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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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Gastric Cancer

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- Guideline
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1 Summary

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

The patient's prognosis is primarily determined by the stage, but also by histology, general condition and comorbidity. In early and localized stages, the treatment approach is curative; in metastatic stages, it is palliative. The main treatment modalities are surgery and systemic tumor therapy. Despite some progress in the last 10 years, the cancer-specific mortality rate is very high at 70%.

This guideline refers to adenocarcinoma of the stomach. Recommendations on localized tumors of the esophago-gastric junction can be found in Onkopedia Esophageal cancer. The recommendations for the treatment of advanced adenocarcinomas of the esophago-gastric junction and esophagus largely correspond to those for gastric cancer. Recommendations for less common, non-epithelial tumors of the stomach can be found in Onkopedia Gastrointestinal Stromal Tumors (GIST) or Onkopedia Extranodal Marginal Zone Lymphomas *(Guideline exists in German language only).*

2 Basics

2.1 Definition and basic information

Gastric cancer arises in the proximal sections of the stomach (subcardial), in the middle third (fundus and corpus) and in the distal stomach (antrum). Subcardial gastric carcinomas often have an anatomic connection 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 carcinomas 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 only addressed cursorily here, as the clinical algorithms must be differentiated from gastric carcinoma.

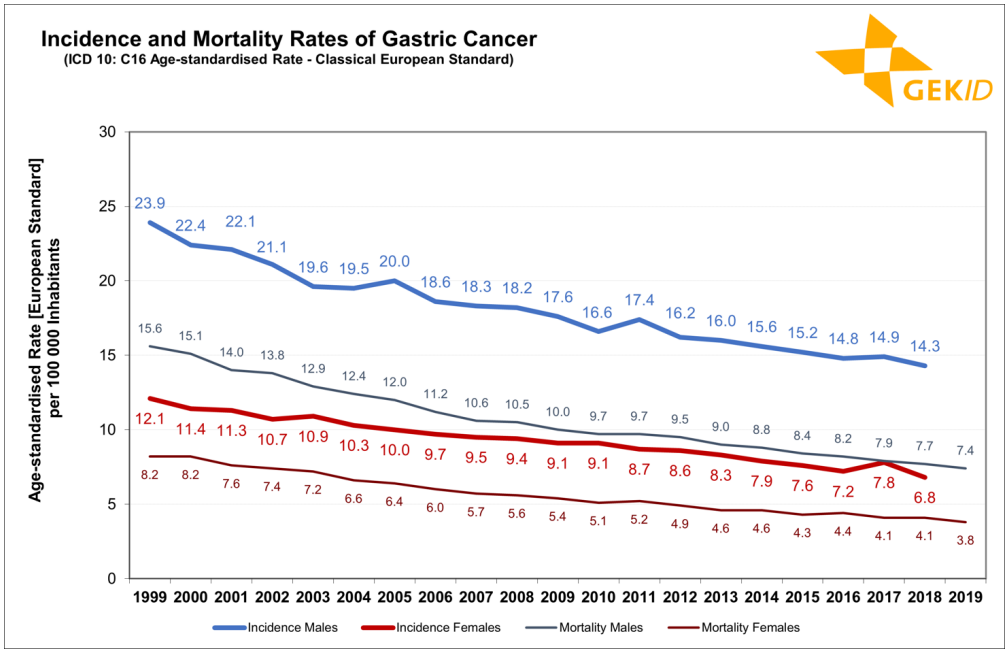
2.2 Epidemiology

Every year, around 9,500 new cases of gastric cancer are diagnosed in men and around 6,000 new cases in women in Germany. This makes gastric cancer the tenth most common cancer in men, accounting for around 3.5% of all malignancies, and the ninth most common malignancy in women, accounting for around 2.4%. In terms of cancer mortality, the relevance of gastric cancer is even higher. It accounts for around 3.5% of all cancer deaths in women and 4.2% in men. The average age of onset is 71 years for men and 76 years for women, which is higher than for cancer as a whole (70 for men, 69 for women). The average age at death is 74 years (men) and 78 years (women) (cancer overall: 75 and 77 years). It can be assumed that there are around 33,000 patients living in Germany who were diagnosed no more than five years ago and 52,000 patients who were diagnosed in the last 10 years.

The age-standardized incidence rates, as well as the age-standardized mortality rates, have been declining for years for both sexes, see Figure 1. The age-standardized incidence rate for men has fallen by an average of 2.2% per year over the past 16 years - the mortality rate has declined by an average of 3.4% per year. The incidence rate for women has declined by an average of 2.7% per year over the last 16 years - the mortality rate by an average of 3.7% per year. Case numbers and (crude) rates for men are around 60% higher than for women.

The decline in incidence was also confirmed by data from the Dutch cancer registry. Here, the incidence fell from 20.3 to 6.1 per 100,000 between 1989 and 2021, with a simultaneous improvement in relative survival rates [143].

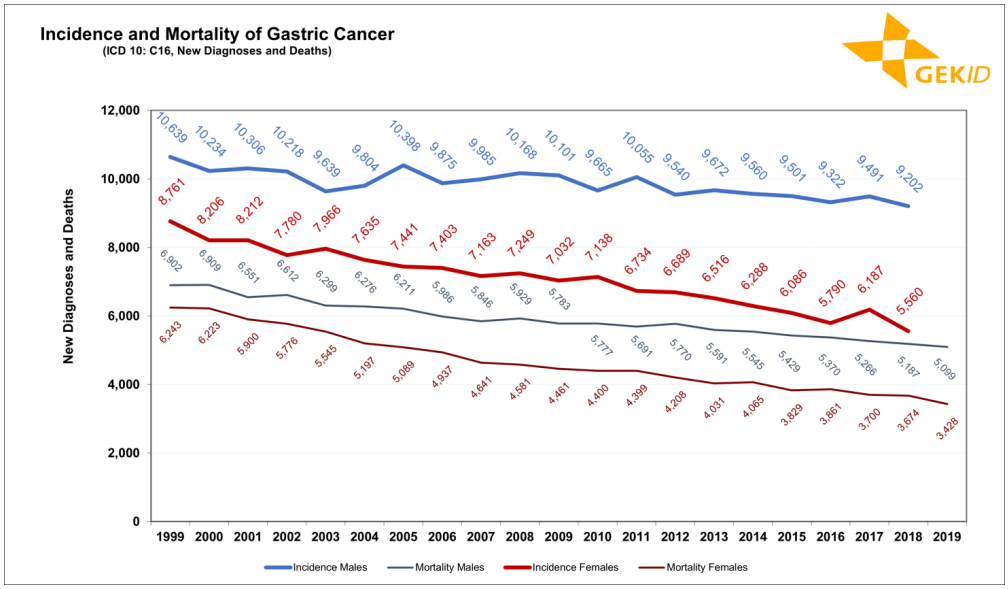
Figure 1: Estimated incidence of stomach cancer (ICD 10: C16) in Germany – age-standardized rates (old European standard) [1]



While the age-standardized new-case rates represent a measure of the probability of disease and are largely independent of the population structure, the number of new cases of disease reflects not only the probability of disease but also the age structure and population size. Due to the shift in the age structure towards an older society and the fact that the “baby boomers” are reaching the age cohorts most likely to develop the disease, the trends in new cases and deaths differ from the trends in rates. This shift is particularly evident in men. Although the number of cases is falling, this is 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 male patients is falling by an average of 1.2% per year, which is also lower than the decline in mortality rates (3.4%). For women, the decline in the number of new cases (2.1% per

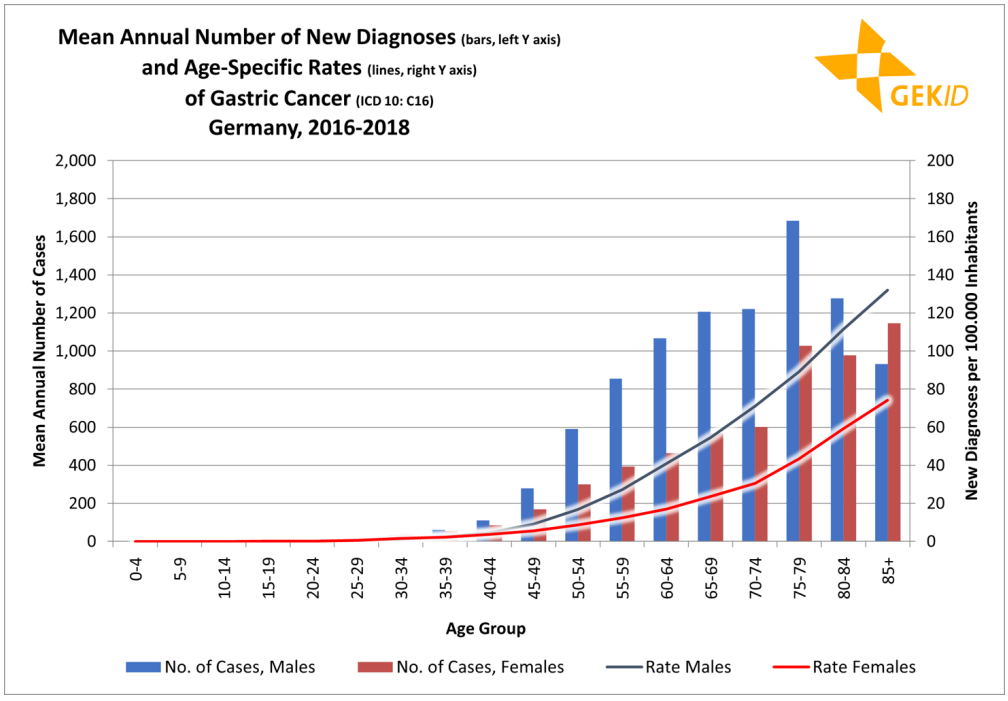
year), and deaths (2.7% per year) is also lower than the corresponding rates. However, the difference is not quite as great (Figure 2).

