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Gastric Cancer

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

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Gastric Cancer

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- Guideline
- Conflict of interests

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1 Summary

Gastric carcinoma is one of the common malignancies. As in other parts of the Western world, the incidence in Germany, Austria and Switzerland has been decreasing continuously during the past decades. Men are affected twice as often as women. Some patients have a hereditary risk. Acquired risk factors include Helicobacter pylori infection of the gastric mucosa. Population-based endoscopic screening to detect early gastric cancer is not currently recommended for Germany.

The prognosis of gastric cancer patients is mainly determined by stage, but also by histologic subentity, general condition, and comorbidity. In early and localized stages, the therapeutic approach is curative, however, palliative in metastatic disease. Main therapeutic modalities are surgery and medical tumor therapy. Despite some progress in the last 10 years, cancer-specific mortality is still very high around 70%.

This guideline refers to adenocarcinoma of the stomach. Recommendations on tumors of the esophago-gastric junction can be found at Onkopedia Esophageal Cancer. Recommendations on less common, non-epithelial tumors of the stomach can be found in Onkopedia Gastrointestinal Stromal Tumors (GIST) or Onkopedia Extranodal Marginal Zone Lymphomas.

2 Basics

2.1 Definition and basic information

Gastric carcinomas arise in the proximal portions of the stomach (subcardiac), in the middle third (fundus and corpus), and in the distal stomach (antrum). Gastric carcinomas arising subcardially often have an anatomic relationship to the esophago-gastric junction and are therefore 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 specific aspects 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 must be distinguished from gastric carcinoma.

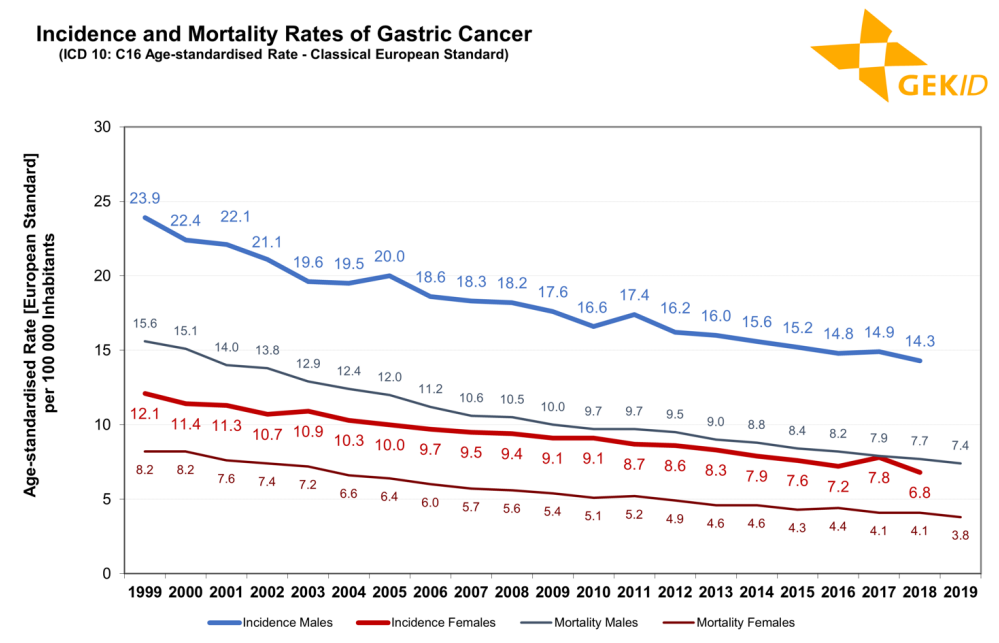
2.2 Epidemiology

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 com-

mon 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.

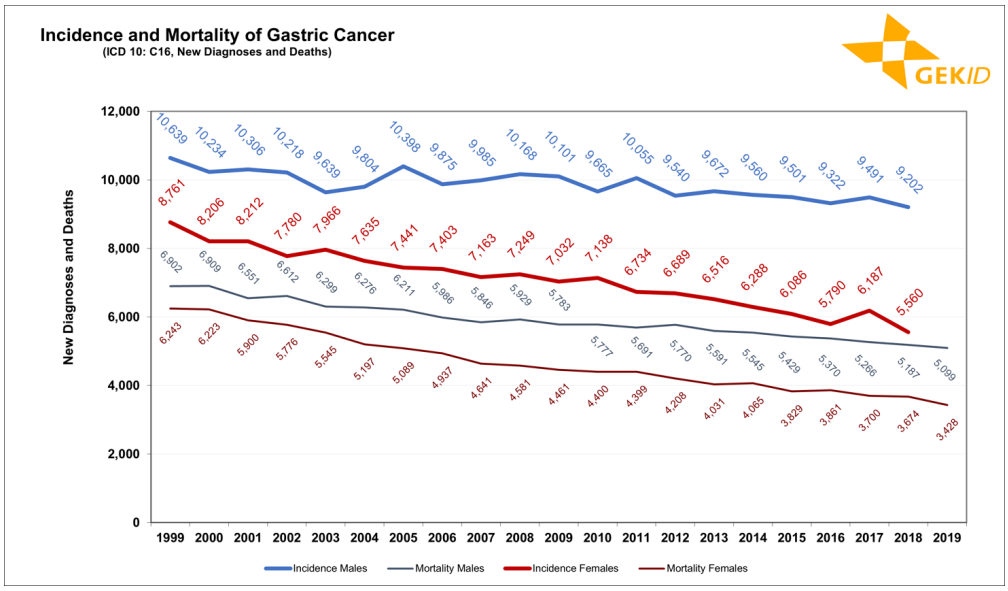
The age-standardized incidence rates, as well as the age-standardized mortality rates, have been decreasing for years in both sexes, see Figure 1. The age-standardized incidence rate in men has decreased by an average of 2.2% per year in the past 16 years - the mortality rate even by an average of 3.4% 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 of gastric cancer (ICD 10: C16) in Germany - age-standardized rates (old European standard) [1].



