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Esophageal Cancer

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

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

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Publisher

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www.onkopedia-guidelines.info

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Esophageal Cancer

Date of document: June 2023

Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Esophageal carcinomas account for about 1% of all malignancies and about 2% of all cancer-related deaths in Germany. Clinically relevant is the distinction between squamous cell and adenocarcinomas.

Approximately 30-40% of patients are in principle in a resectable stage at initial diagnosis. Especially in patients with squamous cell carcinoma, comorbidities are often observed with a resulting limited functional operability. The 5-year survival with resection alone is around 20%. Multimodality approaches improve prognosis in locally advanced tumors; they may also allow organ preservation. After preoperative chemoradiotherapy (CRT) and complete resection, there is an indication for the use of adjuvant immunotherapy (independent of PD-L1 status) in patients with histologic tumor residue (non-PCR) of squamous cell carcinoma or adenocarcinoma (including AEG type I).

For metastatic squamous cell carcinoma, platinum-based chemotherapy remains the treatment of choice despite low evidence. Checkpoint inhibitors are approved either in combination with chemotherapy (pembrolizumab, PD-L1 CPS ≥ 10; nivolumab, PD-L1 TC ≥ 1%) or as so-called dual checkpoint blockade (nivolumab + ipilimumab, PD-L1 TC ≥ 1%) in the first-line setting and as monotherapy (nivolumab, regardless of PD-L1 status) in the second-line setting. For metastatic adenocarcinomas of the esophagus and esophago-gastric junction, in analogy to gastric carcinoma, personalized therapy approaches (HER-2 positive carcinomas) and immunotherapy in combination with chemotherapy (PD-L1 CPS ≥ 5) are available in addition to combined chemotherapy (see chapter 6.1.4.1.2).

2 Basics

2.1 Definition and basic information

In addition to the histological distinction between squamous cell and adenocarcinomas, the localization of the tumor is an essential basis for planning diagnostics and therapy. Depending on the localization as well as the positional relationships within the thorax, esophageal carcinoma is divided into cervical and intrathoracic tumors as well as tumors of the esophago-gastric junction (AEG).

The guideline presented here refers to esophageal carcinomas according to the current 8th edition of the TNM/UICC classification and also includes adenocarcinomas of the esophago-gastric junction type I and type II according to Siewert.

2.2 Epidemiology

There are significant geographic differences in the overall incidence of esophageal cancer, as well as for the ratio of squamous cell to adenocarcinoma.

In the industrialized countries of Europe, North America and Australia, the incidence of adenocarcinomas has increased in recent decades, with a share of now 40-50%. Worldwide, squamous cell carcinomas are significantly more common, especially within the so-called "Asian esophageal cancer-belt". Here, the incidence can rise up to 100/100,000 persons [1].

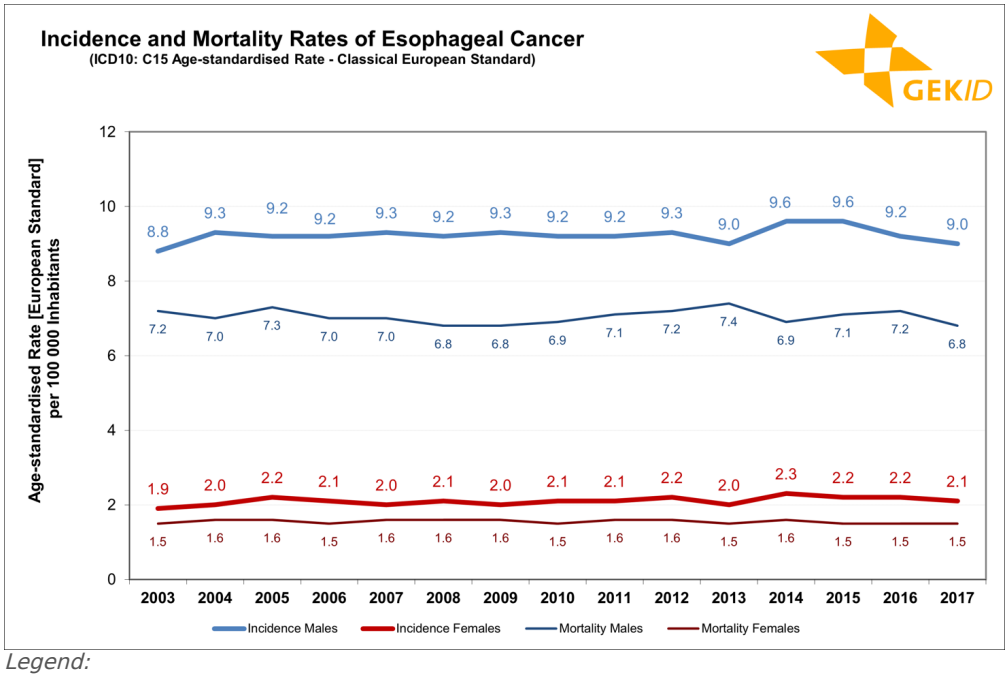
In Germany, approximately 5,700 new cases of cancer are diagnosed in men and approximately 1,850 new cases in women each year. Esophageal cancer ranks 13th among malignancies in men (2.2% of all cancers) and 8th (3.4%) among cancer-related causes of death; in women, it ranks 22nd (0.8%) and 18th (1.3%), respectively. The median age of onset is 67 years for men, lower than for cancer overall (70 years), and 71 years for women, higher than for cancer overall (69 years). The median age at death is 70 years (men) and 74 years (women) (cancer overall: 75 and 76 years). Approximately 16,000 patients with esophageal cancer are living in Germany with a diagnosis no longer than five years ago, or nearly 20,000 patients with a diagnosis in the last 10 years [2].

Squamous cell carcinomas account for approximately 43% of all cancers of the esophagus. The proportion of adenocarcinomas, which occur predominantly at the junction with the stomach, has risen to over 45% in recent years [2].

These epidemiological data are largely consistent with those in Switzerland [3] and Austria [4].

The age-standardized incidence rates as well as the mortality rates of both sexes have been almost constant over the last 15 years. It should be noted that the rates for men are considerably (factor 3.5) higher than those for women, see Figure 1.