Figure 2: Estimated incidence of stomach cancer (ICD 10: C16) in Germany – number of cases [1]



Most gastric cancers in men are diagnosed in men between 75 and 79, see Figure 3 (bar). From the age of 40 until the age of 80, the number of new cases rises 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 the highest age group 85 years and older for both sexes. Case numbers and incidence rates for men are higher than for women in all age groups.

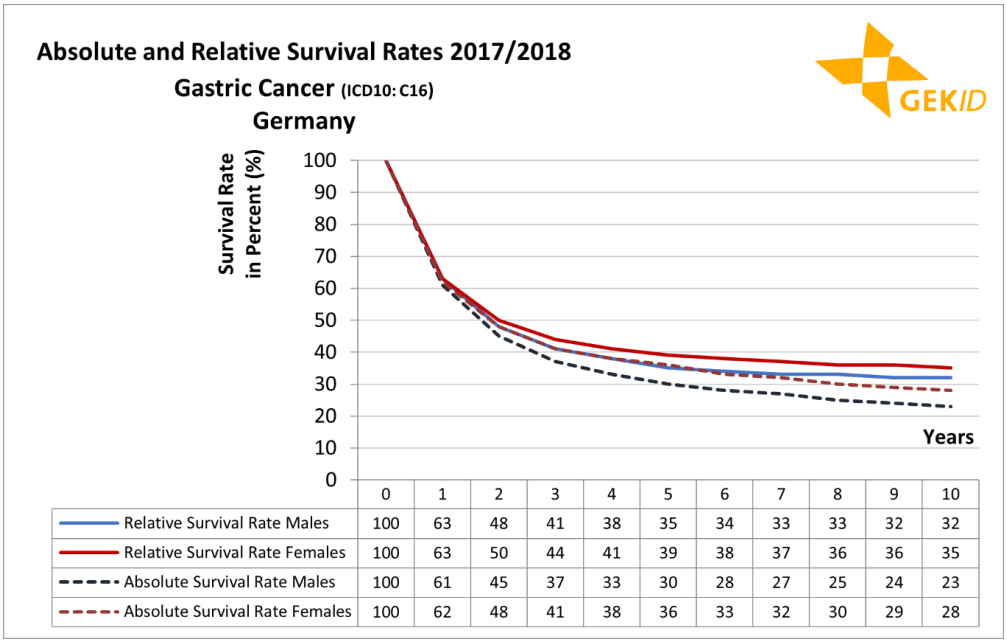
Figure 3: Age distribution of stomach cancer incidence (ICD 10: C16) – age-specific case numbers and rates [1]



The prognosis for gastric cancer is relatively unfavorable, especially during the first two years after diagnosis. Around 40% of patients die in the first year after diagnosis. The small difference between the absolute survival rate - i.e., the percentage of patients who survive for a certain time - and the relative survival rate - i.e., the ratio of absolute survival to the expected sur-

vival in the general population - shows the excess mortality caused by the cancer. From the fifth year after diagnosis, the gap between the absolute and relative survival rates increases, while the relative survival rate remains largely constant. This means that after about five years there are hardly any additional cancer-related deaths. Figure 4 shows the absolute and relative survival rates for the first 10 years after diagnosis. There are hardly any differences in survival between the sexes.

Figure 4: Absolute and relative survival rates for stomach 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

Based on the current incidence of the disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), the number of cases can be expected to increase by around 30% to around 20,000 new cases (2050) over the next 30 years, solely due to the shift in the age structure of the population. In reality, however, the increase is likely to be lower due to falling disease rates.

2.3 Pathogenesis

Gastric cancers - in analogy to carcinomas of the rest of the digestive tract - develop in many cases sequentially in multistage processes via precancerous intermediate stages and histologically defined lesions [2]. Unlike for *Lauré*n'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 carcinoma is associated with the presence of the following risk factors [4]:

- Genetic
  - Hereditary nonpolyposis colorectal cancer (HNPCC, *Lynch* syndrome [5]

- Hereditary diffuse gastric cancer (HDGC) with mutations in the cadherin 1 (*CDH-1*) or catenin alpha-1 (*CTNNA1*) gene [6, 7]
- Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), with autosomal dominant inheritance and involvement of the promoter region of the *APC* gene [97, 154]
- *Peutz-Jeghers* syndrome (mutation in the serine-threonine kinase gene [*STK11*])
- First-degree relatives with gastric carcinoma
- Male gender (incidence in men:women approximately 2:1)
- Blood group A

- Acquired
  - *Helicobacter (H.) pylori* infection of the gastric mucosa
  - *Epstein-Barr* virus infection of the gastric mucosa
  - Dietary factors: high intake of salt-preserved foods, high intake of processed meat, low consumption of fruit
  - Tobacco inhalation
  - Atrophic gastritis
  - Partial gastrectomy
  - *Ménétrier's* disease
  - Gastroesophageal reflux disease and trunk-predominant obesity

Risk factors differ for the various anatomical localizations and histological subtypes. 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 intestinal subtype are more frequently associated with an *H. pylori* infection than carcinomas of the diffuse subtype. The risk of gastric carcinoma is particularly high if there is a genetic predisposition and an *H. pylori* infection [141]. Carcinomas of the esophago-gastric junction are more commonly associated with obesity and gastroesophageal acid reflux.

3 Prevention and early detection

3.1 Prevention

H. pylori eradication with the aim of preventing gastric cancer is recommended for people at risk; see also Chapter 3.2.2. It is currently assumed that the timing of treatment is crucial for the effectiveness of *H.* pylori eradication in preventing gastric cancer. This should be done in adulthood at a time when no pre-neoplastic changes have yet developed [8]. Data from Japan show a particularly high rate of *H. pylori*-associated gastric carcinomas in individuals with germline mutations in genes of particular relevance to homologous recombination capacity (*ATM, BRCA1, BRCA2*, and *PALB2)*, who showed a 40-fold increased risk of developing gastric carcinoma in the presence of H*. pylori* colonization [141]. Results from prospective and controlled intervention studies are not yet available. In a large US population, *H.* pylori eradication was associated with a significantly lower incidence of gastric cancer after 8 years compared to no treatment. After an observation period of 7-10 years, the risk in treated individuals was lower than in the general population. The results show that eradication of H*. pylori* has the potential to significantly reduce the risk of gastric cancer [139].

There is currently insufficient evidence for chemoprevention of gastric cancer, for example with non-steroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, or acetyl salicylic acid [9].

3.2 Early detection

3.2.1 Population

Since Germany/Austria/Switzerland are not high-incidence regions for gastric cancer, it seems unlikely that population-based endoscopic screening would be cost-effective. However, no study has yet been conducted explicitly examining cost-effectiveness under the conditions in German-speaking Central Europe. 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 stomach cancer, the risk is approximately tenfold increased [10]. However, it is not possible to provide a scientifically sound recommendation for screening endoscopy in individuals with a positive family history. Risk groups have been defined in accordance with the recommendations of the DGVS-S2k guideline on *H. pylori* and gastroduodenal ulcer disease [8]. The group of persons-at-risk include first-degree relatives of patients with gastric cancer, persons residing/born in high-prevalence areas, and patients who already have advanced, corpus-predominant atrophic gastritis with or without intestinal metaplasia and patients with previous gastric neoplasms (adenoma, early carcinoma) after endoscopic resection or partial gastric resection [11]. At least these individuals should be screened for *H. pylori* infection and, if the infection is detected, undergo eradication treatment.

Since individuals with a pathogenic *CDH1* germline mutation have a lifetime risk around 10-40% of developing invasive hereditary diffuse gastric carcinoma, a careful family history should be taken. Regular endoscopy is recommended. Previous standard recommendation for gastrectomy in cases of signet ring cells is no longer valid without restrictions. Instead, individuals affected should be offered differentiated genetic, endoscopic, and histopathological diagnostics and counseling. The indication for gastrectomy is based on family history and the individual risk constellation of genetic, endoscopic, and histopathological findings. In many cases, endoscopic monitoring in designated expert centers is now considered an alternative to gastrectomy in young adults [14, 131, 156, 157, 158]. The level of knowledge about the penetrance of pathogenic *CTNNA1* mutations is low, so that a clear recommendation for prophylactic gastrectomy cannot be given at present. At the very least, close endoscopic monitoring in a designated center is recommended. Consultation in a specialized center is recommended [13, 14].

Furthermore, gastric carcinomas can occur more frequently in other hereditary tumor disorders, such as Lynch syndrome (*hMLH1, hMLH2*) and microsatellite instability (MSI).

4 Clinical characteristics

4.1 Symptoms

Early gastric carcinoma is usually asymptomatic. The following symptoms often only occur 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 as liver capsule pain, ileus/subileus from peritoneal metastasis, etc.)
- Vitamin B12 deficiency of undetermined origin

Gastric cancer can be associated with various paraneoplastic syndromes, with cutaneous manifestations being observed more frequently than others [16].