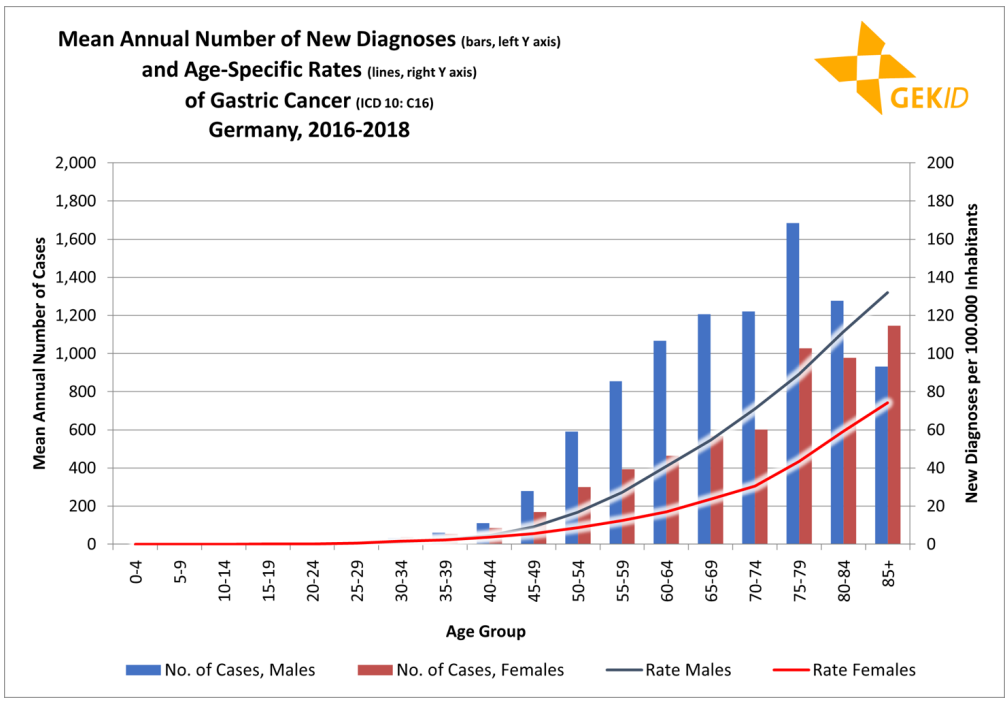
While age-standardized new case rates are a measure of disease probability and are largely independent of the population structure, the number of new cases reflects age structure and population size in addition to disease probability. Due to the shift in the age structure toward an older society and 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 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 85 years and older. Case numbers and incidence rates of males exceed those of females in all age groups.

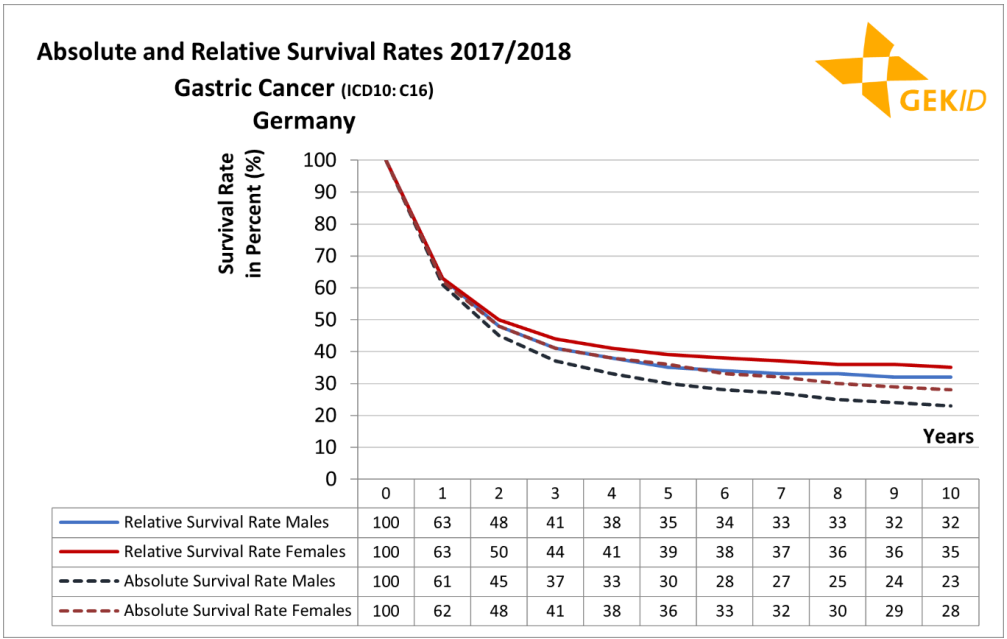
Figure 3: Age distribution of gastric cancer incidence (ICD 10: C16) - age-specific case numbers and rates [1].



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 carcinomas - in analogy to carcinomas of the rest of the digestive tract - develop sequentially in multistage processes via precancerous precursors 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 carcinomas are histologically heterogeneous in up to 30% of cases, i.e., have both intestinal and diffuse components, underscores the importance of local factors of cellular microenvironment and genetic or epigenetic heterogeneity. Generally accepted histological components of the sequential development of gastric carcinoma 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 non-polyposis colorectal carcinoma (HNPCC, Lynch syndrome [5].
  - hereditary diffuse gastric carcinoma (HDGC) with mutations in the cadherin 1- (CDH-) or catenin-alpha-1 (CTNNA1) gene [6, 7].

