledge that loss of HER2 status occurs in approximately 30% of gastric cancers after first-line therapy with trastuzumab [72].

There is initial evidence of efficacy of T-DXd in low HER2 expression [130]. However, data are not yet sufficient to recommend its use.

6.1.4.1.2.4 Third-line therapy

For the treatment of patients with advanced gastric cancer in the third-line and beyond, the best evidence is available for trifluridine-tipiracil (FTD/TPI) based on the phase III TAGS trial. Median overall survival with FTD/TPI versus placebo was significantly improved in the overall patient cohort, in the third-line cohort, and in the fourth-line cohort [77, 79]. Therefore, if oral therapy is feasible, trifluridine-tipiracil (FTD/TPI) should be used; alternatively, if intravenous therapy is preferred, irinotecan or a taxane can be given, if not already used in a previous line of therapy. As shown above, T-DXd is a very effective third-line therapy for HER2-positive carcinoma after trastuzumab pretreatment. Nivolumab also proved to be effective; however, the data from the ATTRACTION-03 trial were obtained exclusively in Asian patients [80], so that nivolumab in the third line of treatment in patients with advanced gastric cancer does not have EMA approval and therefore cannot be recommended.

Following the recommendation of a molecular tumor board, an unapproved therapeutic option may also be preferred in justified cases, especially if the recommendation can be based on an ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) level I or II [81].

6.1.4.1.3 Surgery for metastatic gastric cancer

The randomized phase III REGATTA trial showed that gastrectomy in addition to chemotherapy for metastatic disease did not confer a survival benefit compared with chemotherapy alone [84]. International data analyses show that surgical therapy for oligometastasic disease is increasingly perceived as a treatment option [83, 85]. The AIO-FLOT3 phase II trial reported results on the feasibility of resection for stage IV gastric cancer and survival in highly selected patients with oligometastatic disease that was without primary progression on FLOT chemotherapy [86]. The potential prognostic benefit of resections for oligometastatic gastric cancer is currently being evaluated in randomized phase III trials [RENAISSANCE (NCT0257836) and SURGIGAST (NCT03042169)].

In a Delphi procedure, a definition for oligometastasis was determined in a European expert group (OMEC). According to this definition, oligometastasis can be defined as the following phenotypes: 1-2 metastases in either liver, lung, retroperitoneal lymph nodes, adrenal glands, soft tissue or bone [85].

6.1.4.1.4 Supportive therapy and nutrition

It is recommended that nutritional and symptom screening with appropriate tools be performed regularly in all patients with advanced gastric cancer, and appropriate supportive therapies be derived. A study from China showed that early integration of supportive-palliative care is effective and suggests a survival benefit in patients with advanced gastric cancer [87].

Weight loss is a multifactorial phenomenon and may be due to digestive tract obstruction, malabsorption, or hypermetabolism. Clinical data sets show that weight loss of ≥ 10% before chemotherapy or ≥ 3% during the first cycle of chemotherapy is associated with poorer survival [88]. Also, a change in body composition with impaired muscular capacity was shown to be prognostically unfavorable in patients with advanced gastric cancer [79]. The modified Glasgow Prognostic Score (serum CRP and albumin) can be used to assess the extent of sarcopenia and the prognosis of patients with advanced gastric cancer [90].

From this, it can be concluded that screening for nutritional status should be performed in all patients with advanced gastric cancer (for example, using Nutritional Risk Screening, NRS) [91] and expert nutritional counseling and co-supervision should be offered, if nutritional deficiency is evident.

Dysphagia in proximal gastric cancer can be improved with radiotherapy or stent insertion [92]. Single-dose brachytherapy is the preferred option at some centers and results in longer-lasting symptom control and fewer complications than stent insertion. Stenting is needed for severe dysphagia and especially in patients with limited life expectancy, as the effects of the stent are immediate, whereas radiotherapy improves dysphagic symptoms only after approximately 4-6 weeks [93]. If radiotherapy or a stent are not an option, enteral nutrition via naso-gastric, naso-jejunal, or percutaneously placed feeding tubes may provide relief [94]. The indication for parenteral nutrition follows generally accepted guidelines.

6.2 Therapeutic modalities

6.2.1 Resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for resection of early carcinomas. The criteria for ER are described above (chapter 6.1.1). Methods include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR of early gastric carcinoma is performed as an en-bloc resection. It allows complete histologic assessment of the lateral and basal margins. The recommended endoscopic control intervals are 3 months in the first year and 6 months in the second year. Thereafter, controls should be performed annually. Local recurrences after ER of early gastric carcinoma can be treated endoscopically, if relapse is confined to the mucosa (rT1a cN0 cM0). A (limited) surgical approach is an alternative, see Table 4.