Figure 1: Estimated incidence of esophageal cancer (ICD 10: C15) in Germany

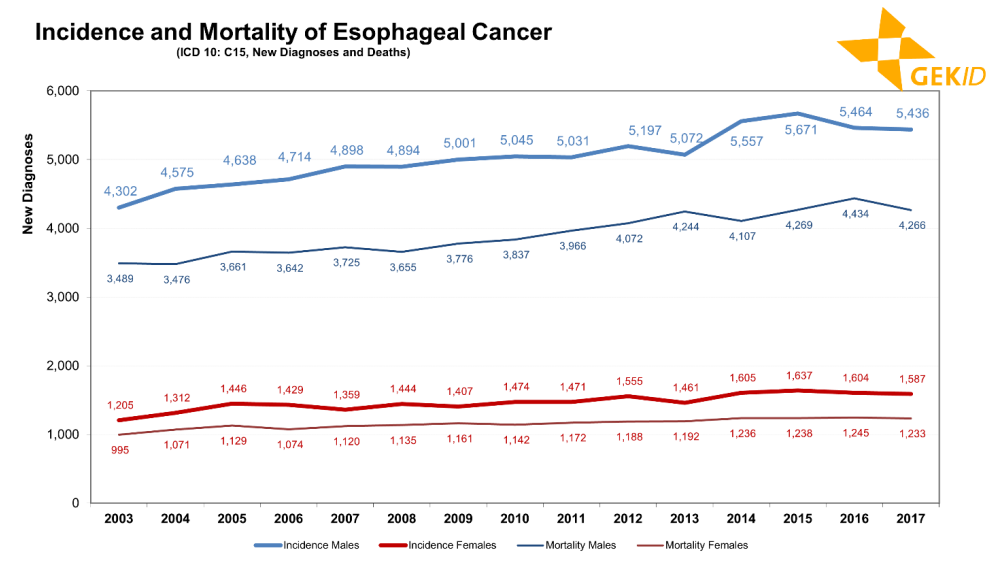


Legend:
Estimated incidence of esophageal cancer (ICD 10: C15) in Germany - age-standardized rates (old European standard); source: Center for Cancer Registry Data, database query [2]

Due to the shift in the age structure towards an older society and because the baby boomers have reached the age of highest disease probability, the courses of new cases and deaths differ from the courses of the rates. This shift has a greater absolute effect on men because of the

higher probability of disease; in relative terms, the increase is the same for both sexes. Despite constant age-standardized disease rates, the number of cases increased by an average of 1.7% per year over the past 15 years. The situation is similar for the number of deaths. Here, the number increased by an average of 1.7% per year for men and 1.3% per year for women, see Figure 2.

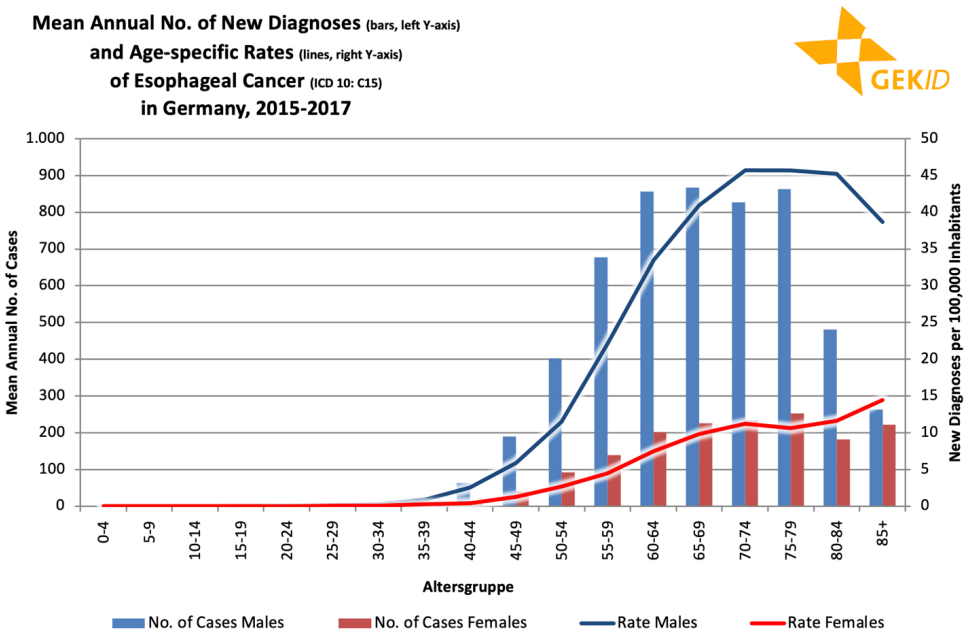
Figure 2: Incidence and mortality of esophageal cancer (ICD 10: C15) in Germany



Legend:
Estimated incidence of esophageal cancer (ICD 10: C15) in Germany - number of cases; source: Center for Cancer Registry Data, database query [2]

Most cases of the disease occur in men between 70 and 79 years of age, see Figure 3 (bars). From the age of 50, the number of new cases increases steadily. The number of cases among 65- to 79-year-olds is almost the same; from the age of 80, the number of cases decreases significantly. In women, the number increases continuously - at a significantly lower level - until the age of 85 and is then almost constant. The highest risk of disease, see Figure 3 (lines), is found in men between 75 and 79 years of age and in women steadily increasing up to the highest age group. Case numbers and incidence rates of men are significantly higher than those of women in all age groups.

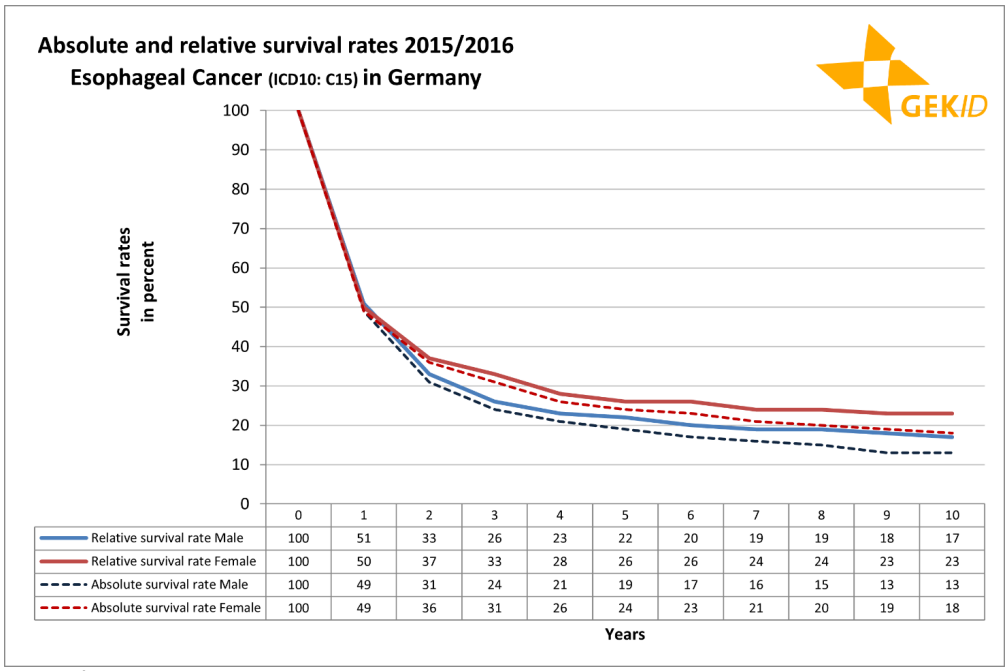
Figure 3: New cases and age-specific rates of esophageal cancer (ICD 10: C15) in Germany



Legend:
Age distribution of esophageal cancer incidence (ICD 10: C15) - age-specific case numbers and rates; source: Center for Cancer Registry Data, database query [2]

The prognosis of patients with esophageal cancer is relatively unfavorable, especially in the first year after diagnosis. About 50% of patients die within the first year after diagnosis. The small difference between absolute survival rate (percentage of patients surviving a certain time) and relative survival rate (ratio of absolute survival and expected survival in the general population) shows the excess mortality caused by this malignancy. From the fifth year after diagnosis, the gap between absolute and relative survival rates increases, and in addition, relative survival rates decrease only slightly; thus, after about five years, significantly fewer cancer-related deaths occur. However, the relative survival rates never reach a completely parallel course to the x-axis, indicating that cancer-related deaths still occur after 8-10 years. Figure 4 shows the absolute and relative survival rates for the first 10 years after diagnosis with only minor differences in survival between genders.