5 Diagnosis

5.2 Diagnostics

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: Diagnostics and staging of gastric cancer

Procedure	Note
Physical examination	
Laboratory (blood)	Blood count, liver and renal function parameters, coagulation
Endoscopy of the upper gastrointestinal tract	Optional use of chromoendoscopy
Endoscopic ultrasound (EUS)[1]	For treatment planning in localized disease
Thoracic computed tomography (CT) including the supraclavicular region, abdomen, and pelvis, with oral and intravenous contrast medium	For imaging of locoregional and distant tumor spread
Abdominal sonography	Supplement to CT
Laparoscopy, with cytology if indicated[2]	In cT3/cT4 without evidence of distant metastases, to detect/rule out peritoneal metastasis

Legend:
[1] see chapter 5.2.3.1
[2] Laparoscopy with cytological examination of the lavage fluid helps to detect clinically occult metastasis of the peritoneum in locally resectable tumors. The detection of macroscopic peritoneal metastasis has a direct impact on treatment planning [17]. Cytological detection of malignant cells in the lavage fluid is an unfavorable prognostic factor, but outside of clinical studies, it has not yet been shown to have a definite impact on treatment recommendations. Abnormal laparoscopic findings are more common in tumors classified as T3/T4 [18].

5.2.2 Histology and subtypes

The histological diagnosis of gastric cancer should be made on the basis of a biopsy, evaluated by two experienced pathologists [11]. Biomarker diagnostics from tumor tissue are now standard practice, at least in case of stage IV gastric cancer. Immunohistochemically determined

biomarker diagnostics should be performed on the basis of 5 tumor-bearing biopsies [51, 132]. In case of non-endoscopically resectable and advanced gastric neoplasms, sufficient samples should include 8-10 biopsies. This makes it possible to obtain vital tumor tissue in 4-5 tissue samples in order to determine molecular biomarkers important for treatment planning, apart from confirming the diagnosis.

Standard diagnostics currently include the determination of the *HER2* status, PD-L1 combined positive score (CPS) and tumor area positivity (TAP), mismatch repair enzymes (or microsatellite instability), and Claudin 18.2. In the near future, routine immunohistochemical determination of fibroblast growth factor receptor 2B (FGFR2B) is also likely to become routine standard [159].

In addition to describing *HER2* positivity according to established criteria [51], the precise specification of the proportion of *HER2*-positive tumor regions [52] and the description of a *HER2*-low status is an option with possible therapeutic consequences in the future. The high rate of discrepancies in findings between different investigators of around 25% must also be taken into account [138, 142]. The routine determination of *Epstein-Barr* virus association by in situ hybridization (EBER-FISH) is under discussion, as it occurs very rarely [22].

5.2.2.1 Laurén classification

Histologically, gastric carcinoma is characterized by a high degree of heterogeneity, with several different histological elements often present in a single tumor. Over the last few decades, histological classification has been based on the *Laurén* classification [19]:

- intestinal type, approximately 54%
- diffuse type, approx. 32%
- unclassifiable, approx. 15%

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

5.2.2.2 World Health Organization (WHO) classification

The World Health Organization (WHO) classification distinguishes between four main types of gastric carcinoma [21].

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

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

5.2.2.3 The Cancer Genome Atlas (TCGA) classification

Molecular genetic studies divide gastric cancer into molecular subtypes based on genomic, transcriptomic, epigenetic and proteomic analyses. The molecular genetic heterogeneity of gastric carcinoma is the subject of extensive genome-wide sequencing studies [133]. The best-known molecular subtyping according to the TCGA distinguishes four subtypes [22].

- Chromosomal instable – CIN
- *Epstein-Barr* virus-associated – EBV
- Microsatellite instable – MSI
- Genomically stable – GS

5.2.3 Stages and staging

5.2.3.1 TNM staging

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

Table 2: UICC-TNM classification, 8th edition – gastric carcinoma [21]

Classification	Tumor
T	**Primary tumor**
T	Superficially invading tumor
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa without invasion of the visceral peritoneum
T4a	Tumor invades subserosa (visceral peritoneum)
T4	Tumor invades adjacent structures
N	**Regional lymph nodes**
N	No regional lymph node metastases
N1	Metastasis 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 N3a	M0 M0 M0 M0
IIIA	T4b T4a T3 T2	N0 N1/N2 N2 N3a	M0 M0 M0 M0
IIIB	T4b T4a T3 T2/T1	N1/N2 N3a N3a N3b	M0 M0 M0 M0
IIIC	T4b T4a/T3	N3a/N3b N3b	M0 M0
IV	Any T	Any N	M1

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

The following characteristics are used to identify malignant lymph nodes in CT imaging [24]:

- Diameter ≥ 6-8 mm (short axis) of 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 estimated to be variable, ranging from 62.5-91.9% in systematic reviews [25].

EUS improves the accurate determination of the T and N categories and can help to determine the proximal and distal ends of the tumor. EUS is less accurate for tumors of the antrum. EUS complements CT in the diagnosis of malignant lymph nodes.

Signs of malignancy in EUS include [26]:

- Hypoechoic
- Round shape
- Blurred demarcation from the surrounding tissue
- Longest diameter >1 cm

In locally advanced gastric cancer (clinical cT3, cT4) that is classified as potentially resectable, diagnostic laparoscopy with peritoneal lavage and examination for malignant cells should be performed before the start of neoadjuvant therapy in order to rule out occult peritoneal metas-

tasis. Since the treatment concept changes significantly if peritoneal carcinomatosis is detected, it should be performed before neoadjuvant therapy and conducted according to a standardized protocol specifying the PCI (Peritoneal Carcinomatosis Index) according to Sugarbaker [160].

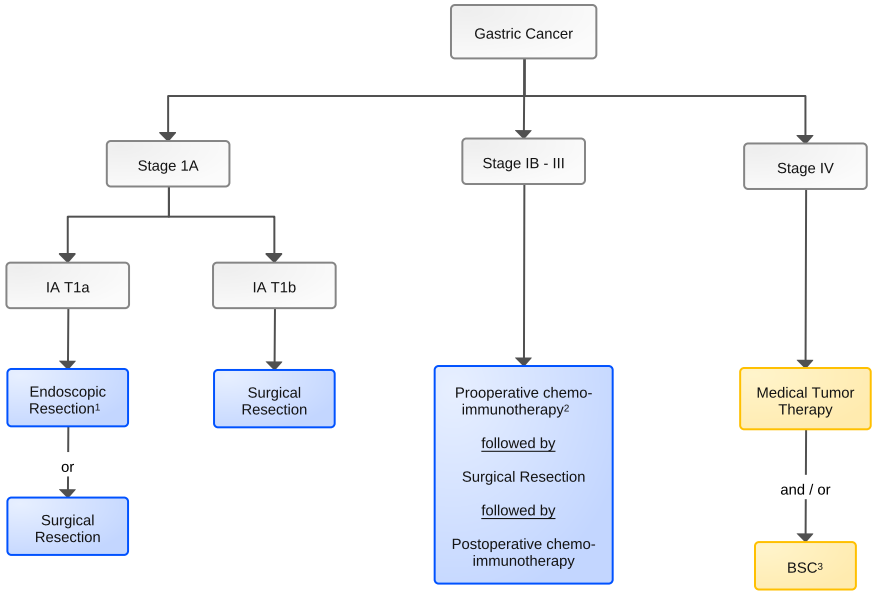
6 Therapy

6.1 Treatment structure

Multidisciplinary planning is required for any initial treatment recommendation. It should be developed by a qualified multidisciplinary tumor board. The core members of the multidisciplinary board include the following disciplines: medical oncology, visceral surgery, radiation oncology, gastroenterology, radiology, and pathology. In addition to determining the best possible standard therapy, possible inclusion in clinical trials should be part of the discussion in the tumor board.

Treatment is stage-adapted. An algorithm for first-line treatment is shown in Figure 5.

Figure 5: Algorithm for primary therapy



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

6.1.1 Stage IA – T1a (early-stage cancer)

Since the probability of lymph node metastasis in mucosal gastric carcinoma (T1a) is very low, endoscopic resection (ER) is considered sufficient [27]. If histopathological examination after endoscopic resection reveals that the tumor has invaded more than 500µm into the submucosa (T1b), surgical resection with systematic lymphadenectomy should be performed, as lymph node metastasis is already present in up to 30% of cases.

Gastric carcinomas classified as pT1a cN0 cM0 should be treated with endoscopic resection in accordance with 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 carcinomas with a maximum of one "extended criterion" can also be resected endoscopically in a curative approach [11]. Endoscopic submucosal dissection (ESD) should be used for resection. If more than one extended criterion is present, oncological surgical resection should be performed. The extended criteria are defined as follows:

- Differentiated mucosal carcinoma (G1/G2) without ulceration and size >2 cm
- Differentiated mucosal carcinoma (G1/G2) with ulceration and size <3 cm
- Well-differentiated carcinomas (G1/G2) with submucosal invasion <500µm and size <3cm
- Undifferentiated mucosal carcinoma (G3/G4) <2 cm in diameter (provided that no tumor cells are detected by biopsy at a distance of ≤1 cm [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

In stage IA gastric carcinomas with submucosal invasion (T1b), the risk of lymph node metastases is 25-28%. The 5-year survival rate in the SEER database for the entire stage IA is 70.8% [29], and the cancer-specific survival rate after 10 years in the Italian IRGGC analysis is 93%. The treatment of choice in stage IA (T1 N0 M0) is radical surgical resection (subtotal, total, or transhiatal extended gastrectomy). Limited resection can only be recommended in exceptional cases due to the limited accuracy of pre-treatment staging. A benefit from perioperative or adjuvant chemotherapy has not been established for stage IA patients.

6.1.3 Stage IB to III

In stage IB to 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 resection margins of 5 cm for intestinal tumor growth and 8 cm for diffuse tumor growth are no longer universally accepted. There scientific evidence for definitive recommendations is low. A negative oral resection margin in the intraoperative frozen section is crucial.