    - Peutz-Jeghers syndrome
    - first-degree relatives with gastric cancer
    - male gender (incidence males:females approximately 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
    - long-term use of proton pump inhibitors

Risk factors differ for different anatomic locations. Distal gastric carcinomas are often found associated with Helicobacter pylori infection of the gastric mucosa, high-salt diet, 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 Section 3.2.2. Currently, it is believed that the timing of treatment is critical for the efficacy of Helicobacter pylori eradication in preventing gastric cancer. This should occur before pre-neoplastic changes have developed [8]. However, data from randomized intervention trials are not available.

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

3.2 Early detection

3.2.1 Population

As Germany, Austria and 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 yet be given. At least a close endoscopic surveillance is recommended. Individual consultation in a specialized center is recommended [13, 14].

4 Clinical characteristics

4.1 Symptoms

Early gastric carcinomas are usually asymptomatic. The following symptoms often appear only 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 organs affected by metastases (such as liver capsule pain or ileus symptoms in peritoneal carcinomatosis).

Gastric carcinoma may present with various paraneoplastic syndromes, with cutaneous manifestations being observed more frequently than other paraneoplastic symptoms [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 endoscopy, it is possible to detect even discrete changes in the color, mucosal surface, and architecture of the gastric mucosa. Endoscopic detection of early lesions can be enhanced by chromoendoscopy.

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

Table 1: Diagnostics and staging in gastric carcinoma

Examination	Note
Physical examination	
Laboratory (blood)	blood count, liver and kidney function parameters, coagulation
Endoscopy of the upper gastrointestinal tract	optional addition of chromoendoscopy
Endoscopic ultrasound (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
Ultrasound abdomen	complementary to computed tomography
Laparoscopy with cytology[2]	in cT2/cT3/cT4 without evidence of distant metastases, to detect/exclude peritoneal metastasis

Legend:
[1] see chapter 5.2.3.1;
[2] Laparoscopy with cytologic examination of the lavage 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]. Laparoscopically abnormal findings are more frequently found in T3/T4 classified tumors [18].

5.2.2 Histology and subtypes

Histological diagnosis of gastric carcinoma should be made from a biopsy, evaluated by two experienced pathologists [11].

5.2.2.1 Laurén classification

Histologically, gastric carcinoma is characterized by a high degree of heterogeneity, as several different histological elements may be present in one tumor. Over the past decades, histological classification has been based on the Laurén classification [19]:

- intestinal type, approx. 54%
- diffuse type, approx. 32%
- indeterminant type, approx. 15%

The diffuse subtype is found more frequently 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.

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

- tubular
- papillary
- mucinous (colloid)
- 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 elements or other histologic patterns.

5.2.2.3 The Cancer Genome Atlas (TCGA) Classification.

Genetic molecular studies divide gastric carcinoma 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 instable - 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

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

Table 2: UICC-TNM classification - gastric cancer [21, 25].

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

Table 3: Classification of tumor stage [21, 25]

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

Endoscopic ultrasound (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 imaging [26]:

- Diameter ≥ 6-8 mm (shorter axis) of perigastric lymph nodes.
- round shape
- central necrosis
- loss of the fat hilus
- heterogeneous or increased contrast uptake.

The sensitivity of CT for lymph node staging is estimated at 62.5% to 91.9% in systematic reviews [27].

EUS improves accurate determination of T and N categories and can help to define the proximal and distal margin 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 [28]:

- hypoechoic
- round shape
- blurred demarcation from the surrounding area
- size in longest diameter > 1cm

6 Therapy

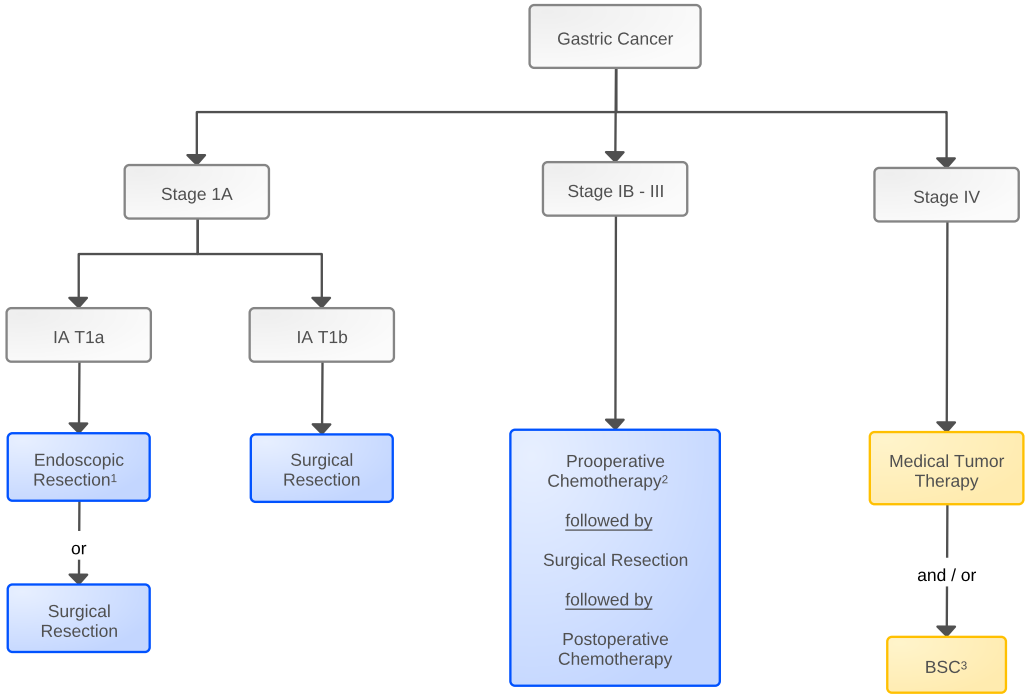
6.1 Treatment structure

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

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.