Figure 4: Absolute and relative survival rates of esophageal cancer (ICD 10: C15)



	0	1	2	3	4	5	6	7	8	9	10
Relative survival rate Male	100	51	33	26	23	22	20	19	19	18	17
Relative survival rate Female	100	50	37	33	28	26	26	24	24	23	23
Absolute survival rate Male	100	49	31	24	21	19	17	16	15	13	13
Absolute survival rate Female	100	49	36	31	26	24	23	21	20	19	18

Legend:
Absolute and relative survival rates in patients with esophageal cancer (ICD 10: C15); source: Center for Cancer Registry Data, database query [2]

Based on the current incidence rate and the 14th coordinated population projection of the German Federal Statistical Office (G2L2W2, moderate development), an increase in the number of cases by around 21% to around 8,500 new cases (2050) can be expected in the next 30 years due to the shift in age structures in the population alone. Due to the relatively low age of onset, especially among men, the expected demographic increase in the number of cases is lower than for most other cancers.

2.3 Pathogenesis

Squamous cell carcinomas typically arise from initial mechanical damage such as in achalasia, after radiation therapy or after acid or alkali burns, and in combination with toxic carcinogenic substances such as alcohol and nicotine. These carcinogens also lead to second squamous cell carcinomas of the head and neck region or in the lungs [5, 6].

For carcinomas of the distal esophagus, the association with chronic acid reflux has been extensively studied and is considered a significant risk factor. Metaplasia of the orthotopic squamous epithelium to a cylindrical epithelium results in preneoplastic Barrett's mucosa. The risk of developing carcinoma has long been overestimated. The rate of progression from Barrett's metaplasia to carcinoma is approximately 0.3% (3 per 1000 patients) per year [7]. Case-control studies also show an increased risk of developing adenocarcinoma in smokers. Use of nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and statins appears to reduce the risk of transition from Barrett's carcinoma to invasive adenocarcinoma [8]. However, due to inconsistent data, prophylactic drug treatment cannot be recommended [9].

Pathogenetically, transformation of the cylinder epithelium to cylinder epithelial dysplasia occurs via inactivation of p53, which is present in up to 50% of all squamous cell carcinomas of the esophagus. Other common mutations include allelic loss in p16 and amplification/overexpression of cyclin D1. Allelic losses in the fragile histidine triad (Fhit) gene inactivate this tumor suppressor gene, which is particularly sensitive to exposure to chemical carcinogens [10].

Carcinogenesis of adenocarcinomas not arising from Barrett's mucosa occurs sequentially in analogy to carcinomas of the rest of the digestive tract in multistage processes via precancer-

ous stages. Low-grade dysplasia progresses to high-grade dysplasia and invasive carcinoma. Infection with Helicobacter (H.) pylori could be considered protective against the development of adenocarcinoma of the esophago-gastric junction. Conversely, with increased use of H. pylori eradication therapies, an increase in these carcinomas was shown, although this could also be explained by more intensive surveillance strategies [11].

2.4 Risk factors

Risk factors differ depending on histology and localization. Squamous cell carcinomas are frequently associated with alcohol and nicotine abuse. In contrast, obesity and gastroesophageal acid reflux are more commonly found in carcinomas of the esophago-gastric junction. Nicotine abuse is a common risk factor for carcinogenesis.

The risk of developing esophageal cancer is being increased by the following factors [6]:

- Squamous cell carcinoma:
  - Smoking and alcohol, dose-dependent
  - Male gender
  - Tylosis (autosomal dominant dys/hyperkeratosis of the feet and hands): up to 90% develop squamous cell carcinoma of the esophagus
  - Achalasia
  - Stenoses after chemical burns with alkalis or acids
  - Pre-irradiation in the neck/thorax area (dose-dependent)
  - Pre-diagnosis of squamous cell carcinoma of the head and neck or lungs
- Adenocarcinomas:
  - Gastroesophageal reflux disease (GERD): Barrett's esophagus
  - Smoking
  - Obesity
  - Achalasia
  - Stenosis after chemical burns with acids or alkalis

3 Prevention and early detection

3.1 Prevention

Recommendations for the prevention of esophageal cancer are based on the acquired risk factors identified to date [9]:

- Abstaining from excessive alcohol consumption
- Abstaining from tobacco use
- Diet rich of vegetables and fruits
- Treatment of gastroesophageal reflux disease

Currently, no recommendation can be made for drug prophylaxis (ASA, antioxidants), although there are indications from case-control studies for a risk reduction by ASA [12]). However, even low doses significantly increase the risk of gastrointestinal bleeding (by 14%) [13].

3.2 Early detection

No screening measures have been established for the general population in Germany, and their impact on the development of carcinoma in the esophagus or even on the prognosis would also be difficult to prove due to the low incidence. In some Asian countries, general screening is discussed due to the high prevalence.

In patients with Barrett's esophagus, regular endoscopy and a 4-quadrant biopsy every 2 cm are common practice. However, data demonstrating an effective risk reduction and a reduction of cancer-specific mortality are not available [14].

4 Clinical characteristics

4.1 Symptoms

Early carcinomas are usually asymptomatic. The following symptoms often occur only in locally advanced tumors with obstruction of approximately two-thirds of the esophageal lumen or in metastatic carcinomas:

- Dysphagia, odynophagia
- Recurrent vomiting, nausea
- Loss of appetite
- Early feeling of satiety
- Weight loss, asthenia
- Thoracic pain
- Gastrointestinal bleeding, anemia

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis/local findings

Endoscopy is the most important and usually primary method in the diagnosis of esophageal cancer. The aim is to determine the location and extent of the tumor and to detect metaplastic changes of the epithelium in the lower esophagus (Barrett's esophagus). Using high-resolution video endoscopy, it is possible to detect even discrete changes in the color, relief, and architecture of the mucosa. Endoscopic detection of dysplasia and early carcinoma can be improved by chromo-endoscopy (e.g., Lugol's solution) or by computer-assisted digital techniques (e.g., narrow-band imaging) in the endoscope [15, 16].

As the prognosis of patients with esophageal cancer is closely correlated with local tumor spread and lymph node involvement, the most accurate pretherapeutic staging is critical to guide therapy. The goals of diagnostics are to determine the stage of the disease and to clarify the patient’s capacity to tolerate cancer treatment. In this context, the depth of invasion of the tumor (T category) and its proximity to adjacent structures play a special role, the predictive accuracy of which can be improved by endosonography, see Table 1. Endosonography has the highest accuracy of all methods due to its high local spatial resolution. Data (evidence level 1b) from Russell et al [17] suggest that consistent EUS tumor staging of esophageal cancer leads to improved survival rates of patients examined by EUS (approximately 3 months superior to the

comparator group). Limitations are one hand the dependence on the investigator's expertise and on the other hand the limited technical feasibility in case of highly stenosing tumors.