6.2.1.2 Gastrectomy and lymphadenectomy

Surgery of the primary tumor is essential for curative therapy. The goal of surgery is to achieve an R0 situation.

Regarding lymphadenectomy, a consensus has been reached in the Western world that patients with normal surgical risks should undergo D2 lymphadenectomy. D1 resection includes removal of the perigastric lymph nodes; D2 lymphadenectomy includes additional removal the lymph nodes along the A. gastrica sinistra artery, A. hepatica communis artery, splenic artery, and coeliac axis [95]. Long-term results of a randomized trial from the Netherlands showed a lower local recurrence rate and better cancer-specific survival after D2 versus D1 lymphadenectomy [96]. The current UICC/AJCC TNM (8th edition) classification recommends removal and examination of at least 15 lymph nodes for reliable staging [21]. In the current German S3 guideline on gastric cancer, removal of at least 25 lymph nodes is considered adequate [11].

Surgery should be performed at a certified *high-volume* center with adequate surgical expertise and perioperative care [11]. Numerous studies demonstrate better short-term and long-term survival for patients treated at centers with proven expertise [98, 100]. Perioperative morbidity and mortality should not exceed 15% and 3%, respectively [101]. The concept of "enhanced recovery" is presented in the Enhanced Recovery After Surgery (ERAS®) Society Guidelines and encompasses all aspects of optimized perioperative care [102].

In patients after gastrectomy, regular substitution of vitamin B12 is required for life. After Roux-Y reconstruction, pancreatic enzyme substitution is indicated.

6.2.2 Radiotherapy

6.2.2.1 Adjuvant radiochemotherapy

The North American Intergroup-0116 trial showed that adjuvant therapy with 5- FU/folinic acid plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) improved overall survival compared with surgery alone (50% vs. 41% 3-year survival [66, 103]). This therapy was therefore recommended as a standard of care in North America. It did not find acceptance in Germany and Europe because of inadequate surgical quality within the INT-0116 trial. This reluctance is justified by the randomized controlled phase III CRITICS trial, which suggested that

adjuvant radiochemotherapy reduces the local recurrence rate after D1 lymphadenectomy, but shows no benefit after D2 lymphadenectomy [104].

The results of the Dutch-Scandinavian CRITICS trial show that adjuvant radiochemotherapy after neoadjuvant chemotherapy and quality-assured surgery does not confer a survival benefit [105]. The ARTIST-2 trial conducted in Korea also failed to find value for adjuvant radiochemotherapy compared with adjuvant chemotherapy with a platinum-fluoropyrimidine doublet in adequately (D2 lymphadenectomy) and curatively (R0) resected patients with gastric cancer and positive nodal tumor status [106].

In patients with R1 resection, retrospective studies suggest that adjuvant radiochemotherapy may improve prognosis [100, 107]. Therefore, in individual cases, after weighing the benefits against the potential risks and burdens, adjuvant radiochemotherapy may be considered in the presence of R1 status.

6.2.3 Systemic tumor therapy

6.2.3.1 Anticancer Agents

6.2.3.1.1 Cisplatin

In combination with other cytostatic drugs, cisplatin is part of the standard of care in perioperative and palliative therapy. In palliative therapy, cisplatin in combination with fluoropyrimidines achieves remission rates of up to 30%. Specific severe side effects (grade 3/4) include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte shifts, and diarrhea.

6.2.3.1.2 Docetaxel

Docetaxel belongs to the taxanes. Docetaxel is an effective combination partner of fluoropyrimidines and platinum derivatives in perioperative and palliative therapy, and is a component of the FLOT regimen [32, 45, 111]. Severe grade 3/4 side effects include infection, nail changes, stomatitis, and diarrhea; grade 2 distressing side effects include alopecia. Particularly harmful is polyneuropathy, which can be irreversible. Common side effects such as nausea/vomiting and allergic reactions can be prevented by adequate supportive therapy, see Onkopedia Antiemesis *(German Version)*.

6.2.3.1.3 Fluoropyrimidines (5-fluorouracil, capecitabine, S-1, tegafur)

5-Fluorouracil is used in almost all forms of drug therapy for patients with gastric cancer. Efficacy is increased by combination with folinic acid. Severe side effects include diarrhea and stomatitis. Patients with functionally relevant polymorphisms of the genes of 5-FU degradation have an increased risk of severe side effects.