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

Figure 5: Algorithm for first-line therapy



Legend:

curative intended therapy; non-curative intended therapy;

[1] *see Table 4*

[2] *adjuvant chemotherapy or radiochemotherapy, if preoperative chemotherapy was not performed (e.g., due to misdiagnosed tumor stage prior to surgery).*

[3] *Best Supportive Care*

6.1.1 Stage IA - T1a (early carcinoma)

Since the probability of lymph node metastasis in mucosal gastric carcinoma (T1a) is very low, endoscopic resection (ER) may be sufficient [29]. If histopathological 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 will already be present in up to 30% of cases.

Gastric carcinomas classified as pT1a cN0 cM0 can be treated with endoscopic resection considering the adapted Japanese criteria if the following criteria are met [11, 30], see Table 4.

Table 4: Criteria for endoscopic resection in stage IA T1a [11, 109]

- Lesions ≤ 2 cm in elevated types
- Lesions ≤ 1 cm in flat types
- Histologic grade of differentiation good or moderate (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 curatively resected via endoscopy [11]. Endoscopic submucosal dissection (ESD) should be technique of choice for endoscopic resection. If more than one extended criterion is present, oncologic surgical resection should be performed. The extended criteria are defined as follows:

- Differentiated mucosal carcinoma (G1/2) without ulceration and size > 2cm.
- Differentiated mucosal carcinoma with ulceration and size < 3cm.
- Well-differentiated carcinoma with submucosal invasion < 500µm and size < 3cm
- Poorly differentiated mucosal carcinoma < 2cm in diameter (unless there is histological evidence of tumor cells at a distance ≤ 1cm [11])
- ER of early gastric carcinoma is performed as en-bloc resection. It allows complete histological evaluation 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 of follow-up. Thereafter, endoscopy 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.

6.1.2 Stage IA - T1b

In stage IA gastric carcinoma 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 gastric cancers in the SEER database [31], and the cancer-specific survival rate at 10 years in the Italian IRGGC analysis is 93%. The treatment of choice in stage T1b 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.

The value of perioperative or adjuvant chemotherapy is not proven 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 are no longer accepted. The scientific evidence for definitive 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 [32]. In the French FNCLCC/FFCD multicenter trial, perioperative chemotherapy with a platinum derivative and a fluoropyrimidine without an anthracycline showed a comparable overall survival improvement [33].

Treatment according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) further improved progression-free survival (hazard ratio 0.75) and overall survival (hazard ratio 0.77) in patients with stage ≥ cT2 and/or cN+ compared with therapy analogous to MAGIC; see also Section 6.2.3.1. The higher efficacy of FLOT was shown consistently across relevant subgroups defined by age, histology, and localization. The rate of perioperative complications was comparable between regimens [34].

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

In HER2-positive tumors, the value of combining perioperative chemotherapy with an HER2 antibody in the perioperative setting in terms of overall survival has not yet been proven and therefore cannot be recommended outside clinical trials.

In microsatellite instability (MSI)-high localized gastric carcinoma, the efficacy of perioperative chemotherapy has been controversially discussed, based on retrospective analyses [35]. However, recent data from the DANTE trial show that complete and subtotal tumor remissions can be achieved by FLOT chemotherapy even in gastric carcinomas of the MSI-H subtype [35, 36]. Thus, perioperative chemotherapy with the FLOT regimen is currently indicated for MSI-H gastric carcinomas, if tumor response is pursued.

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

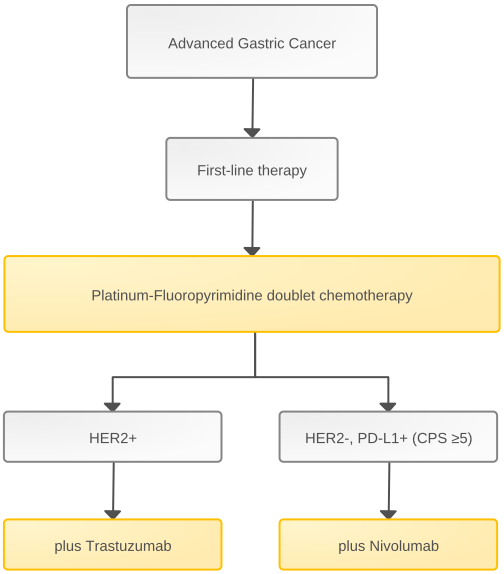
6.1.4 Stage IV

The goal of therapy is usually not curative. The first priority is systemic treatment, 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 (here: "advanced") gastric cancer is unfavorable. Studies evaluating the benefit from chemotherapy showed a median survival of less than one year [37]. Study results show that chemotherapy can prolong survival of patients with advanced gastric cancer compared with best supportive therapy alone and maintain quality of life longer [38].

6.1.4.1 Systemic tumor therapy

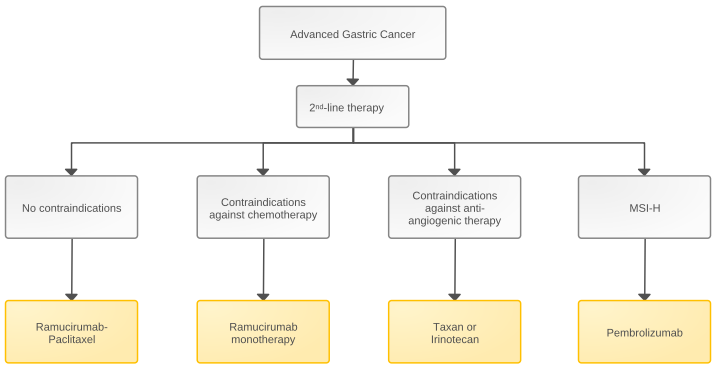
The recommended algorithms for systemic treatment of patients with advanced gastric cancer are shown in Figures 6-8.