5.2.2 Staging

5.2.2.1 Sonography

B-scan sonography is the initial imaging procedure in staging diagnostics to exclude liver metastases. The additional use of contrast-enhanced sonography significantly increases sensitivity and specificity. Furthermore, B-scan ultrasonography of the neck can be used as a complementary procedure to exclude cervical lymph node metastases, which are present in 10-28% of patients, especially when the primary tumor is located cervically or upper-level intrathoracically.

5.2.2.2 X-ray Barium swallow

The X-ray Barium swallow should not be used to diagnose esophageal cancer.

5.2.2.3 Computed tomography (CT)/ Multidetector computed tomography (MDCT)

Patients with newly diagnosed esophageal cancer should undergo CT of the neck/thorax and abdomen with multiplanar reconstructions and additional wall distention by negative contrast and IV contrast for primary staging. It is recommended to include the neck with the fast scanner technologies commonly used today; thereby eliminating the need for supplementary ultrasound of the neck.

5.2.2.4 Magnetic resonance imaging (MRI)

MRI can be performed as a substitute procedure when CT cannot be performed (contraindication to contrast media) or as a complementary procedure to CT/EUS. MRI is particularly useful in the area of the esophago-gastric junction and in the evaluation of liver metastases (with the use of liver-specific contrast medium). For pulmonary focal findings, it is less accurate than CT.

5.2.2.5 Positron emission tomography (PET/CT)

In locally advanced tumors (cT2-4 and cN+), PET/CT may additionally be used for excluding distant metastases if a curative therapy is intended and/or if the result has practical consequences. The assessment of PET/CT in esophageal cancer shows considerable differences in the international literature. Two recent meta-analyses deal with PET/CT in the context of primary staging [18, 19]. Both confirm the known high diagnostic specificity but low sensitivity, especially with regard to locoregional lymph node metastases. Although the false-negative rate is not insignificant, the detection of locoregional lymph node metastases in PET/CT nevertheless entails the clinical consequence of an extension of the radiation field or an expansion of the lymph node dissection.

Note on the reimbursement situation: PET or PET/CT for the detection of distant metastases is available for gastrointestinal tumors and tumors of the abdominal cavity within the framework of outpatient specialized medical care ("ASV") for patients with severe courses of disease.

For response assessment post (radio-) chemotherapy, the utility of PET/CT is discussed controversially. Although most studies show a strong correlation between metabolic response in PET/CT and clinical/histopathological response, no studies provided cut-off values in order to derive decisions for surgical resection. Therefore, PET/CT cannot be routinely recommended for this setting.

5.2.2.6 Evaluation of operability

In the case of potentially resectable tumors, an extended anesthesiological assessment should be performed to clarify the functional operability of the frequently comorbid patients, including age, nutritional status, comorbidities, and prevalent cardiopulmonary and hepatic diseases (alcohol history, cirrhosis?) or functional reserve. In patients over 70 years of age, a geriatric assessment is also recommended.

In various studies, a systematic recording of risk factors showed a good correlation with postoperative morbidity and mortality. For esophagectomy surgery, for example, the "Cologne Risk Score" and "O-Possum for Esophagectomy" are available [20, 21].

Table 1: Diagnostics and staging in esophageal cancer

Investigation	Note
Physical examination	
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation, TSH
Endoscopy upper gastrointestinal tract	Optionally supplemented by chromo-endoscopy
Histology	Histopathological findings with immunohistology
Endoscopic ultrasound (EUS)	in patients with curative therapy intention
Computed tomography neck, thorax, abdomen with contrast medium	CT neck for cervical tumors, if PET-CT is not performed
Sonography of abdomen and neck	Complementary to computed tomography, if necessary
Laparoscopy with cytology[1]	For adenocarcinomas of the esophago-gastric junction, category cT3/T4, if preoperative therapy is planned
Positron emission tomography (PET-CT)	Exclusion of distant metastases, surgical planning, radiotherapy planning
Laryngoscopy; ENT; panendoscopy	For squamous cell carcinomas for surgical planning and exclusion of secondary carcinomas
Bronchoscopy	In case of anatomical adjacency to the trachea and the bronchial system
Risk analysis of important organ functions	Question of functional operability
Screening for malnutrition	Patients at risk for malnutrition
Anesthesiological assessment	Early registration recommended in curative situation, as many patients have relevant co-morbidity

Legend:
[1] Laparoscopy helps detect clinically occult metastasis to the peritoneum in AEG I and II carcinomas in locally resectable tumors. Detection of macroscopic peritoneal carcinomatosis has immediate implications for treatment planning. Laparoscopically abnormal findings are rarely found in T1/T2 tumors; ENT – Ear-Nose-Throat examination

Histopathologic findings on local resected tissues (endoscopic resection; ER) should include the following:

- Size of the neoplastic lesion in 3 dimensions.
- Graduation of dysplasia or intraepithelial neoplasia according to WHO, if applicable.

- Histological type according to WHO (especially differentiation squamous cell versus adenocarcinoma, other rare types).
- Immunohistochemical information on the biomarkers PD-L1 (as a combined score, CPS, and as a proportion of positive tumor cells, TPS), HER-2 and microsatellite status (both in adenocarcinomas).
- For invasive carcinomas:
  - Degree of differentiation (grading) according to current WHO classification
  - Maximum depth of invasion: pT1a (mucosa m1, m2, m3, m4), pT1b (submucosa sm1, sm2, sm3) plus depth of invasion in µm (or higher pT category)
  - Lymphatic vessel and/or venous invasion
- Summarized assessment of LK metastatic risk:
  - Low risk vs. high risk
  - Resection margins with regard to the neoplasia: in the case of ER in toto, circular and basal resection margin; in the case of "piece-meal" ER, basal resection margin, since here the circular resection margin must usually be evaluated histopathologically as “RX”.

After neoadjuvant therapy, re-staging should be performed to exclude metastases. If there is clinical evidence of tumor progression during neoadjuvant therapy, symptom-based diagnostics are recommended to plan the next therapeutic steps [9].

5.3 Classification

5.3.1 Classification according to localization

Depending on the localization (distance "from tooth row", TR) as well as the positional relationships within the thorax, according to the current TNM classification 8th edition [22], a distinction is made between carcinomas of the

- Cervical esophagus (C15.0): from the inferior margin of the cricoid cartilage to the entry of esophagus into the thorax (suprasternal fossa), about 18 cm from TR
- Intrathoracic esophagus
  - Upper thoracic segment (C15.3): from the entry of the esophagus into the thorax to the level of the tracheal bifurcation, 18 to 24 cm from TR
  - Middle thoracic segment (C15.4): upper half of esophagus between tracheal bifurcation and esophago-gastric junction, 24 to 32 cm from TR
  - Lower thoracic segment (C15.5): distal half of esophagus between tracheal bifurcation and esophago-gastric junction. Lower border is the Z line approximately 40 cm from TR
- Esophago-gastric junction (C16.0): Tumors involving the esophago-gastric junction with center within 2 cm above or below and crossing the Z line (Siewert types I and II), synonym AEG (adenocarcinoma of esophago-gastric junction).
  - Type I: main tumor in the distal esophagus
  - Type II: Main tumor in the cardia of the stomach
  - (Type III: adenocarcinoma of the subcardiac stomach, belongs to the gastric carcinomas).