Perioperative chemotherapy based on a platinum derivative and a fluoropyrimidine in patients with resectable gastric carcinoma led to a significant improvement in overall survival [30, 31]. Treatment according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) led to a further improvement in progression-free survival [PFS] (hazard ratio [HR] 0.75) and overall survival [OS] (HR 0.77) in patients with stage ≥cT2 and/or cN+; see also chapter 6.2.3.1. The higher efficacy of FLOT was consistent across relevant subgroup analyses such as age, histology, and tumor location. The rate of perioperative complications was comparable [32].

Additional treatment with a PD-L1- or PD-1-targeted immune checkpoint inhibitor in combination with FLOT chemotherapy resulted in an increased histopathological response rate [34, 136, 140]. Recently, the phase III MATTERHORN study demonstrated an improvement in event-free survival [EFS] when the PD-L1 inhibitor durvalumab was added to perioperative FLOT chemotherapy and continued to be administered for up to a total of one year following combined chemoimmunotherapy. The two-year EFS rate (Kaplan-Meier estimate) was 67.4% in participants in the durvalumab group and 58.5% in participants in the placebo group (HR for event or death: 0.71; 95% confidence interval [CI] 0.58-0.86; $p < 0.001$). The two-year OS rate, which has not yet been finalized, was 75.7% in the durvalumab group and 70.4% in the placebo group. The final evaluation of OS requires a longer follow-up period [136]. The benefit in terms of EFS also appeared to be achieved in the subgroup of PD-L1-negative tumors. The addition of durvalumab to perioperative therapy with FLOT is currently not approved, but should be applied for as off-label use.

There is currently no indication outside of clinical trials for perioperative immunotherapy alone without chemotherapy in microsatellite-stable tumors. Adjuvant immunotherapy proved to be insufficiently effective in the EORTC1707 VESTIGE study (nivolumab and ipilimumab) and in the Asian ATTRACTION-5 study (nivolumab and chemotherapy) [147, 148].

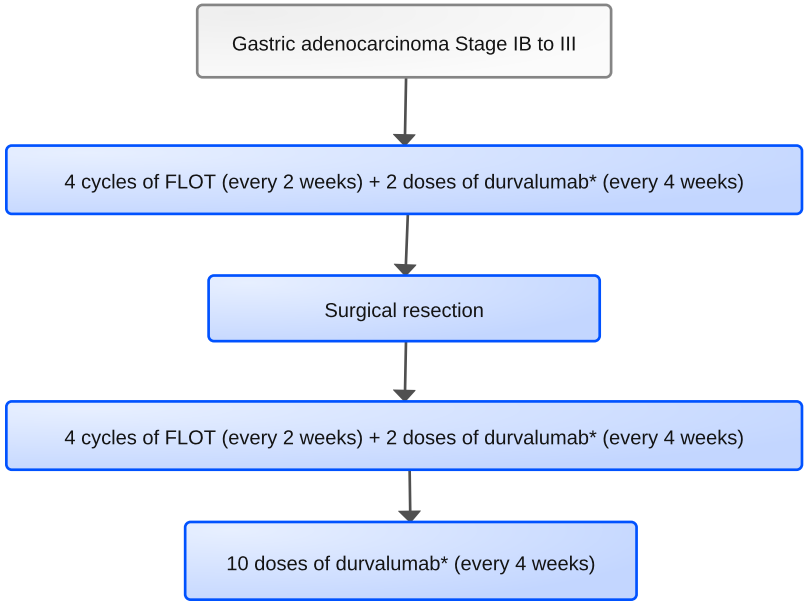
For patients with gastric cancer ≥ stage IB who underwent resection without prior chemotherapy (e.g., due to incorrect tumor staging prior to surgery), adjuvant chemotherapy may be considered, see chapter 6.2.3.1.

In *HER2*-positive tumors, the benefit of combining perioperative chemotherapy with a *HER2* antibody in the perioperative setting in terms of OS has not yet been proven. The AIO-Petrarca phase 2 study shows a higher histopathological remission rate when FLOT chemotherapy is combined with trastuzumab + pertuzumab and a trend toward better PFS and OS [121]. The multinational EORTC1203-INNOVATION study shows promising response rates with the combination of FLOT + trastuzumab and good feasibility of the regimen, while FLOT + trastuzumab + pertuzumab did not prove to be effective due to increased toxicity. According to currently available data, neither trastuzumab alone nor trastuzumab + pertuzumab led to improved survival [144].

Based on retrospective data analyses, there are doubts about the effectiveness of perioperative chemotherapy in microsatellite-instable [MSI] localized gastric carcinomas [35]. Data from the DANTE study show that complete and subtotal tumor remissions can also be achieved with FLOT chemotherapy in gastric carcinomas of the MSI subtype. However, the response rate is significantly higher with the combination of chemotherapy and immunotherapy, and there is a significant risk of non-response and progression with chemotherapy alone [35, 36]. The identification of the best approach for resectable MSI-high gastric carcinomas is the subject of ongoing studies. A clear recommendation cannot be given at this time. Several studies show that the addition of an immune checkpoint inhibitor to neoadjuvant chemotherapy in cases of deficient DNA mismatch repair/microsatellite instability [dMMR/MSI] leads to significantly increased remission rates [34, 136]. In addition, exploratory subgroup analyses also show that EFS and OS are significantly improved when perioperative chemotherapy is supplemented with an immune checkpoint inhibitor in MSI-high gastric carcinomas [140]. The FFCD-NEONIPIGA phase 2 study shows a high histopathological remission rate after 12 weeks of therapy with nivolumab + ipilimumab without chemotherapy in resectable MSI carcinomas [122]. The same observation was reported in the GONO Infinity study in a small group of patients who received neoadjuvant treatment with durvalumab + tremelimumab [146]. The data still need to be validated in larger and independent cohorts. Nevertheless, preoperative immunotherapy - currently most likely in combination with FLOT chemotherapy, as tested in the randomized and controlled studies Dante, Keynote-585, and Matterhorn in terms of safety, response rate, and EFS (Matterhorn) - can be considered in cases of confirmed MSI-high status, regardless of the approval status of the drugs.

There is currently no established indication for pre- or postoperative radiotherapy, regardless of the underlying tumor subtype. Following publication of the ESOPEC and TOPGEAR studies, this applies to subcardial gastric carcinomas and adenocarcinomas of the esophagogastric junction [149, 150]. Adjuvant chemoradiotherapy may only be considered after R1 resection; see chapter 6.2.2.1.

Figure 6: Perioperative systemic therapy for gastric adenocarcinoma in stages IB to III



Legend:
FLOT: 5-fluorouracil, folinic acid, oxaliplatin, docetaxel;
**Currently off-label (as of August 2025), but significant benefit in event-free survival demonstrated in randomized placebo-controlled phase III Matterhorn trial.*

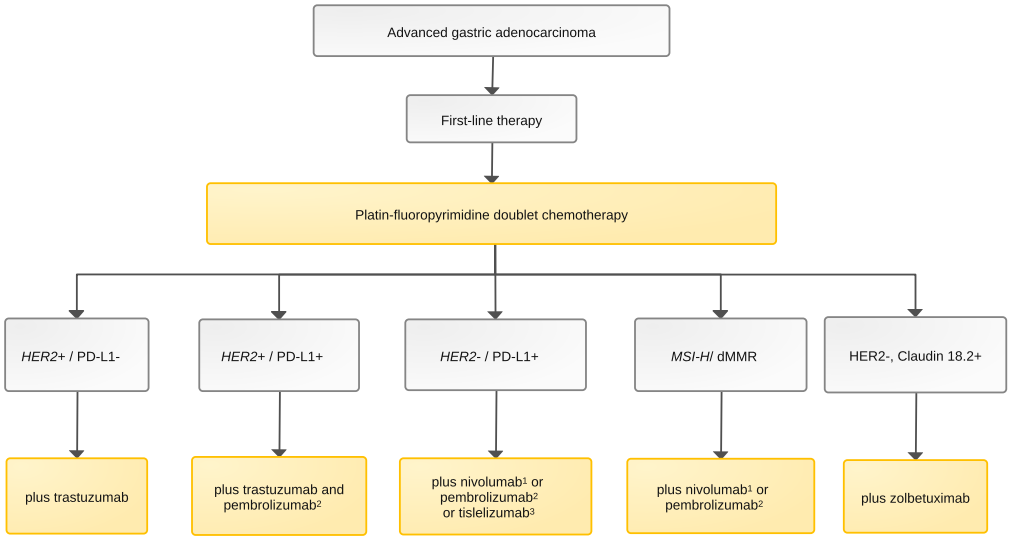
6.1.4 Stage IV

In stage IV gastric cancer, the goal of therapy is generally non-curative. Systemic drug therapy is the first line of treatment, supplemented by local therapeutic measures in individual cases. Active symptom control and supportive measures such as nutritional counseling, psychosocial support, and palliative care are an integral part of treatment. The prognosis for patients with locally advanced and unresectable or metastatic (here: "advanced") gastric cancer is poor. Studies evaluating the value of chemotherapy have shown a median survival time of less than one year in the past [35]. However, it has been proven that chemotherapy can prolong the survival of patients with advanced gastric cancer compared to best supportive care alone, while maintaining quality of life for longer [36]. Long-term survival rates have improved significantly with the introduction of *HER2*- and Claudin18.2-targeted therapies and the introduction of immune checkpoint inhibitors.