Capecitabine is an oral fluoropyrimidine that is metabolized to 5-FU. In comparative clinical trials, it is at least as effective as 5-FU / folinic acid. It can be used in place of 5-fluorouracil in palliative therapy. In combination with platinum derivatives, remission rates up to 45% are achieved. Severe side effects (grade 3 / 4) occurring in more than 5% of patients in pivotal

studies are diarrhea and hand-foot syndrome. Patients with functionally relevant polymorphisms of the genes of 5-FU degradation have an increased risk for severe side effects.

Another orally bioavailable fluoropyrimidine consisting of tegafur in combination with two modulators of 5-fluorouracil (5-FU) activity, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate, in a molar ratio of 1:0, 4:1 is S-1. Tegafur is a prodrug of 5-fluorouracil, an antimetabolite that inhibits thymidylate synthase, DNA synthesis, and cell division and competes with uridine triphosphate, inhibiting RNA and protein synthesis. CDHP is a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), which is responsible for the rapid degradation of 5-FU to inactive metabolites. Potassium oxonate localizes preferentially in the intestine and inhibits the enzyme orotate phosphoribosyl transferase (OPRT), thereby reducing the activation of 5-FU in the intestine and the gastrointestinal toxicity associated with 5-FU.

Since 2020, all fluoropyrimidines mentioned have been subject to the recommendation of the European Medicine Agency that patients be tested for deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD) prior to initiation of therapy to prevent severe side effects caused by 5-fluorouracil or capecitabine or tegafur (https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine).

6.2.3.1.4 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with fluoropyrimidines, remission rates are up to 40%. FOLFIRI is at least as effective as cisplatin-fluoropyrimidine-based therapies in terms of progression-free survival and overall survival. Serious adverse events (grade 3/4), which occurred in more than 5% of patients in pivotal trials, include diarrhea, nausea/vomiting, neutropenia, and neutropenic fever. The substance can be applied as monotherapy weekly, biweekly or tri-weekly.

6.2.3.1.5 Oxaliplatin

This platinum derivative is effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line therapy for stage IV gastric cancer, it increases remission rates to 45%. Severe side effects (grade 3/4), which occurred in more than 5% of patients in pivotal trials, include nausea/vomiting, diarrhea, mucositis, and polyneuropathy. Oxaliplatin is part of the FLOT regimen recommended perioperatively.

6.2.3.1.6 Paclitaxel

Paclitaxel belongs to the taxanes. Paclitaxel is effective as monotherapy in second-line palliative therapy. Severe side effects (grade 3/4) include infections, stomatitis and diarrhea, and allergic reactions to the contained solvent cremophore; grade 2 distressing side effects include alopecia. Particularly burdensome is a partly irreversible polyneuropathy. Common side effects such as allergic reactions can be partially prevented by adequate supportive therapy.

6.2.3.1.7 Ramucirumab

Ramucirumab is a VEGF receptor2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab leads to prolongation of progression-free survival (HR 0.64; median 1.5 months), prolongation of overall survival (HR 0.81; median 2.2 months), and an increase in

remission rate compared to paclitaxel monotherapy. In patients ineligible for paclitaxel therapy, ramucirumab monotherapy versus placebo also results in prolonged progression-free survival (HR 0.48; median 0.8 months) and overall survival (HR 0.78; median 1.4 months). The only side effect of CTCAE grade 3/4 that occurred in more than 5% of patients on ramucirumab monotherapy was arterial hypertension. More common side effects in combination therapy were fatigue (12%), neuropathy (8%), and abdominal pain (6%).

6.2.3.1.8 Trastuzumab

Trastuzumab is the first monoclonal antibody that specifically interferes with the HER2/neu receptor and has been approved for the treatment of patients with HER2 overexpression or gene amplification. It is effective in the palliative setting. In HER2-positive gastric cancer, trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone results in prolonged overall survival (HR 0.74; median 2.7 months). Severe adverse events (grade 3/4) are rare.