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



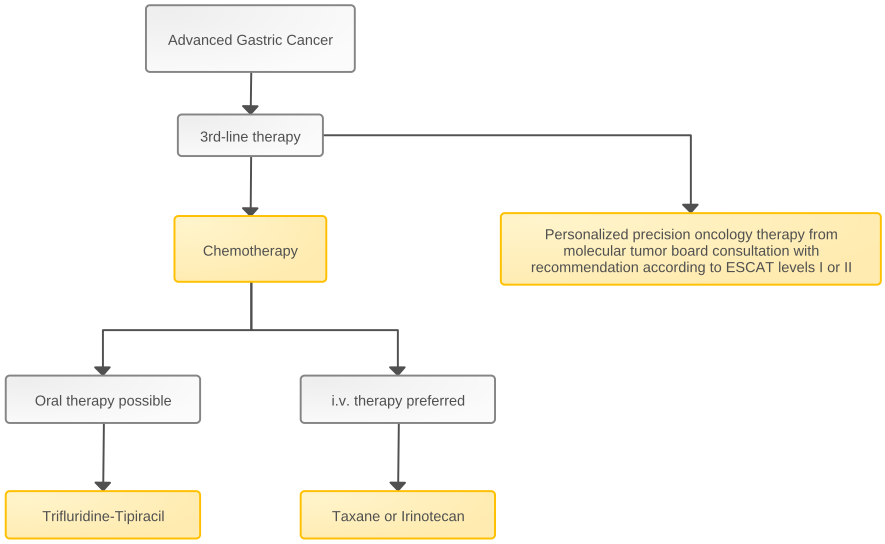
Legend:
HER2+, Human Epidermal Growth Factor Receptor-2 (see text); PD-L1, Programmed Cell Death Protein-1 (see text); CPS, Combined Positive Score

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



Legend:
MSI-H, Microsatellite Instability-high

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



Legend:
ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets [83]; i.v., intravenous

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

6.1.4.1.1.1 Chemotherapy

Standard for first-line chemotherapy of advanced gastric carcinoma is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with some advantages for oxaliplatin in terms of side effects. This may result in better efficacy, especially in patients > 65 years [39, 23]. Fluoropyrimidines can be administered as infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparably effective to infused 5-FU [40- 43]. 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 standard in Japan and approved in Europe for palliative initial therapy in combination with cisplatin. Infused 5-FU should be preferred to oral medications in cases of 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 from the beginning, resulting in fewer side effects with comparable efficacy [44].

The addition of docetaxel to a platinum-fluoropyrimidine combination (three-week DCF regimen) improved radiographic response rates and prolonged overall survival in a historical phase III trial, but also resulted in significantly increased side effects [45]. Phase II trials on modified docetaxel-platinum-fluoropyrimidine triplets showed reduced toxicity compared with DCF in some cases [46- 49]. The higher response rate of a triplet (37% versus 25% [45] does not translate into prolonged survival in recent trials, including more frequent use of effective second-line regimens. In the phase III JCOG1013 trial, patients with advanced gastric cancer received either cisplatin-S-1 or cisplatin-S1-docetaxel. There were no differences in radiographic response, progression-free survival, or overall survival [50]. Therefore, with increased toxicity and uncertain impact on overall survival, no standard 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 response is urgently required, first-line therapy with a platinum-fluoropyrimidine-docetaxel triplet may be indicated.

Irinotecan plus 5-FU has been compared with cisplatin-5-FU and with epirubicin-cisplatin-capecitabine in randomized phase III trials and showed comparable survival with manageable side effects [51, 52]. Irinotecan-5-FU can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to scientific evidence; however, use of irinotecan in gastric cancer is off-label in Germany.

6.1.4.1.1.2 HER2-positive gastric carcinoma

HER2 positivity is defined in gastric carcinoma as the presence of protein expression with immunohistochemistry score [IHC] 3+ or IHC 2+ and concomitant gene amplification on in situ hybridization [ISH] HER2/CEP17 ratio ≥ 2.0. HER2 diagnosis should be quality-controlled [53, 54]. Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer [38, 55]. 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 with the above selection criteria; the additional trastuzumab side effects are minor and manageable [55]. Combinations of trastuzumb and oxaliplatin plus fluoropyrimidine produce comparable results to the historical cisplatin-containing ToGA regimen [56- 58].

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/leucovorin-oxaliplatin) in patients with previously untreated gastric, esophagogastric junction, or esophageal adenocarcinoma [59]. The study included patients regardless of 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 yielded a significant improvement over chemotherapy alone in overall survival and progression-free survival in patients with a PD-L1 CPS ≥ 5.

The Asian phase II/III ATTRACTION-04 trial also demonstrated a significant improvement in progression-free survival in patients treated with nivolumab and first-line CTX, but with no improvement in overall survival compared with first-line chemotherapy alone. It can be assumed that the 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 chemotherapy [60].

6.1.4.1.2 Second- and third-line therapy.

Figure 5 shows the algorithm for second- and third-line therapy in 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 [61- 64]. Irinotecan can be used preferentially in patients with pre-existing neuropathy, but is not approved by the EMA for gastric carcinoma. 5-FU/folinic acid plus irinotecan (FOLFIRI) is also occasionally used, but the scientific evidence for its use in second and third line is limited [65]. Ramucirumab plus paclitaxel is approved by the EMA. The addition of this anti-vascular endothelial growth factor receptor-2 (VEGFR-2) antibody to paclitaxel increases tumor response rates and prolongs progression-free and overall survival according to the results of the phase III RAINBOW trial [66]. In the phase III REGARD trial, ramucirumab monotherapy showed prolonged survival compared to placebo, albeit with a low radiological response rate [67].