6.1.4.1 Systemic tumor therapy – Stage IV

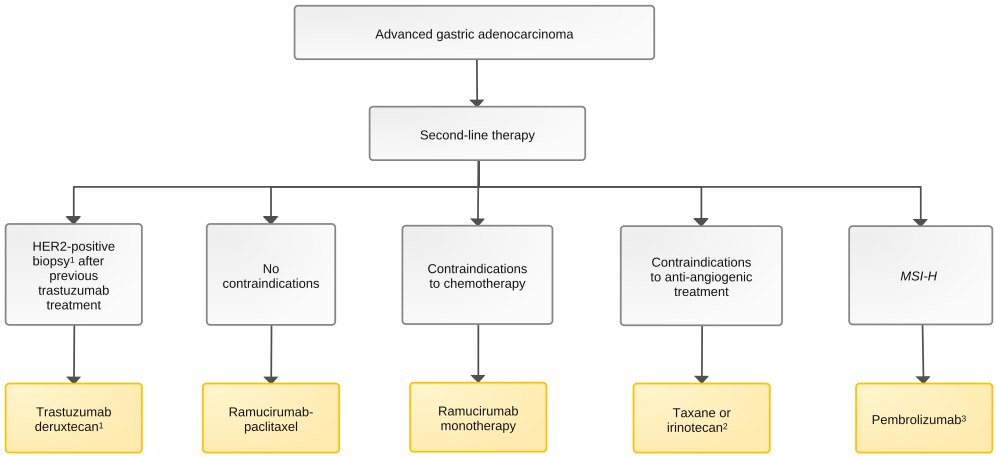
The currently recommended algorithms for systemic tumor therapy in patients with advanced gastric cancer are shown in Figure 7, Figure 8 and Figure 9.

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



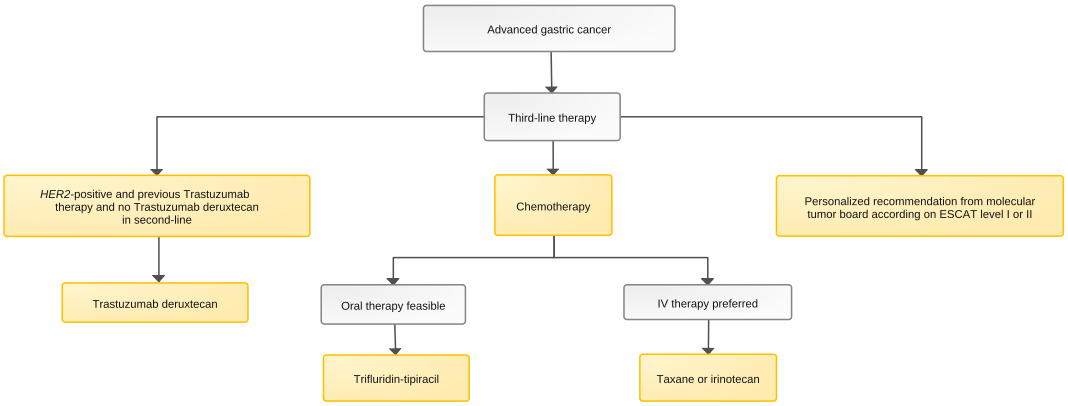
Legend:
:
[1]Nivolumab is approved in Europe for PD-L1 CPS ≥ 5 according to the Checkmate 649 study;
[2]Pembrolizumab is approved in Europe for adenocarcinoma of the esophagus with PD-L1 CPS ≥ 10 according to the Keynote-590 study and for HER2-negative and HER2-positive adenocarcinoma of the stomach and esophagogastric junction with PD-L1 CPS ≥ 1 according to the Keynote-859study and Keynote 811 study;
[3]Tislelizumab is approved in Europe for adenocarcinoma of the stomach and esophagogastric junction with PD-L1 TAP≥ 5%.

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



Legend:
[1] Since many tumors lose their HER2 overexpression after trastuzumab failure, it is recommended to re-evaluate the current HER2 status using a fresh biopsy before T-DXd therapy in the second line
[2] 5-FU/folinic acid-irinotecan is also used in some cases due to higher response rates compared to irinotecan monotherapy
[3] Pembrolizumab in second line therapy only if no PD-1/PD-L1 inhibitor was administered first-line

Figure 9: Algorithm for third-line therapy of advanced gastric cancer



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

6.1.4.1.1 First-line chemotherapy, targeted therapy, and immunotherapy

6.1.4.1.1.1 Chemotherapy

The standard first-line chemotherapy for advanced gastric cancer is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with oxaliplatin offering advantages in terms of its side effect profile. This can contribute to a tendency toward better efficacy, especially in older patients (>65 years) [23, 37]. Fluoropyrimidines can be administered as an infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparable in efficacy to infused 5-FU [38, 41]. Capecitabine is approved in combination with a platinum derivative and has been tested with both cisplatin and oxaliplatin in Europeans. S-1 is established as the standard in Japan and is approved in Europe for first-line palliative therapy in combination with cisplatin. Infusional 5-FU (e.g., FLO / FOLFOX) should be preferred over oral medications in cases of dysphagia or other nutritional problems. In elderly or frail patients, the results of the phase III GO-2 study support the use of dose-reduced oxaliplatin-fluoropyrimidine chemotherapy (at 80% or 60% of the standard dose from the start), which achieved comparable efficacy with fewer side effects [42].

The addition of docetaxel to a platinum-fluoropyrimidine combination (three-weekly DCF regimen) improved the radiological response rate and prolonged overall survival in an older phase-III-study, but at the same time led to significantly increased side effects [43]. Further phase II studies investigated modified docetaxel-platinum-fluoropyrimidine triplets. Some of these showed reduced toxicity compared to DCF [46, 49]. In the phase III JCOG1013 study, patients with advanced gastric cancer received either cisplatin/S-1 or cisplatin/S1/docetaxel. There were no differences in radiological response, PFS or OS [48]. However, the subgroup of patients who had already received adjuvant fluoropyrimidine-based chemotherapy after gastrectomy benefited significantly from the addition of the taxane in palliative therapy. The investigators also discuss that 79% of patients had received second-line therapy after the study, which may have influenced OS. A recently published French investigator-initiated phase III study showed significantly prolonged PFS and significantly prolonged OS for a platinum-fluoropyrimidine-docetaxel triplet (modified FLOT, called T-FOX) compared to the FOLFOX doublet. Median OS was improved from 12 to 15 months (HR 0.76, 95% CI 0.62-0.93; p=0.008) [145]. It should be noted that all patients were docetaxel-naive and that these effects were not observed in patients over the age of 65, in patients with an ECOG performance status worse than 0, and in patients with Laurén intestinal-type carcinomas. The toxicity rate was increased in numerous categories (hematological, gastrointestinal, neurological) with mFLOT/T-FOX. Nevertheless, the time to

deterioration in quality of life was significantly prolonged in the mFLOT/T-FOX group. Given the increased toxicity and uncertain effects on OS, no general recommendation can be made for first-line therapy with docetaxel-platinum-fluoropyrimidine. mFLOT/TFOX triplet chemotherapy is an individually applicable regimen for patients with high remission pressure, who have not been treated with docetaxel and who do not have the option of biomarker-based targeted or immune therapy. The standard remains a platinum-fluoropyrimidine doublet.

Irinotecan-5-FU was compared with cisplatin-5-FU and with epirubicin/cisplatin/capecitabine in randomized phase III studies and showed comparable survival times with controllable side effects [49, 50]. Irinotecan-5-FU (FOLFIRI) can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to scientific evidence, even though irinotecan is not approved for gastric cancer in Europe.

6.1.4.1.1.2 HER2-positive gastric cancer

HER2 positivity in gastric cancer is defined as the presence of protein expression with immunohistochemistry (IHC) score 3+ or IHC 2+ and simultaneous gene amplification in situ hybridization (ISH) *HER2*/CEP17 ratio ≥2.0. *HER2* diagnostics should be subject to quality control [51, 52]. Trastuzumab should be added to chemotherapy (e.g., CAPOX, FOLFOX or FLO) in patients with *HER2*-positive advanced gastric cancer [36, 53]. This recommendation is based on data from the phase III ToGA study, which showed a higher response rate and prolonged survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy versus chemotherapy alone in patients meeting the above selection criteria; the additional trastuzumab side effects are minor and controllable [53]. Combinations of trastuzumab and oxaliplatin plus fluoropyrimidine lead to comparable results to the historical cisplatin-containing ToGA regimen [54, 56]. Based on the randomized phase III Keynote-811 study [137], the EMA approved the combination of pembrolizumab plus trastuzumab and chemotherapy as first-line therapy for *HER2*-positive advanced gastric or esophagogastric (GEJ) adenocarcinomas with PD-L1 expression of CPS≥1 in September 2023 [134]. 698 patients with *HER-2* positive advanced carcinomas of the stomach or esophagogastric junction were randomized between platinum, fluoropyrimidine, trastuzumab with pembrolizumab, or placebo. 85% of patients received an oxaliplatin-based chemotherapy. In the 85% of patients whose tumors showed PD-L1 overexpression (PD-L1 CPS≥1), PFS was significantly prolonged in the pembrolizumab arm (HR 0.70; 95% CI 0.58-0.85). Median OS was prolonged from 15.7 to 20.1 months (HR 0.79; 95% CI 0.66-0.95) [137]. Patients with PD-L1-negative tumors do not benefit from the addition of pembrolizumab. In *HER2*- and PD-L1-positive tumors, pembrolizumab should therefore now be added to the chemo-trastuzumab combination.