6.2.3.1.9 Trastuzumab deruxtecan (T-DXd)

Trastuzumab deruxtecan is an antibody-drug conjugate containing a humanized anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently bound to DXd, an exatecan derivative and topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 8 DXd molecules are bound to each antibody molecule. T-DXd is used as monotherapy to treat adult patients with advanced HER2-positive adenocarcinoma of the stomach or esophago-gastric junction who have received a prior trastuzumab-based therapeutic regimen. Patients treated with T-DXd must have a documented HER2-positive tumor status, defined either immunohistochemically (IHC) by a score of 3+ or by a gene copy number ratio relative to CEP17 of ≥ 2 measured by in situ hybridization (ISH).

The recommended dose of T-DXd in gastric cancer (different from breast cancer) is 6.4 mg/kg and is given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The initial dose is to be given as a 90-minute intravenous infusion. If the preceding infusion was well tolerated, subsequent T-DXd may be given as a 30-minute infusion. If the patient exhibits infusion-related symptoms, the infusion rate of T-DXd must be decreased or the infusion must be discontinued. If severe reactions to the infusion occur, T-DXd must be permanently discontinued. Special attention should be paid to the possible occurrence of pulmonary toxicity in the form of interstitial lung disease or pneumonitis. It should also be noted that trastuzumab deruxtecan has moderate to high acute and delayed emetogenic potential. We therefore recommend the prophylactic use of 3 antiemetics (dexamethasone, 5-HT3 antagonist, NK-1 antagonist).

6.2.3.1.10 Trifluridine-Tipiracil (FTD-TPI)

The fixed drug combination FTD-TPI consists of the nucleoside thymidine analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil (TPI). The molar ratio of trifluridine/tipiracil is 1 : 0.5 (exact mass ratio: 1 : 0.471). TF is phosphorylated intracellularly by the enzyme thymidine kinase to monophosphate (TF-MP) and subsequently by the enzyme thymidylate kinase to di- (TF-DP) and triphosphate (TF-TP). TF-TP is incorporated into the DNA as a defective component. This incorporation results in long-lasting DNA damage and DNA strand breaks. TF-MP, in turn, binds covalently to thyrosine-146 in the active site of the enzyme thymidilate synthetase (TS, also thymidilate synthase) and inhibits its activity. TS is responsible

for the conversion of uracil nucleotides to the thymidine nucleotides and is thus vital for DNA synthesis by maintaining sufficient amounts of thymidine. FTD-TPI proved superior to placebo in the third line of treatment of metastatic gastric cancer, prolonging overall survival (HR 0.69; $p < 0.001$) and was satisfactorily tolerated: Grade ≥ 3 adverse events occurred in 267 (80%) patients in the trifluridine/tipiracil group and in 97 (58%) in the placebo group.

6.2.3.1.11 Nivolumab

Nivolumab is an immune checkpoint inhibitor. It is a fully human monoclonal antibody of the immunoglobulin G4 (IgG4) class that binds to the PD-1 receptor on T cells and prevents interaction with the PD1 receptor ligand that binds here. In this way, the cellular immune system is indirectly stimulated by suppressing the inhibitory influence of the PD1 ligand/PD1 receptor interaction. Nivolumab is indicated in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of HER2-negative advanced or metastatic adenocarcinomas of the stomach, esophago-gastric junction, or esophagus in adults whose tumors express PD-L1 (combined positive score [CPS] ≥ 5). The recommended dose is 360 mg nivolumab intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 3 weeks or 240 mg nivolumab intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 2 weeks. Treatment with nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

6.2.3.1.12 Pembrolizumab

Pembrolizumab is an immune checkpoint inhibitor. It is a fully human monoclonal antibody of the immunoglobulin G4 (IgG4) class that binds to the PD-1 receptor on T cells and prevents interaction with the PD1 receptor ligand that actually binds here. In this way, the cellular immune system is indirectly stimulated by suppressing the inhibitory influence of the PD1 ligand/PD1 receptor interaction. Pembrolizumab is indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for first-line treatment of locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the esophago-gastric junction in adults with PD-L1-expressing tumors (CPS ≥ 10). Pembrolizumab is also indicated as monotherapy for the treatment of gastric cancer with MSI-H or with a deficient DNA mismatch-repair (dMMR) in adults after at least one prior systemic therapy.