In the phase III KEYNOTE-061 trial, pembrolizumab monotherapy did not show prolonged overall survival compared with chemotherapy [68]. However, an exploratory subgroup analysis recognized a clear benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric cancer [69]. Therefore, PD-1 inhibition is recommended in advanced MSI carcinomas at latest in the second-

line treatment. Pembrolizumab has a European approval for this indication based on the KEYNOTE-158 trial [70]. Other biomarkers, particularly EBV and tumor mutation burden, are also discussed as predictive factors for PD-1 immune checkpoint inhibitor efficacy [71- 73]. However, the evidence to date is insufficient for a positive recommendation for immunotherapy based upon the presence of these biomarkers.

Studies investigating trastuzumab, lapatinib, and trastuzumab emtansine in the second-line treatment of patients with HER2-positive carcinomas were negative [74- 77]. Therefore, these drugs should not be used in gastric carcinoma outside of clinical trials. A recently published randomized phase II trial showed an improvement in overall survival for the antibody-chemotherapy conjugate trastuzumab-deruxtecan (TDx-1), compared with standard chemotherapy in patients with pretreated HER2-positive advanced gastric carcinoma [78]. This led to a Food and Drug Association (FDA) approval of the drug by the, but not yet by the European Medicines Agency (EMA). Therefore, TDx-1 should not be used for use outside of clinical trials in Europe. Confirmatory studies on the efficacy of TDx-1 in HER2-positive gastric cancer are currently ongoing in Europe.

In the treatment of patients with advanced gastric cancer in 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, third-line, and fourth-line group [79- 81]. Therefore, if oral therapy is feasible, trifluridine-tipiracil (FTD/TPI) should be used. Alternatively, if i.v. therapy is preferred, irinotecan or a taxane can be given, if not already used in a previous line of therapy. Nivolumab also proved effective; however, the data from the ATTRACTION-03 trial were obtained exclusively in Asian patients [82], so nivolumab for third-line treatment in patients with advanced gastric cancer has no EMA approval and cannot be recommended for clinical use.

If recommended by a molecular tumor board, an off-label drug therapy may also be justified, particularly if the recommendation can be based on a level of evidence according to ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) level I or II [83].

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 does not confer a survival benefit compared with chemotherapy alone [84]. International data analyses show that surgical resection for oligometastastic disease is increasingly perceived as a treatment option [85- 87]. 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 without primary progression on FLOT chemotherapy [88]. The potential prognostic benefit of resection for oligometastatic gastric cancer is currently being evaluated in randomized phase III trials (RENAISSANCE, NCT0257836) and SURGIGAST, NCT03042169.

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 provided. A study from China showed that early integration of supportive palliative care is effective and appears to confer a survival benefit in patients with advanced gastric cancer [89].

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 [90]. A change in body composition with impaired muscular capacity was also shown to be prognostically unfavorable in patients with advanced gastric cancer [91]. The modified Glasgow Prognostic Score (serum C-reactive protein and albumin) can be used to assess the extent of sarcopenia and predict the prognosis of patients with advanced gastric cancer [92].

It can be recommended that screening for nutritional status should be performed in every patient with advanced gastric cancer (for example, using Nutritional Risk Screening, NRS) [93] and expert nutritional counseling and co-supervision should be offered if there is evidence of malnutrition.

Dysphagia in proximal gastric carcinoma can be ameliorated by radiotherapy or stent insertion [94]. 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 takes approximately 4-6 weeks to improve dysphagic symptoms [95]. When radiotherapy or a stent are not an option, enteral nutrition via naso-gastric, naso-jejunal, or percutaneously placed feeding tubes may provide relief [96]. 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 cancers. The criteria for ER are described above (Section 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 evaluation 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, endoscopy should be performed annually. Local recurrences after ER of early gastric carcinoma can be treated endoscopically 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 receive D2 lymphadenectomy. D1 resection includes removal of the perigastric lymph nodes; D2 lymphadenectomy includes additional removal of the lymph nodes along the A. gastrica sinistra, A. hepatica communis, splenic artery, and coeliac axis [97]. 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 [98]. The current UICC/AJCC TNM (8th edition) classification recommends removal and examination of at least 15 lymph nodes for reliable staging [99]. 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 specific surgical expertise and perioperative care [11].

Numerous studies demonstrate better short-term and long-term survival for patients treated at centers with certified expertise [100- 102]. Perioperative morbidity and mortality should not exceed 15% and 3%, respectively [103]. The concept of "enhanced recovery" is outlined in the Enhanced Recovery After Surgery (ERAS®) Society Guidelines and encompasses all aspects of optimized perioperative care [104].

In patients after gastrectomy, regular parenteral substitution of vitamin B12 is required throughout 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 study showed that adjuvant therapy with 5-FU/leucovorin plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) improved overall survival compared with surgery alone (50% vs. 41% 3-year survival [68, 105]). 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 a Dutch study suggesting that adjuvant radiochemotherapy reduces the local recurrence rate after D1 lymphadenectomy, but shows no benefit after D2 lymphadenectomy [106].

The presented results of the Dutch-Scandinavian CRITICS trial show that adjuvant radiochemotherapy does not confer a survival benefit after neoadjuvant chemotherapy and quality-assured surgery [107]. The ARTIST-2 trial from Korea 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 [108].

In conclusion, after curative resection of gastric carcinoma with adequate lymphadenectomy, adjuvant radiochemotherapy is now obsolete.