6.1.4.1.1.3 Immunotherapy

The phase III CheckMate 649 study investigated the addition of nivolumab to chemotherapy (capecitabine–oxaliplatin or 5-FU/folinic acid-oxaliplatin) in patients with untreated advanced gastric, esophagogastric junction, or esophageal adenocarcinoma [57]. The study included patients regardless of tumor PD-L1 status; the dual primary endpoints were OS and PFS. Approximately 60% of the study population had tumors with a PD-L1 CPS ≥ 5. Nivolumab plus chemotherapy resulted in a significant improvement in OS compared to chemotherapy alone (14.4 vs. 11.1 months, HR 0.71 [98.4% CI 0.59-0.86]; p<0.0001) and in PFS (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. Long-term data confirm these results [135].

The Asian phase II/III ATTRACTION-04 study also showed a significant improvement in PFS with nivolumab added to first-line chemotherapy [58].

The multinational randomized phase III Keynote-859 study included 1,589 patients with advanced incurable gastric cancer. Patients received either platinum-fluoropyrimidine and pembrolizumab or the same chemotherapy and placebo intravenously every 3 weeks. OS was pro-

longed in the pembrolizumab group (HR 0.78 [95% CI 0.70-0.87], p< 0.0001). The effect was particularly pronounced in the subgroup with PD-L1 CPS ≥ 10 (HR 0.64). With PD-L1 CPS ≥ 1, there was a 26% reduction in the risk of death (HR 74 [95% CI 0.65-0.85], p<0.0001) [123].

The results thus complement the positive 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 a CPS ≥ 10 [124]. In January 2024, pembrolizumab was also approved in combination with first-line platinum-fluoropyrimidine chemotherapy for PD-L1 CPS ≥ 1.

In the phase III Rationale 305 study, tislelizumab prolonged OS in combination with platinum-fluoropyrimidine or platinum-investigator's choice chemotherapy in patients with a positive PD-L1 score (TAP ≥ 5%). TAP stands for tumor area proportion and is expressed as a percentage of the PD-L1-positive tumor area [126].

Patients with carcinomas with weak PD-L1 expression benefit only marginally in terms of OS from the addition of an immune checkpoint inhibitor to first-line chemotherapy. A combined analysis of the studies relevant for approval in Europe (CheckMate 649, Keynote-859, and Rationale-305) showed minimal efficacy: PD-L1 CPS 1-9, median survival 12.4 vs. 11.9 months, HR 0.84, p=0.002; PD-L1 CPS 1-4, median survival 12.1 vs. 12.0 months, HR 0.87, p=0.018; PD-L1 CPS 5-9, median survival 13.1 vs. 12.2 months, HR 0.87, p=0.18 [125].

6.1.4.1.1.4 Microsatellite-instable carcinomas

Due to the convincing effectiveness of PD-1/PD-L1 inhibitors in carcinomas with DNA mismatch repair deficiency (dMMR/MSI type), all patients with MSI-high gastric carcinomas or adenocarcinomas of the esophagogastric junction should be administered one of the approved PD-1 immune checkpoint inhibitors as first-line therapy. The subgroup analyses in all studies relevant to approval (CheckMate 649, Keynote-859) and also in studies that could not be used for approval (including Keynote-062) are convincingly positive for the administration of an immune checkpoint inhibitor plus chemotherapy. Based on the currently available data, it is uncertain whether the additional administration of chemotherapy can generally be dispensed with in this situation, and this should be investigated in studies.

6.1.4.1.1.5 Claudin 18.2

Data from the multinational phase III Spotlight study show that in patients with advanced unresectable 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 OS (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 few applications [127]. The results of the phase III Spotlight study are largely confirmed by the multinational phase III GLOW study, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab [128]. The aggregated data from Spotlight and Glow show an improvement in PFS (median 9.2 versus 8.2 months, HR 0.71 (95% CI 0.61–0.83) and an improvement in OS (median 16.4 versus 13.4 months, HR 0.77 (95% CI 0.67–0.89) [128].

Zolbetuximab was approved in September 2024 for the following indication: in combination with chemotherapy containing a fluoropyrimidine and a platinum analogue, for the first-line treatment of adult patients with locally advanced, unresectable, or metastatic HER2-negative adenocarcinoma of the stomach or esophagogastric junction whose tumors are Claudin18.2-positive.

Due to the high emetogenicity of zolbetuximab, special attention must be paid to consistent antiemetic prophylaxis and patient care. Current recommendations for highly emetogenic ther-

apies suggest the use of a four-drug antiemetic prophylaxis regimen comprising a 5-HT3 antagonist (setron), an NK-1 antagonist, dexamethasone, and olanzapine. Sufficient time must be planned for the first infusions of zolbetuximab, so that, if nausea and vomiting occur, infusion breaks can be taken. After recovery, restarting at a lower infusion rate is possible [152, 153].

6.1.4.1.2 Second- and third-line therapy

6.1.4.1.2.1 Chemotherapy and anti-angiogenic therapy

Figures 8 and 9 show the algorithm for second- and third-line therapy in patients with advanced gastric cancer. The evidence-based chemotherapy options in this situation are paclitaxel, docetaxel, and irinotecan, which have comparable efficacy with different substance-specific toxicities [59, 62]. Irinotecan may be preferred in cases of pre-existing neuropathy, even though it is still not approved in the EU for this indication. 5-FU/folinic acid–irinotecan (FOLFIRI) is also used occasionally, but the scientific evidence for this is limited [63]. Ramucirumab plus paclitaxel is the recommended standard therapy in the second line of treatment and is approved in the EU. The addition of the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) antibody ramucirumab to paclitaxel increased the tumor response rate and prolonged PFS and OS in the phase III RAINBOW study [64]. In the phase III REGARD study, ramucirumab monotherapy already had shown 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 study, pembrolizumab monotherapy did not show prolonged OS compared to chemotherapy [64]. However, an exploratory subgroup analysis identified a very clear benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric carcinomas [67]. PD-1 inhibition is therefore indicated in advanced MSI carcinomas at the latest in the second line of treatment. Pembrolizumab has a European approval for this indication based on the Keynote-061 and Keynote-158 studies [68]. Other biomarkers, in particular EBV and tumor mutation burden, are also being discussed as predictive factors for the efficacy of PD-1 immune checkpoint inhibitors [69, 71]. However, the evidence is not yet sufficient to make a positive recommendation for immunotherapy based on the presence of these biomarkers.

6.1.4.1.2.3 HER2-targeted therapy

Studies investigating trastuzumab, lapatinib, and trastuzumab emtansine as second-line treatments in patients with *HER2*-positive carcinomas yielded negative results [72, 75]. These drugs should therefore not be used in gastric carcinoma outside of clinical trials for this indication.

A randomized phase II study showed that the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) improved tumor response rates and OS compared to standard chemotherapy in patients with pretreated *HER2*-positive advanced gastric cancer [76]. The prerequisites for inclusion in the Destiny-GC-01 study were at least two previous lines of therapy, previous treatment with a platinum derivative, a fluoropyrimidine, and trastuzumab, as well as previously confirmed *HER2* positivity. The study was recruited exclusively in East Asia. The results of Destiny GC-01 were largely confirmed in the non-randomized phase II Destiny GC-02 study, which included non-Asian patients in the second line of therapy. Platinum-fluoropyrimidine-trastuzumab pretreatment and confirmed *HER2* positivity of the tumor in a recent re-biopsy were mandatory before T-DXd therapy was initiated [129]. Most recently, the Destiny GC-04 study demonstrated the superiority of T-DXd over ramucirumab plus paclitaxel in terms of OS (median 14.7 vs. 11.4 months; HR for death 0.70; 95% CI 0.55-0.90; p = 0.004) in patients with *HER2*-positive metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction confirmed by re-biopsy after disease progression during trastuzumab-based therapy [161]. The

EU approval includes the following use of T-DXd: monotherapy for the treatment of adult patients with advanced *HER2*-positive adenocarcinoma of the stomach or esophagogastric junction who have already received a previous trastuzumab-based therapy regimen.

In accordance with the classic established *HER2* diagnostic criteria, we recommend checking the *HER2* status before therapy with T-DXd, especially if it is to be used as a second-line therapy, where a valid alternative with paclitaxel-ramucirumab is available. This recommendation is based on the inclusion criteria of the Destiny-GC-02 study and the knowledge that approximately 30% of gastric carcinomas lose their *HER2*-positive status during first-line therapy with trastuzumab [72].

There is evidence of the efficacy of T-DXd in cases of low *HER2* expression [130]. However, this evidence is not yet sufficient to recommend its use.

6.1.4.1.2.4 Third-line therapy

In the treatment of patients with advanced gastric cancer in the third line and beyond, the best evidence for trifluridine–tipiracil (FTD/TPI; TAS-102) is based on the phase III TAGS study. Median OS with FTD/TPI versus placebo was significantly improved in the overall group, in the third-line cohort, and in the fourth-line cohort [77, 79]. If oral therapy is feasible, trifluridine–tipiracil (FTD/TPI) should therefore 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 carcinomas after trastuzumab pretreatment. Nivolumab has also proven to be effective; however, the data from the ATTRACTION-03 study were obtained exclusively from Asian patients [80], meaning that nivolumab is not approved by the EMA for third-line treatment in patients with advanced gastric cancer and therefore cannot be recommended.

Following the recommendation from a molecular tumor board, an unapproved treatment option may also be preferable in select cases, especially if the recommendation is based on a level of evidence corresponding to 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 study showed that gastrectomy in addition to chemotherapy in metastatic disease does not provide a survival advantage compared to chemotherapy alone [84]. International data collection shows that surgical therapy is increasingly being considered as a treatment option for oligometastasis [83, 85]. The AIO-FLOT3 phase II study reported results on the feasibility of resections in stage IV gastric cancer and survival times in highly selected patients with oligometastatic disease who were receiving FLOT chemotherapy without primary progression [86]. The randomized phase III RENAISSANCE study failed to show a survival benefit for surgical resection of the primary tumor and metastases in patients with stage IV gastric cancer [151].