6.3 Special situations

6.3.1 Peritoneal carcinomatosis

Several small randomized trials from Asia suggest a survival benefit for adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with curatively resected gastric cancer at high risk of recurrence [109, 110]. The ongoing randomized GASTRICHIP trial seeks to clarify the efficacy of this approach in a European patient population [111]. For patients with peritoneal metastasis, smaller randomized trials from Asia also exist suggesting an advantage for cytoreductive surgery and HIPEC [112]. A larger multicenter case series from France showed a median survival for surgery plus HIPEC of 9.2 months, with a 5-year survival of 13% for all patients and 23% for patients with complete cytoreduction [113]. The approach of peritonectomy plus HIPEC plus perioperative chemotherapy was compared with peritonectomy without HIPEC plus perioperative chemotherapy in Germany in the multicenter prospective randomized GASTRIPEC trial. The trial had to be closed prematurely due to slow recruitment [114].

Based on current knowledge, adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and peritonectomy are not standard therapies in this indication.

6.3.2 Signet ring cell carcinoma in locally advanced stages

Gastric cancers with signet ring cells are associated with a poorer prognosis. This is at least partly due to a later diagnosis with presence of higher tumor stages at initial diagnosis [115]. Retrospective case series suggest that signet ring carcinomas respond less well to chemotherapy and radiochemotherapy [116, 117]. A retrospective study from a French national registry, albeit without a central histopathologic review of the tumor samples, suggests a worse prognosis for patients with signet ring carcinomas who receive perioperative chemotherapy in addition to resection [118]. However, the evidence from these studies is insufficient to make specific treatment recommendations. A French study [PRODIGE 19 - FFCD1103 - DCI002 (NCT01717924)] addressed the issue of perioperative chemotherapy for resectable signet ring carcinoma of the stomach and compared this standard with adjuvant chemotherapy alone [119]. An evaluation published as an abstract yielded the result of sufficient efficacy of perioperative chemotherapy in patients with signet ring carcinoma [120]. In the German FLOT-4 study, the remission rate was the same under FLOT and ECF/ECX, but in a subgroup analysis, overall survival in the FLOT arm was also significantly prolonged in patients with signet-ring cell carcinoma [32]. Therefore, based on current knowledge, the same perioperative treatment recommendations apply to patients with locally advanced signet-ring cell carcinoma as to patients with non-signet-ring cell carcinoma.

7 Rehabilitation

Gastric cancer as well as its treatment, both surgical and non-surgical, can lead to significant sequelae such as weight loss, maldigestion, and neuropathy. In addition, patients are often psychologically stressed and exhibit a fatigue syndrome. Therefore, targeted rehabilitative measures are necessary. These should be started promptly after completion of primary therapy.

When selecting the rehabilitation facility, the approval of the clinic for gastric cancer patients by the funding agencies (pension insurance, health insurance) is a prerequisite; in addition, the patient's preferences according to §9 SGB IX should be taken into account.

During rehabilitation, comprehensive nutritional counseling should be provided, patients should be instructed in a teaching kitchen, and it should be possible to administer all scientifically recognized forms of nutrition, from normal whole foods to complete parenteral nutrition. All patients should be offered psycho-oncological care. Rehabilitation facilities should be able to continue systemic tumor therapies, including chemotherapy and immunotherapy, as indicated.

Patients who have not yet reached the statutory retirement age should be informed about services for participation in working life within the framework of medical-occupational rehabilitation (MBOR). Socio-medical questions as well as the possibly necessary further care of the patients should be clarified during the rehabilitation.

8 Monitoring and Follow-up

8.1 Monitoring

During ongoing chemotherapy, patients’ general condition and vital body functions should generally be checked once a week, or more frequently if indicated [11]. Imaging follow-up examinations, preferably by computed tomography, are indicated every 6-12 weeks in order to detect

negative developments of the disease in time and not to expose patients to ineffective therapies for an unnecessarily long time, or to open up the chance of more effective therapies.

8.2 Follow-up

There are no prospective data on the basis of which a specific follow-up regimen can be recommended. The German S3 guideline recommends to offer patients a structured follow-up after curative therapy, which includes clinical control, endoscopic and imaging control. The intervals should be at least semiannual for the first two years and then at least annual until the 5th year. In past and ongoing studies, the scheme shown in Table 5 has been established.

Table 5: Structured monitoring and follow-up in patients after curative therapy

Procedure	**Months after end of treatment**													
	(3)	6	(9)	12	(15)	18	(21)	24	(30)	36	(42)	48	54	60
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Blood count and routine clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy [1]	X		X		X		X		X		X	X	X	X
Imaging: Abdominal ultrasound or if necessary CT thorax/ abdomen/ pelvis	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Legend:
[1] optional in the absence of symptoms, recommended promptly in the presence of signs and symptoms suspicious of tumor recurrence, postoperative complications, or other endoscopically detectable pathology

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

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