5.3.2 Stages and TNM

Classification of the extent of the primary tumor and metastasis is based on the UICC/AJCC TNM criteria. Since January 1, 2017, the 8th edition has been used in Europe [22]. The TNM criteria are summarized in Table 2, the staging for squamous cell carcinoma in Table 3, and for adenocarcinoma in Table 4.

Regional lymph nodes (LK) are those located in the lymphatic drainage area of the esophagus. Included are the celiac LK and paraesophageal lymph nodes of the neck, but not the supraclavicular lymph nodes.

Table 2: UICC (2018) TNM classification - esophageal cancer

Classification	Tumor
T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia (malignant cells confined by basement membrane)
T1	Tumor invades lamina propria or muscularis mucosae or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in 1-2 regional lymph nodes
N2	Metastases in 3-6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes
M	**Distant metastases**
M0	No distant metastases
M1	Distant metastases

Table 3: Squamous cell carcinoma of the esophagus - clinical staging according to UICC 2018

Stage	T	N	M
I	T1	N0, N1	M0
II	T2	N0, N1	M0
	T3	N0	M0
III	T1, T2	N2	M0
	T3	N1, N2	M0
IVa	T4a, T4b	Each N	M0
	Each T	N3	M0
IVb	Each T	Each N	M1

Table 4: Adenocarcinoma de esophagus - clinical staging according to UICC 2018

Stage	T	N	M
I	T1	N0	M0
IIa	T1	N1	M0
IIb	T2	N0	M0
III	T1	N2	M0
	T2	N1, N2	M0
	T3, T4a	N0, N1, N2	M0
IVa	T4b	N0, N1, N2	M0
	Each T	N3	M0
IVb	Each T	Any N	M1

5.3.3 Histological subtypes

- Carcinoma in situ (CIS): macroscopically raised or flat epithelial thickening or sunken thinning of the mucosal epithelium, appearing whitish (leukoplakia), reddish (erythroplasia) or unchanged in color (occult type); solitary in 10-20% and multiple in 80-90%.
- Polypoid carcinoma: most common at approximately 60%.
- Diffuse infiltrating carcinoma: approximately 15% of cases.
- Ulcerative carcinoma: in about 25% of cases, the tumor presents as an irregularly circumscribed hemorrhagic ulcer with mural-like raised margins.
- Varicose carcinoma: Tumors resembling esophageal varices in their endoscopic and radiographic appearance have been described under this designation.

5.3.4 The Cancer Genome Atlas (TCGA) classification

Current studies divide esophageal cancer into three molecular subtypes [23]:

- BRCA and BRCA-like mutations (BRCAness) and alteration of DNA repair genes by homologous recombination (HRD)
- Mutation pattern with predominant exchange of bases T>G and an association with a high mutation load and the emergence of neoantigens

- Mutation pattern with predominant exchange of bases C>A and an association with accelerated cellular aging.

These subtypes have yet to impact clinical practice and therapeutic decisions.

6 Treatment

6.1 Treatment structure

Due to the complex therapeutic options, recommendations should always be discussed and decided by a multidisciplinary tumor board.

In addition to the tumor-specific factors, patient-specific factors play a crucial role, since entity-typical comorbidities with potential cardiovascular, pulmonary or hepatic limitations are often present and can significantly complicate treatment and lead to functional inoperability in resectable tumors [11].

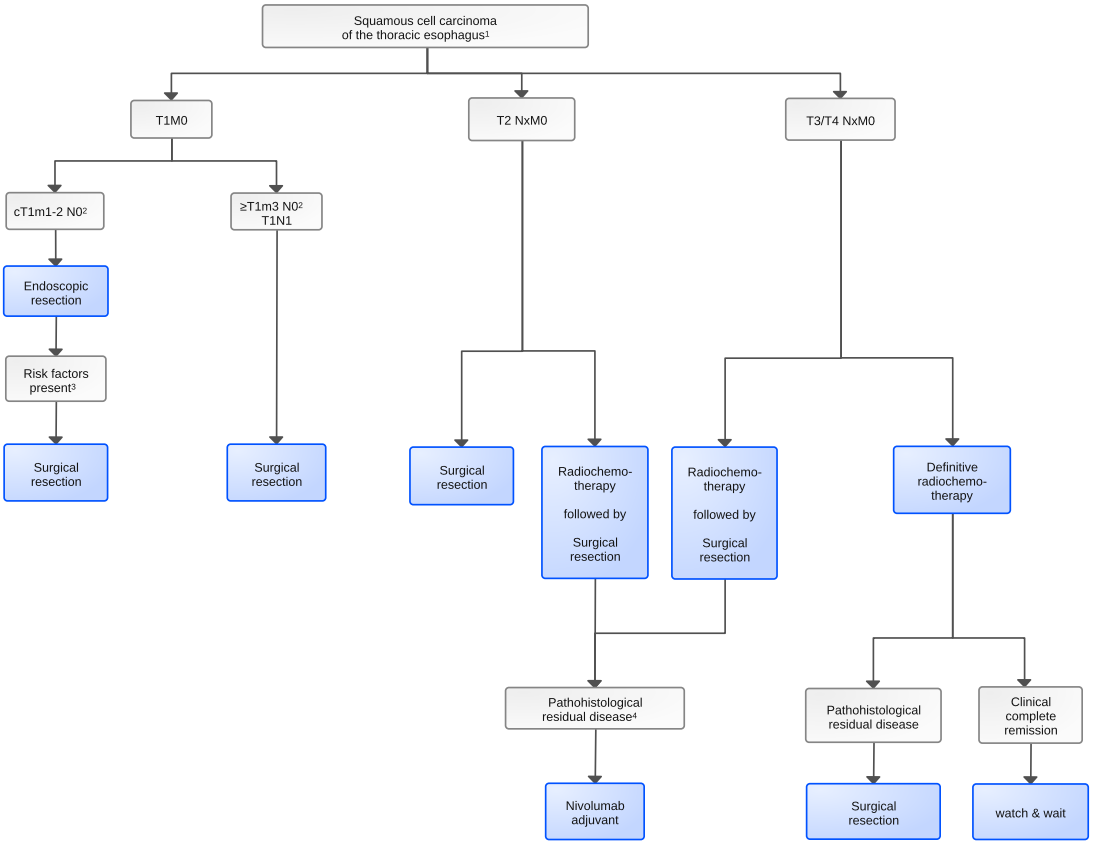
Many patients are in a reduced general performance at diagnosis, and substantial malnutrition is common, especially in patients with squamous cell carcinoma. Due to the high metabolic risk, patients should be fed before surgery, even if surgery has to be postponed because of this. After surgery, (parenteral) nutrition should be started early (within 24 hours).