In patients with R1 resection, retrospective studies suggest that adjuvant radiochemotherapy may improve prognosis [102, 109]. Therefore, in individual cases, after weighing the questionable 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 Capecitabine

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 (DPD) have an increased risk of severe side effects.

6.2.3.1.2 Cisplatin

In combination with other cytostatic drugs, cisplatin is part of the standard treatment 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 loss, and diarrhea.

6.2.3.1.3 Docetaxel

Docetaxel belongs to the taxane class. Docetaxel is an effective combination partner of fluoropyrimidines and platinum derivatives in perioperative and palliative therapy, and is a component of the FLOT regimen [34, 47, 113]. Severe grade 3/4 side effects include infection, nail changes, stomatitis, and diarrhea; grade 2 side effects include alopecia. Particularly harmful is polyneuropathy, which may be irreversible. Common side effects such as nausea/vomiting and allergic reactions can be prevented by adequate supportive therapy, see Onkopedia Antiemesis.

6.2.3.1.4 -fluorouracil / capecitabine / tegafur/S-1

5-Fluorouracil is found in almost all forms of systemic therapy for patients with gastric cancer. Its efficacy is increased by combination with folinic acid. Serious side effects include diarrhea and stomatitis. Patients with functionally relevant polymorphisms of the genes involved in 5-FU degradation (DPD) are at increased risk for 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 (DPD) have an increased risk of 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), reducing 5-FU activation in the intestine and gastrointestinal toxicity associated with 5-FU.

Since 2020, all of the aforementioned fluoropyrimidines have been subject to the European Medicine Agency recommendation that patients be tested for dihydropyrimidine dehydrogenase (DPD) enzyme deficiency prior to therapy initiation to prevent severe adverse reactions 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).

6.2.3.1.5 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with fluoropyrimidines, remission rates may reach 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) occurring in more than 5% of patients in pivotal studies included diarrhea, nausea / vomiting, neutropenia, and neutropenic fever. The compound can be applied as monotherapy weekly, bi-weekly or tri-weekly.

6.2.3.1.6 Oxaliplatin

This platinum derivative is effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line stage IV therapy, 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.

6.2.3.1.7 Paclitaxel

Paclitaxel is one of the taxanes. Paclitaxel is effective as monotherapy in second-line palliative therapy. Severe side effects (grade 3/4) include infection, stomatitis and diarrhea, and allergic reactions to the agent’s solvent cremophore; grade 2 side effects include alopecia. Particularly burdensome is a partly irreversible polyneuropathy. Common side effects such as allergic reactions can be partally prevented at least in part by adequate supportive therapy.

6.2.3.1.8 Ramucirumab

Ramucirumab is a VEGF receptor type 2 antibody that inhibits angiogenesis. In combination with paclitaxel, ramucirumab leads to prolongation of progression-free survival (hazard ratio 0.64; median 1.5 months), prolongation of overall survival (hazard ratio 0.81; median 2.2 months), and an increase in remission rate compared with paclitaxel monotherapy. In patients ineligible for paclitaxel therapy, ramucirumab monotherapy versus placebo also results in prolonged progression-free survival (hazard ratio 0.48; median 0.8 months) and overall survival (hazard ratio 0.78; median 1.4 months). The only adverse event in 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%).

6.2.3.1.9 Trastuzumab

Trastuzumab is the first developed monoclonal antibody to specifically interfere with the HER2/neu receptor and has been approved for the treatment of patients with tumor 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 (hazard ratio 0.74; median 2.7 months). Severe adverse events (grade 3/4) are rare.

6.2.3.1.10 Trifluridine/Tipiracil (FTD/TPI).

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/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 defective component. This incorrect 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 thymidine nucleotides and is thus essential for DNA synthesis by maintaining sufficient amounts of thymidine. TAS-102 proved superior to placebo in the third-line treatment of metastatic gastric cancer, prolonging overall survival (HR 0.69; $p < 0.001$) and was moderately 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 immunoglobulin G4 (IgG4) class monoclonal antibody 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 immunoglobulin G4 (IgG4) class monoclonal antibody 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 carcinoma with MSI-H or with a dMMR in adults after at least one prior 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 carcinoma at high risk of recurrence [111, 112]. The ongoing randomized GASTRICHIP trial aims to clarify the efficacy of this approach in a European patient population [113]. Smaller randomized trials from Asia also exist for patients with peritoneal metastasis, suggesting an advantage for cytoreductive surgery and HIPEC [114]. 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 [115]. 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 [116].

Based on current knowledge, adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and peritonectomy are no standard therapies.

6.3.2 Signet ring cell carcinoma in locally advanced stages.

Gastric carcinomas with signet ring cells are associated with a poor prognosis. This is at least partly due to late diagnosis with occurrence of higher tumor stages at initial diagnosis [117]. Retrospective case series suggest that signet ring carcinomas respond less well to chemotherapy and radiochemotherapy [118, 119]. A retrospective study from a French national registry, albeit without a central histopathologic review of tumor samples, suggests a worse prognosis for patients with signet ring carcinomas who receive perioperative chemotherapy in addition to resection [120]. 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. An evaluation published as an abstract showed sufficient efficacy of perioperative chemotherapy in patients with signet ring carcinoma [121]. In the German FLOT-4 trial, the remission rate for signet-ring cell cancers was the same under FLOT and under ECF/ECX chemotherapy; however, in a subgroup analysis, overall survival in the FLOT arm was significantly prolonged in patients with signet-ring cell carcinoma [34]. 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 carcinoma as well as therapies for gastric cancer, both surgical and systemic, can lead to significant sequelae such as weight loss, maldigestion, and neuropathy. In addition, patients are often psychologically stressed and exhibit fatigue syndrome.