A definition for oligometastasis was determined in a Delphi procedure by a European expert group (OMEC). According to this definition, the following phenotypes can be referred to as oligometastasis: 1-2 metastases in either the liver, lungs, retroperitoneal lymph nodes, adrenal glands, soft tissue, or bones [85]. In selected cases of oligometastasis, the tumor board may agree on the concept of primary systemic tumor therapy and, in case of remission, subsequent resection of the primary tumor with resection or ablation of metastases, provided that all tumor manifestations can be completely removed.

The current data do not allow for a recommendation for radical tumor resection in stage IV. Any decisions are individual approaches with an unclear survival benefit. Possible complications of surgery possibly resulting in shortening of life must be taken into account and should not be excluded from the consultation. Other local ablative procedures (stereotactic radiotherapy, radiofrequency ablation, etc.) have not yet been evaluated in this regard and therefore cannot be assessed.

6.1.4.1.4 Supportive care and nutrition

It is recommended that all patients with advanced gastric cancer undergo regular nutritional and symptom screening using appropriate instruments, and that adequate supportive care be derived from this. 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 obstruction of the digestive tract, malabsorption, or hypermetabolism. Clinical data show that weight loss of ≥10% before chemotherapy or ≥3% during the first cycle of chemotherapy is associated with reduced survival times [88]. A change in body composition with a reduction in muscle quality has also been 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]. It can therefore be concluded that all patients with advanced gastric cancer should undergo nutritional screening (e.g., using Nutritional Risk Screening, NRS) [91] and, if there are signs of nutritional deficiency, professional nutritional medical advice and support should be offered.

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

6.2 Treatment modalities

6.2.1 Surgical resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for the resection of early-stage carcinomas. The criteria for ER are outlined above (chapter 6.1.1). The methods used are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR of early gastric carcinomas is performed as en-bloc resection. It allows complete histological assessment of the lateral and basal margins. The recommended endoscopic follow-up intervals are 3 months in the first year and 6 months in the second year. After that, follow-ups should take place annually. Local recurrences after ER of early gastric cancer can be treated endoscopically if there is again solely mucosal involvement (rT1a cN0 cM0). A (limited) surgical procedure is an alternative, see Table 4.

6.2.1.1.1 Gastrectomy and lymphadenectomy

Surgery of the primary tumor is a central element of curative therapy. The goal is to achieve an R0 situation. Surgical therapy has a significant impact on the patient's prognosis. Depending on the location of the tumor, the standard procedures are total, subtotal, or transhiatal extended gastrectomy, each with systematic D2 lymphadenectomy. If the tumor has directly invaded adjacent organs/structures (spleen, diaphragm, pancreas), resection of these organs/structures is indicated. Diffusely invading carcinomas and early-stage carcinomas differ significantly in terms of resection strategy and the necessary safety margin. The passage is usually restored by Roux-Y reconstruction.

With regard to lymphadenectomy, a consensus has been reached in the Western world that patients with normal surgical risks should undergo D2 lymphadenectomy. D1 resection involves the removal of the perigastric lymph nodes; while D2 lymphadenectomy additionally removes the lymph nodes along the left gastric artery, common hepatic artery, splenic artery, and celiac axis [95]. Long-term results from a randomized study in 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 the resection and histopathological examination of at least 15 lymph nodes for reliable staging [21]. In the current German AWMF S3 guideline on gastric cancer, the removal of at least 25 lymph nodes is considered adequate [11]. The surgery should be performed at a certified high-volume center with sufficient surgical expertise and perioperative care [11]. Numerous studies demonstrate better short-term and long-term survival rates 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 covers all aspects of optimized perioperative care [102].

Patients who have undergone gastrectomy require regular vitamin B12 supplementation for the rest of their lives. Pancreatic enzyme supplementation is indicated after Roux-Y reconstruction.

6.2.2 Radiotherapy

6.2.2.1 Adjuvant radiochemotherapy

The North American Intergroup 0116 study showed that adjuvant therapy with 5-FU/folinic acid plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) improves OS compared to surgery alone (50% vs. 41% 3-year survival [66, 103]). This therapy was therefore recommended as a standard treatment in North America. In Germany and Europe, it was not universally accepted due to the inadequate surgical quality within the INT-0116 study. This reluctance is justified by the randomized controlled phase III CRITICS study, which suggested that adjuvant chemoradiotherapy reduces the local recurrence rate after D1 lymphadenectomy, but has no benefit after D2 lymphadenectomy [104]. The results presented in the Dutch-Scandinavian CRITICS study show that adjuvant chemoradiotherapy after neoadjuvant chemotherapy and quality-assured surgery does not provide a survival benefit [105]. The ARTIST-2 study conducted in Korea also failed to find any significance for adjuvant chemoradiotherapy compared to 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].

The multinational TOPGEAR study investigated whether preoperative chemoradiotherapy plus perioperative chemotherapy improves survival in patients with resectable gastric cancer or cancer of the esophagogastric junction compared to perioperative chemotherapy without pre-

operative chemoradiotherapy. The study did not achieve its primary endpoint. The median OS was 46 months with preoperative chemoradiotherapy and 49 months with perioperative chemotherapy (HR for death 1.05; 95% CI 0.83-1.31), and the median PFS was 31 months and 32 months, respectively [150].

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

6.2.3 Systemic tumor therapy

6.2.3.1 Systemic tumor therapy – anticancer agents

6.2.3.1.1 Cisplatin

In combination with other cytostatic drugs, cisplatin is part of the standard drug therapy in perioperative and palliative care. 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 dysbalance, and diarrhea.

6.2.3.1.2 Docetaxel

Docetaxel belongs to the taxane family and is an effective combination partner for fluoropyrimidines and platinum derivatives in perioperative and palliative therapy, e.g., as part of the FLOT regimen [32, 45, 111]. Severe grade 3 / 4 side effects include infections, nail changes, stomatitis, and diarrhea, while grade 2 side effects include alopecia. Particularly burdensome is polyneuropathy, which can be irreversible in some cases. Common side effects such as nausea/vomiting and allergic reactions can be prevented with adequate supportive care; see Onkopedia Antiemesis *(Guideline exists in German language only)*.

6.2.3.1.3 Fluoropyrimidines: 5-fluorouracil / capecitabine / tegafur (S-1)

5-fluorouracil is used in almost all forms of systemic tumor therapy for patients with gastric cancer. Its effectiveness is increased when combined with folinic acid. Severe side effects include diarrhea and stomatitis. Patients with functionally relevant polymorphisms of the 5-FU degradation genes have an increased risk of severe side effects.

Capecitabine is an oral fluoropyrimidine that is metabolized to 5-FU. In comparative clinical studies, it is at least as effective as 5-FU/folinic acid. It can be used in palliative therapy instead of 5-fluorouracil. In combination with platinum derivatives, remission rates of up to 45% are achieved. Severe side effects (grade 3 / 4) occurring in more than 5% of patients in the approval studies include diarrhea and hand-foot syndrome. Patients with functionally relevant polymorphisms of the 5-FU degradation genes have an increased risk of severe side effects.

Another orally bioavailable fluoropyrimidine, consisting of tegafur in combination with two modulators of the activity of 5-fluorouracil (5-FU), 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 com-

petes with uridine triphosphate, thereby 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, the European Medicine Agency has recommended that all patients taking the above-mentioned fluoropyrimidines be tested for dihydropyrimidine dehydrogenase (DPD) deficiency prior to initiation of therapy in order to prevent severe side effects caused by 5-fluorouracil, 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 of up to 40% may be achieved. FOLFIRI is at least as effective as cisplatin-fluoropyrimidine-based therapies in terms of PFS and OS. Severe side effects (grade 3 / 4) that occurred in more than 5% of patients in the approval studies include diarrhea, nausea/vomiting, neutropenia, and neutropenic fever. The substance can be administered as monotherapy weekly, biweekly, or triweekly.

6.2.3.1.5 Oxaliplatin

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

6.2.3.1.6 Paclitaxel

Paclitaxel belongs to the taxane family and is effective as monotherapy in palliative second-line therapy. Severe side effects (grade 3 / 4) include infections, stomatitis, diarrhea, and allergic reactions to the solvent Cremophor. Alopecia is one of the more distressing grade 2 side effects. Particularly burdensome is polyneuropathy, which can be irreversible in some cases. Frequent side effects such as allergic reactions can be prevented in some cases by adequate supportive care.

6.2.3.1.7 Ramucirumab

Ramucirumab is a VEGF receptor 2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab leads to a prolongation of PFS (HR 0.64; median 1.5 months) and OS (HR 0.81; median 2.2 months) and increases the remission rate. In patients who are not suitable for paclitaxel therapy, monotherapy with ramucirumab also prolongs PFS (HR 0.48; median 0.8 months) and OS (HR 0.78; median 1.4 months) compared with placebo. The only CTCAE grade 3 / 4 adverse event that occurred in more than 5% of patients receiving ramucirumab monotherapy was arterial hypertension. More common adverse events 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 palliative situations. In *HER2*-positive gastric cancer, trastuzumab in combination with a fluoropyrimidine and cisplatin leads to a prolongation of OS (HR 0.74; median 2.7 months) compared to chemotherapy alone. Severe side effects (grade 3 / 4) in this treatment setting are rare.