More than 50% of patients with esophageal cancer are over 65 years of age at diagnosis. However, data on the treatment of patients over 70 years of age are sparse. Older British analyses suggest that the benefit from preoperative CRT compared to surgery alone decreases with age and is no longer significant for patients 65 years and older. A randomized British study (GO2 study) in metastatic disease shows, at least for older patients with adenocarcinoma, that a primary dose reduction vs. standard dosage of chemotherapy does not worsen the prognosis, but improves the quality of life during therapy [60] (see Chapter 6.1.4.1.2).

The treatment decision is primarily based on the T category and the presence of distant metastasis. Lymph node involvement is only considered of secondary importance in the treatment algorithms.

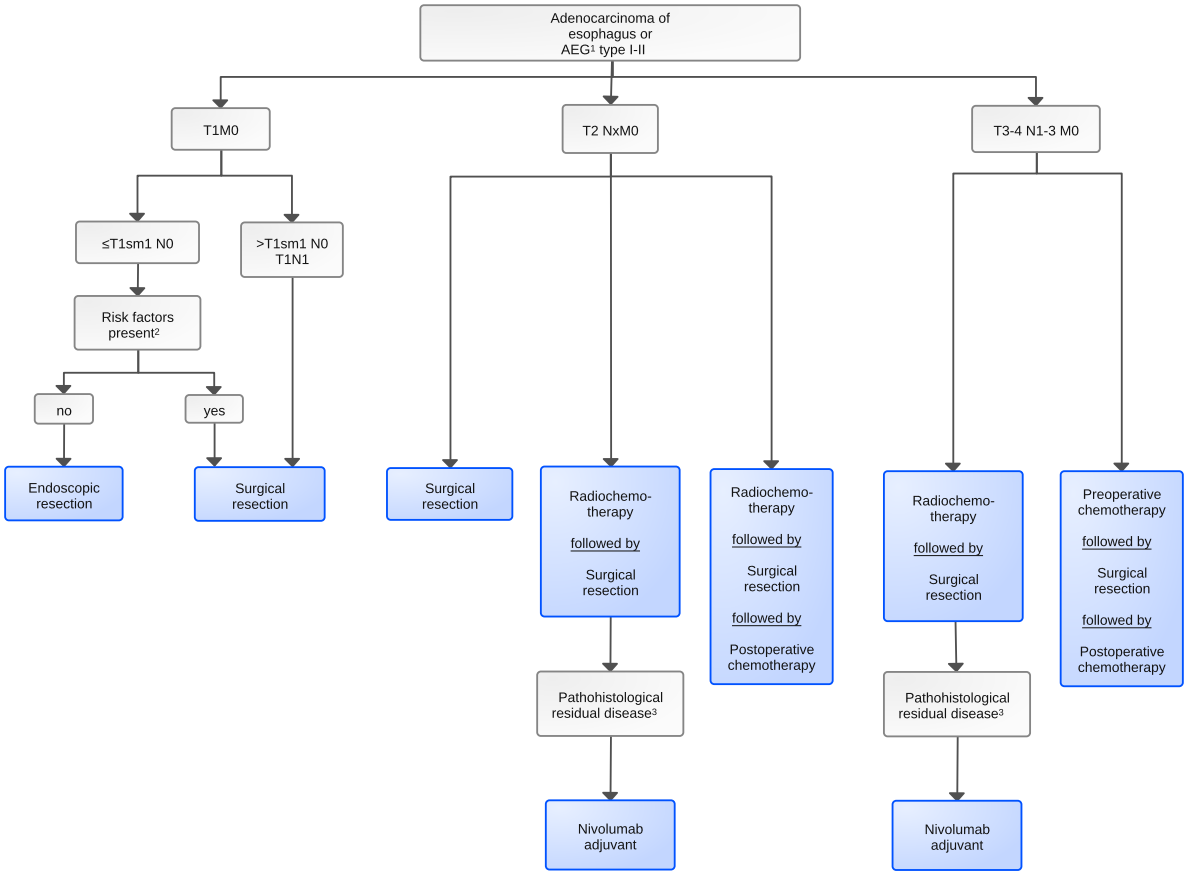
A treatment algorithm for resectable squamous cell carcinomas is shown in Figure 5, for resectable adenocarcinomas in Figure 6, and for metastatic tumors in Figures 7, 8, 9, and 10.

Figure 5: Algorithm for primary therapy in esophageal squamous cell carcinoma



Legend:
Therapy with curative intent
[1] More than 16 cm below tooth row
[2] m - mucosal, sm - submucosal
[3] Risk factors: ulceration, L1, V1, G3, R1 basal, deep submucosal invasion
[4] R0 resection if ypT ≥1 or ypN ≥1

Figure 6: Algorithm for primary therapy in esophageal adenocarcinoma



Legend:
Therapy with curative intent
[1] *AEG - Adenocarcinoma of the esophago-gastric junction*
[2] *Risk factors: ulceration, L1, V1, G3, R1 basal deep submucosal invasion, multifocal/non-ablatable Barrett's lesions*
[3] *R0 resection if ypT ≥1 or ypN ≥1*

6.1.1 T1a N0 M0 (early carcinomas)

Since the probability of lymph node metastasis in mucosal esophageal carcinoma (T1a) is very low (1-2%), mucosectomy by endoscopic resection (ER) is considered the standard of care, for category pT1 m1-sm1 in early adenocarcinoma and for category pT1 m1-m2 in early squamous cell carcinoma. Here, en bloc resection should be aimed at, thus enabling complete histologic assessment of the lateral and basal margins.

The goal of this procedure must be an R0 resection. Technically, endoscopic mucosal resection (EMR / ER) and endoscopic submucosal dissection (ESD) [24] are accepted techniques.

In Europe, EMR is well established. However, only lesions up to max. 15 mm can be completely resected en-bloc. Larger tumors must be resected using the so-called "piecemeal" technique, which increases the risk of incomplete resections. Local recurrences or second manifestations occur in up to 30% of Barrett's neoplasms after EMR [25].

Data for ESD are so far available mainly from Asian countries for squamous cell carcinoma. Here, superiority compared to EMR was shown with regard to en-bloc resection rate, curative resection rate, and local recurrence rate. Data from Japan demonstrate that ESD is also possible in principle for Barrett's carcinoma and that an R0 resection can be achieved in 85%. However, the value of ESD in adeno/Barrett's carcinoma has not yet been conclusively established [25, 26].

In patients with superficial mucosal invasion of squamous cell carcinoma without risk factors (T1m3, L0, V0, G1/2, < 20 mm, no ulceration), endoscopic resection may be a sufficient alternative to surgery after multidisciplinary discussion.

Surgical resection of the tumor should be performed instead of endoscopic resection if the following risk factors are present [9]:

- Residual tumor at basal resection margin (R1 basal)
- Multifocal or non-ablatable Barrett's lesions.

After endoscopic resection and histopathological diagnosis of a tumor of category T1sm1-3 (squamous cell carcinoma) or T1sm2-3 (adenocarcinoma), surgical resection with systematic lymphadenectomy should be performed. Surgical resection should also always be considered if there is lymphatic or venous invasion (L1, V1), G3 grade, or deep submucosal invasion (> 500 µm) after ER [9].