Therefore, specific rehabilitative measures are necessary. These should be carried out promptly after completion of primary therapy.

When selecting the rehabilitation facility, the approval of a clinic specifically for gastric cancer patients by the providers (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.

Every patient should be offered psycho-oncological care.

Rehabilitation facilities should be able to continue systemic tumor therapies, if necessary.

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, the patient's general condition and vital body functions should generally be checked once a week, or more frequently if necessary [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 for 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 offering patients a structured follow-up after curative therapy, which includes clinical, 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 in Table 5 has been established.

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

Procedure	**after end of treatment (months)**													
	(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	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

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16 Disclosure of Potential Conflicts of Interest

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

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Al-Batran, Salah-Ed-din	Conflict of interest declarations pending							
Arnold, Dirk	Asklepios Kliniken Hamburg	**Yes** Amgen, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Janssen Cilag, Merck Sharp and Dome, Pierre Fabre Pharma, Roche, Samsung, Servier, Terumo	**No**	**No**	**Yes** AstraZeneca, Boston Scientific, Bristol Myers Squibb, Ipsen, Janssen Cilag, Merck Sharp and Dome, Merck (Darmstadt) Novartis, Pierre Fabre Pharma, Roche, Sanofi, Servier, Terumo Verschiedene CME-Provider	**Yes** OncoLytics	**No**	**No**
Borner, Markus		**No**	**No**	**No**	**No**	**No**	**No**	**No**
Bruns, Christiane J.	Conflict of interest declarations pending							
Eisterer, Wolfgang	Allgemein öffentliches Klinikum Klagenfurt am Wörthersee Innere Medizin 1 St. Veiter Str. 47 9020 Klagenfurt	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Faber, Gerhard	CELENUS Teufelsbad Fachklinik Michaelstein 18 38889 Blankenburg/Harz	**Yes** Gutachter für die Deutsche Rentenversicherung Mitteldeutschland	**No**	**No**	**Yes** Vortragshonorare für Vorträge für Bristol-Myers-Squibb	**No**	**No**	**No**
Gockel, Ines	Universitätsklinikum Leipzig AöR Liebigstraße 20 04103 Leipzig	**Yes** onkowissen.de GmbH Roche GmbH	**No**	**No**	**Yes** ETHICON Johnson & Johnson streamed-up! GmbH FALK Foundation	**No**	**No**	**No**
Köberle, Dieter	St. Claraspital (Basel) Medizinische Klinik, Onkologie Kleinriehenstr. 30	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Lordick, Florian	Universitätsklinikum Leipzig	**Yes**	**No**	**No**	**Yes** AstraZeneca, Bayer, BMS, Eli Lilly, Elsevier, Incyte, MedUpdate GmbH, Merck, MSD, Novartis, Roche, Servier, Springer-Nature, StreamedUp!	**Yes** BMS, MSD (jeweils an Institution)	**No**	**No**

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
		Amgen, Astellas, Astra Zeneca, Bayer, Biontech, BMS, Eli Lilly, Incyte, MSD, Novartis, Roche, Servier,						
Lorenzen, Sylvie	Klinikum rechts der Isar, Technische Universität München	**Yes** Eli-Lilly, Servier, MSD, BMS, Daiichi-Sankyo, Astra Zeneca	**No**	**No**	**Yes** Eli-Lilly, Servier, MSD, BMS, Daiichi-Sankyo, Astra Zeneca	**No**	**No**	**No**
Möhler, Markus	Leiter Gastrointestinale Onkologie, UCT, Universitätsmedizin Mainz	**Yes** Beratungstätigkeit Amgen, Astellas, Beigene, BMS, Dragonfly, Lilly, Macrogenics, Merck, MSD, Pfizer, Roche, Sanofi, Taiho	**No**	**No**	**Yes** Honorare Amgen, BMS, Lilly, mci, MSD, Merck	**Yes** Finanzierung wissenschaftlicher Untersuchungen Amgen, BMS, EORTC, Merck, MSD,	**No**	**No**
Pritzkuleit, Ron	Institut für Krebsepidemiologie an der Universität zu Lübeck Registerstelle des Krebsregisters Schleswig-Holstein	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Stahl, Michael	Evang. Huyssens-Stiftung Kliniken Essen-Mitte Klinik für Intern. Onkologie und Hämatologie	**Yes** Novartis, BMS, Lilly, Daiichy-Sankyo, MSD, Roche, Amgen	**No**	**No**	**Yes** BMS, Lilly, Daiichy-Sankyo, MSD, Roche, Amgen, Merck, Servier	**No**	**No**	**No**
Thuss-Patience, Peter	Charité	**No**	**No**	**No**	**Yes** Advisory Board für AstraZeneca, BMS, Merck Serono, MSD, Lilly, Servier, Novartis, Daiichi, Roche,	**Yes** Merck Serono	**No**	**No**
Wöll, Ewald	St. Vinzenz Krankenhaus Betriebs Ges.m.b.H	**Yes** Astra Zeneca, Astella Pharma, BMS, Daiichi Sankyo Austria, Eli Lilly MSD, Merck, Novartis, Eisai, Roche, Servier	**No**	**No**	**Yes** Amgen, Astra Zeneca, BMS, Celgen, Ebewe, Eli Lilly, Eisai, Janssen Cilag, Merck, MSD, Pierre Fabre, Pfizer, Ratiopharm, Roche, Sanofi Aventis, Takeda, Daiichi Sankyo Austria	**No**	**No**	**No**
Zander, Thomas	Universitätsklinik Köln	**Yes**	**No**	**No**	**Yes** Roche Novartis BMS MSD AstraZeneca	**No**	**No**	**No**

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
		Roche Novartis BMS MSD AstraZeneca						

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