6.2.3.1.9 Trastuzumab deruxtecan (T-DXd)

Trastuzumab deruxtecan is an antibody-drug conjugate that contains a humanized monoclonal anti-*HER2* IgG1 antibody (mAb) with the same amino acid sequence as trastuzumab, which is 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 for the treatment of adult patients with advanced *HER2*-positive adenocarcinoma of the stomach or esophagogastric junction who have already received a previous trastuzumab-based therapy regimen. Patients treated with T-DXd must have 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 for gastric cancer (in contrast to breast cancer) is 6.4 mg/kg and is administered as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity occurs. The initial dose should be administered as a 90-minute intravenous infusion. If the first infusion was well tolerated, T-DXd can subsequently be administered as a 30-minute infusion. If the patient shows infusion-related symptoms, the infusion rate of T-DXd must be reduced or the infusion interrupted. In case of severe reactions to the infusion, T-DXd must be permanently discontinued. Particular attention must be paid to the possible occurrence of lung toxicity in terms of interstitial lung disease or pneumonitis. It should also be noted that trastuzumab deruxtecan has a moderate to high acute and delayed emetogenic potential. Therefore, prophylaxis with 3 antiemetics (dexamethasone, 5-HT3 antagonist, NK-1 antagonist) is recommended.

6.2.3.1.10 Trifluridine/tipiracil (FTD/TPI; TAS-102)

The combination drug FTD/TPI consists of the nucleoside thymidine analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil (TPI). The molar ratio of trifluridine to 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 diphosphate (TF-DP) and triphosphate (TF-TP). TF-TP is incorporated into DNA as a false building block. This incorrect incorporation results in long-lasting DNA damage and DNA strand breaks. TF-MP, in turn, binds covalently to tyrosine-146 in the active center of the enzyme thymidylate synthetase (TS, also thymidylate synthase) and inhibits its activity. TS is responsible for the conversion of uracil nucleotides into thymidine nucleotides and is therefore of vital importance for DNA synthesis by maintaining sufficient amounts of thymidine. TAS-102 proved superior to placebo in the third line of treatment for metastatic gastric cancer, prolonging OS (HR 0.69; $p<0.001$) and was tolerated satisfactorily: 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 Durvalumab

Durvalumab is a monoclonal anti-PD-L1 antibody that belongs to the substance class of immune checkpoint inhibitors (ICI). At the time of publication of this guideline, it is not yet approved for the treatment of gastric cancer, but it is approved for the treatment of small cell and non-small cell lung cancer, biliary tumors, and hepatocellular carcinoma (HCC). Durvalumab is administered as an intravenous infusion and, according to the study data on gastric cancer, can be administered perioperatively in combination with oxaliplatin plus 5-fluorouracil plus docetaxel (FLOT) chemotherapy and also, after a pre- and postoperative combined therapy phase, as subsequent monotherapy for a total duration of one year. The side effects are specific to the substance class. In the course of ICI-based therapy, immune-related adverse events (irAE) may occur due to autoimmune inflammation of various tissues or organs. For detection and management, we refer to current guidelines. After irAE have subsided, and after weighing the benefits as antitumor therapy against the risks of renewed, higher-grade irAE, ICI therapy may be continued in certain settings.

6.2.3.1.12 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 normally binds here. This indirectly stimulates the cellular immune system 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, esophagogastric junction, or esophagus in adults whose tumors express PD-L1 (combined positive score [CPS] ≥ 5). The recommended dose is 360 mg of nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine and platinum-based chemotherapy every 3 weeks, or 240 mg of nivolumab administered 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.

6.2.3.1.13 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 normally 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 the first-line treatment of locally advanced unresectable or metastatic *HER2*-negative adenocarcinoma of the stomach and esophagogastric junction in adults with PD-L1-expressing tumors (CPS ≥ 1). Pembrolizumab is also indicated as monotherapy for the treatment of gastric cancer with MSI-H or dMMR in adults after at least one prior line of therapy.

6.2.3.1.14 Tislelizumab

Tislelizumab is a drug from the group of monoclonal antibodies for the treatment of adult patients with esophageal cancer (squamous cell carcinoma of the esophagus), lung cancer

(non-small cell lung cancer), and gastric cancer or tumors of the gastroesophageal junction. As a PD-1 inhibitor, tislelizumab is classified as an immune checkpoint inhibitor. The active ingredient is a humanized monoclonal IgG4 antibody modified in the Fc region and was developed with the aim of minimizing binding to Fcγ receptors on macrophages and increasing the functional activity of T cells, which has been demonstrated in cell-based in vitro tests. Tislelizumab is indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the stomach and esophagogastric junction in adults with PD-L1-expressing tumors (TAP ≥ 5%).

6.2.3.1.15 Zolbetuximab

Zolbetuximab is a monoclonal antibody approved in combination with 5-fluorouracil and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced, unresectable, or metastatic *HER2*-negative adenocarcinoma of the stomach or esophagogastric junction. Patients with a Claudin-18.2-positive tumor (≥75% of tumor cells stain positive with an ICH score of 2+ or 3+) are eligible for therapy with zolbetuximab. Claudin-18.2 is a transmembrane protein that is expressed in approximately 38% of patients with the aforementioned types of cancer. Zolbetuximab is administered as an intravenous infusion. Prior to the infusion of zolbetuximab, premedication with antiemetics is recommended:

- Antiemesis with zolbetuximab should be based on the guideline recommendations for highly emetogenic substances [152, 153].
- The focus of prophylaxis and management is on the first two doses, as studies have shown that nausea and vomiting occur most frequently during these doses. Patients should be made aware of the efficacy of zolbetuximab and it should be emphasized that nausea and vomiting occur less frequently from the second cycle onwards.
- It is particularly important to actively ask patients about side effects during and after the first dose. Nursing staff play an important role in monitoring and managing side effects.

6.3 Special settings

6.3.1 Peritoneal metastasis

Several smaller randomized studies from Asia suggest a survival advantage for adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with curatively resected gastric carcinomas with a high risk of recurrence [109, 110]. The ongoing randomized GASTRICHIP study is attempting to clarify the efficacy of this approach in a European patient population [111]. For patients with peritoneal metastasis, there are also smaller randomized studies from Asia that suggest a benefit 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 rate 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 study. The study had to be terminated prematurely after 105 patients due to slow recruitment and showed no survival benefit [114]. Based on current knowledge, adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and peritonectomy are not standard therapies.

6.3.2 Signet ring cell carcinoma in locally advanced stages

Gastric carcinomas with signet ring cells are associated with a poorer prognosis. This is at least partly due to late diagnosis with higher tumor stages at initial diagnosis [115]. Retrospective case series suggest that signet ring carcinomas respond less well to chemotherapy and chemoradiotherapy [116, 117]. A retrospective study from a French national registry, albeit without a central histopathological review of the findings, suggests a poorer prognosis for patients with signet ring cell carcinoma who receive perioperative chemotherapy in addition to resection [118]. However, the evidence from these studies is insufficient for specific treatment recommendations. A French study (PRODIGE 19 - FFCD1103 - DCI002) addressed the question of perioperative chemotherapy for resectable signet ring cell carcinomas of the stomach and compared this standard with adjuvant chemotherapy alone [119]. An evaluation published as an abstract showed that perioperative chemotherapy was sufficiently effective in patients with signet ring cell carcinoma [120]. In the FLOT-4 study, the remission rate was the same under FLOT and under ECF/ECX, but in a subgroup analysis, the OS 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 carcinomas.

7 Rehabilitation

Gastric carcinoma and the treatments, both surgical and medicinal, can lead to considerable secondary disorders such as weight loss, tumor cachexia, maldigestion and neuropathy. In addition, patients are often psychologically stressed and suffer from fatigue syndrome. Targeted rehabilitative measures are therefore necessary. When selecting the rehabilitation facility, the approval of the clinic for gastric carcinoma patients by the health insurance (pension insurance, health insurance) is a prerequisite; in addition, the patient's right of wish and choice according to §9 of the German SGB IX should be taken into account. During rehabilitation, comprehensive nutritional advice should be given, patients should be included in the training kitchen, and there should be the possibility of administering all scientifically recognized diets, from normal whole foods to complete parenteral nutrition. All patients should be offered psycho-oncological care. Rehabilitation facilities should be able to continue ongoing drug therapies, including chemotherapy and immunotherapy, in accordance with the pre-treatment centers. Patients who have not yet reached the statutory retirement age should be informed about benefits for participation in working life as part of medical-occupational rehabilitation (German MBOR). Social-medical issues and any further care that the patient may require should be clarified during 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 timely detect an unfavorable course of the disease in time and not to expose patients to ineffective therapies for an unnecessarily long time, or to maintain the chance of more effective therapies.

8.2 Follow-up

There are no prospective data on which a recommendation for a specific follow-up regimen could be based. The AWMF S3 guideline recommends offering patients structured follow-up

care after curative therapy, including clinical monitoring, endoscopic monitoring, and imaging monitoring. The follow-up should be repeated at least every six months for the first two years and then at least annually until the fifth year. In past and ongoing studies, the regimen shown in Table 5 has become established.

Table 5: Structured monitoring and follow-up in the setting of curative-intended therapy

Procedure	Monthly interval since surgery (optional intervals in parentheses)													
	(3)	6	(9)	12	(15)	18	(21)	24	(30)	36	(42)	48	54	60
Medical history, physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory: Blood count and routine serum tests	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 scan of the chest/ abdomen/ pelvis	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Legend:
[1] Optional if no symptoms, recommended promptly if signs and symptoms suggestive of tumor recurrence, postoperative complications, or other endoscopically detectable pathologies are present.

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.