Since a local recurrence limited to the mucosa after ER or an early second carcinoma can be treated again endoscopically with curative intent, regular endoscopic follow-up is indicated. Recommended follow-up intervals are 3 months in the first year and 6 months in the second year. Thereafter, controls should take place annually.

In Barrett's esophagus, the non-neoplastic Barrett's mucosa should be thermoablated after successful endoscopic resection, as this can reduce the rate of second neoplasms.

6.1.2 T1b-T2 M0 (localized tumors)

The risk of lymph node metastases ranges from 7% to 35% for esophageal carcinomas of category pT1b (invasion of the submucosa), and is higher for squamous cell carcinomas than for adenocarcinomas.

Therapy of choice for thoracic carcinomas and carcinomas of the esophago-gastric junction is primary surgical resection with complete removal of the tumor orally, aborally, and circumferentially, as well as dissection of the regional lymph nodes.

The type and extent of surgery and the associated lymph node dissection depends on the localization of the tumor and any affected lymph nodes, see Chapter 6.2.1. Treatment modalities - resection.

The value of perioperative or adjuvant chemotherapy has not been established for patients with T1b carcinoma regardless of lymph node involvement.

Independent from the tumor localization in the esophagus and the histology (adenocarcinoma or squamous cell carcinoma), definitive chemoradiotherapy (CRT) is an alternative for patients who are not suitable for surgery due to comorbidities, with the goal of long-term loco-regional tumor control. For these patients, endoscopic resection may be the treatment of choice for a T1b tumor despite an increased risk of recurrence [9].

In the case of a tumor of category T2, especially in case of high-grade suspect or evidence of lymph node metastases, the use of multimodal therapy concepts can be useful, as they are presented below for T3/T4 tumors (see chapter 6.1.3). The recommendation for such a procedure should be discussed on a multidisciplinary tumor board, and advantages and disadvantages should be discussed with the patients [27]. In any case, patients with T2 tumors were also included in published randomized trials on perioperative chemotherapy [28] and preoperative CRT [29]. A significant survival benefit has not been demonstrated in this subgroup [30, 31].

If preoperative therapy is given, care must be taken not to compromise the goal of secondary tumor resection. Deterioration of the general condition must be recognized early and its cause clarified (toxicity, non-response with persistent or increasing symptoms due to the underlying malignancy). Preoperative chemotherapy should be shortened in these cases if necessary and - if distant metastases have been excluded - surgery should be preferred. In the case of preoperative CRT, it should be discussed whether chemotherapy should be held. However, continuation of radiotherapy to an effective dose (more than 40 Gy) should be strongly encouraged.

6.1.3 T3-T4 M0 (locally advanced tumors)

Both squamous cell and adenocarcinomas of the esophagus of or beyond category cT3 should be treated within the framework of multimodal therapy concepts. In addition to curative resection, preoperative CRT or, in the case of adenocarcinomas of the esophago-gastric junction (AEG), perioperative chemotherapy, are available with good evidence from study results [9].

Preoperative CRT showed a survival benefit in the CROSS study for both histological subgroups (median overall survival 49 versus 24 months, HR 0.66, p= 0.003), which, however, was only significant for the squamous cell carcinoma group after long-term follow-up [30]. In this randomized trial, 368 patients (75% of whom had adenocarcinoma) were treated by preoperative CRT up to 41.4 Gy in combination with weekly administration of carboplatin and paclitaxel plus subsequent surgery or primary surgery. The beneficial effect of CRT was more pronounced for patients with squamous cell carcinoma (survival at 10 years 46% vs. 23% HR 0.48, p=0.007), but also persisted for patients with adenocarcinoma (survival at 10 years 36% vs. 26%, HR 0.73; p=0.061). Postoperative complications were comparable in both groups [28]. In the assessment of this study, the high patient selection must be taken into account. Patients with tumors of the distal esophagus / AEG in best general condition (84% of grade 0 performance scale according to WHO) were almost exclusively included, and patients with early tumors were also included (17% category T1 or T2). Further studies have shown that 5-year-survival rates of more than 40% are possible even in patients with locally advanced carcinomas after optimized radiotherapy in combination with platin/taxane-based chemotherapy and surgery.

The benefit from preoperative CRT versus primary surgery has also been confirmed in meta-analyses [32, 33], so it can be used as the first-choice therapy for squamous cell and adenocarcinomas with a tumor category ≥T3.

After preoperative CRT and surgery, there was no indication for adjuvant therapy as yet. This has changed resulting from the international phase III CheckMate 577 trial. The study investigated whether immunotherapy with nivolumab improves survival after CRT and R0 resection, if no histopathological complete remission has been achieved. In this study, 794 patients were randomized to placebo vs. nivolumab for 1 year after completion of preoperative CRT and recovery from subsequent surgery [34]. The results show that immunotherapy is feasible and does not worsen patient quality of life compared with placebo. The primary endpoint was met with a significant prolongation of disease-free survival (median from 11.0 to 22.4 months, p=0.0003, HR=0.69 (CI 0.56-0.86)). Nivolumab particularly reduced the rate of distant recurrence (29% vs. 39%). Patients with carcinomas of both histologies benefited significantly (HR=0.61 for squamous cell carcinomas, HR=0.75 for adenocarcinomas). Outcome did not differ between PD-L1 positive (72% of patients) or negative tumors, with only tumor cells before CRT considered for assessment (PD-L1 TPS ≥ 1% or <1%). DFS in the control arm appears short at a median of 11 months. In a registry study from the Netherlands published so far only as a congress presentation, median OS for patients with residual tumor after CRT without retreatment was 19.2 months. The unfavorable DFS in the CheckMate 577 study may be due to the high proportion of high-risk patients with lack of downsizing (ypT3-4) or persistently positive

lymph nodes (ypN+), which was close to 60%. This information is not yet available from the Dutch study.

Although overall survival data have not yet been reported in the CheckMate 577 trial, the European Commission granted approval for adjuvant immunotherapy with nivolumab for both histologic types in Europe in September 2021. ASCO, in an update to its statement on esophageal cancer, also strongly recommended adjuvant therapy with nivolumab after CRT and surgery if malignant cells were still detectable in resected tumor tissue [35].

6.1.3.1 Locally advanced squamous cell carcinoma*

**see* Figure 5

In patients with squamous cell carcinoma of the upper or middle thoracic esophagus with a good response to CRT, the benefit from additional surgery should be critically evaluated. Although adjunctive surgery may improve local tumor control, two randomized trials have failed to demonstrate a beneficial effect on overall survival, and therapy-related mortality was significantly higher with surgery [36, 38, 39]. According to German DRG data, hospital mortality after complex esophageal surgery from 2006 to 2013 was 9.2% in high-volume centers (median 62 cases of esophageal surgery per year) and 12.1% in low-volume centers [37].

On this background, a watch & wait strategy can be recommended in patients with a clinical complete remission 12 weeks post CRT (50.4 Gy radiotherapy dose), documented by CT and endoscopy including biopsies in the former tumor region. Thereafter, short-term controls (every 8 weeks) must be performed to preserve the possibility for cure by salvage surgery in case of isolated local tumor progression. Before salvage surgery after definitive CRT, the recurrence/residual tumor should also be histologically confirmed, since wall thickening of the esophagus persists for a long time after CRT and is therefore sometimes difficult to distinguish clinically between sustained remission and progression.

For cervical (almost always squamous cell) carcinoma of the esophagus, definitive CRT is considered standard therapy [46]. Only a few centers in Europe perform surgical resection (usually with laryngectomy) for tumors of this location. It should be taken into account that resections up to the upper esophageal sphincter are associated with a high complication rate and high postoperative morbidity, such as dysphagia, aspiration tendency, and paresis of *N. laryngeus recurrens*, so that surgery should not be performed for highly seated esophageal carcinomas.

Definitive radiotherapy alone without chemotherapy, preoperative radiotherapy without chemotherapy, or preoperative chemotherapy is not recommended for squamous cell carcinoma of the esophagus [39]. However, preliminary data from a Japanese multicenter study (NEXT study) are available that suggest an improvement in prognosis with preoperative chemotherapy [87]. In this 3-arm study, 2 courses of standard chemotherapy (cisplatin / 5-FU) were compared with 3 courses of intensified chemotherapy (docetaxel / cisplatin / 5-FU) or combined CRT (41.4 Gy + 2 courses of cisplatin / 5-FU). Of 200 patients per therapy group, more than 98% had squamous cell carcinoma, about one third had category cT1 and cT2. Overall survival was significantly improved over cisplatin / 5-FU only by intensified chemotherapy (survival at 3 years 72% vs. 63%, HR 0.68 (0.50-0.92)), but not by combined CRT (survival at 3 years 68% vs. 63%, HR 0.84 (0.63-1.12)). Only with respect to histologic tumor response was CRT superior (pathologic complete remission 37% with CRT vs. 19% with DCF vs. 2% with CF). The rate of postoperative complications was not different between treatment groups.

Evidence from Asian studies and meta-analyses [40, 41] indicating that adjuvant radiotherapy may improve local tumor control and possibly overall survival should be tested in phase III trials with "Western" patients. Adjuvant radiotherapy (or CRT) is not a standard of care.

6.1.3.2 Locally advanced AEG*

*see Figure 6

In patients with adenocarcinomas of the esophago-gastric junction (AEG) of category ≥T3 or N+, perioperative chemotherapy is an evidence-based and well-established therapeutic option. Perioperative chemotherapy consisting of anthracycline, platinum derivative, and a fluoropyrimidine (epirubicin, cisplatin, and 5-FU, ECF) has long been considered the standard perioperative therapy based on data from the MAGIC trial. However, data from a German phase III trial demonstrate that chemotherapy according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) is superior to a combination of ECF or epirubicin, cisplatin, and capecitabine (ECX) in patients with locally advanced AEG (≥cT2 and/or cN+). FLOT resulted in a significant prolongation of progression-free (hazard ratio 0.75) and overall survival (HR 0.77 (0.63-0.94), p=0.012). This effect was consistent across all relevant subgroups such as age, histologic type, or localization. The rate of perioperative complications was comparable in both arms [28].

Comparative data between preoperative CRT and perioperative chemotherapy for locally advanced AEG failed to demonstrate a statistically significant survival benefit from additional radiotherapy. Data from a US phase III trial (Neo-AEGIS) showed no difference in overall survival (survival at 3 years 55% vs. 57%, HR 1.03 (0.77-1.38)) between perioperative chemotherapy (90% of patients received epirubicin/platinum/fluoropyrimidine) and preoperative CRT analogous to the CROSS trial [88]. About 80% of the patients had an AEG of category cT3. However, because only 10% of patients in the perioperative treatment group received the best-possible chemotherapy with FLOT, the data are not conclusive. Preoperative CRT according to the CROSS regimen is also not optimal for AEG because the chosen chemotherapy does not induce a reduction in the rate of distant metastases [39]. An older German phase III trial indicates that suboptimal preoperative chemotherapy (PLF regimen) can be improved by additional CRT (HR 0.65 (0.42-1.01), p=0.055) [63].

The currently recruiting German phase III RACE trial therefore remains important for the question of which multimodal therapy will be the future standard for locally advanced AEG because it includes perioperative chemotherapy with FLOT as a control arm.

In summary, both therapeutic concepts are still considered equivalent options in AEG. In patients with locally extensive tumors, preoperative CRT may be favored because of the high risk of incomplete resection and local recurrence, whereas perioperative chemotherapy may be favored for predominantly regional lymph node metastases [9]. Direct comparison between the two treatment modalities is currently being investigated in several phase III trials. The suggestion that perioperative chemotherapy may not be effective in patients with signet ring carcinomas or microsatellite unstable (MSI-H) adenocarcinomas is not justified according to recent analyses [32].

Therapy of locally advanced adenocarcinomas remains independent of HER2 status. For perioperative chemotherapy, phase II data suggest a higher rate of complete histologic response with the combination of chemotherapy (FLOT) and HER2 antibodies [43]. However, results from the randomized phase II INNOVATION trial are still pending. In a combined preoperative CRT (CROSS) regimen, the addition of trastuzumab does not improve outcomes [44].

Patients with locally advanced AEG who have undergone surgical resection without pretreatment (e.g., due to erroneously low tumor stage prior to surgery) may receive adjuvant therapy if there is an increased risk of local recurrence, such as extensive lymph node involvement (pN2-3). It is currently unclear whether adjuvant chemotherapy or CRT should be preferred. However, according to data from an Asian phase III trial, combined CRT (45 Gy + cisplatin/

capecitabine) does not lead to (further) improvement in disease-free survival compared to combination chemotherapy alone (cisplatin/capecitabine) (ARTIST2 trial) [45].

After R1 resection, adjuvant CRT is recommended because of the high risk of local recurrence [9, 40, 41].

6.1.3.3 Locally advanced adenocarcinoma of the esophagus*

**see* Figure 6

In patients with adenocarcinoma of the esophagus who are functionally inoperable or whose tumors are technically unresectable, definitive CRT appears to achieve outcomes comparable to those in squamous cell carcinoma.

For **definitive** CRT, a radiation dose of 50.4 Gy should be aimed for. Higher doses do not improve local tumor control or overall survival in either squamous cell or adenocarcinoma according to mature data from a Dutch phase III trial (ARTDECO) [47]. Regarding chemotherapy within combined CRT, data favor a combination of platinum and fluoropyrimidine or carboplatin and paclitaxel [38]. A French phase III trial showed comparable efficacy for a combination of oxaliplatin and 5-FU (FOLFOX regimen) versus the standard combination of cisplatin and 5-FU in combination with definitive radiotherapy [49]. The combination of radiotherapy plus carboplatin and paclitaxel, which is well proven in preoperative therapy, is apparently also suitable for definitive CRT [48], with no data available from comparative studies. Tolerability in combination with 50.4 Gy seems better than with cisplatin and FU. The addition of cetuximab did not increase efficacy or showed negative effects in several studies [50, 51, 52].

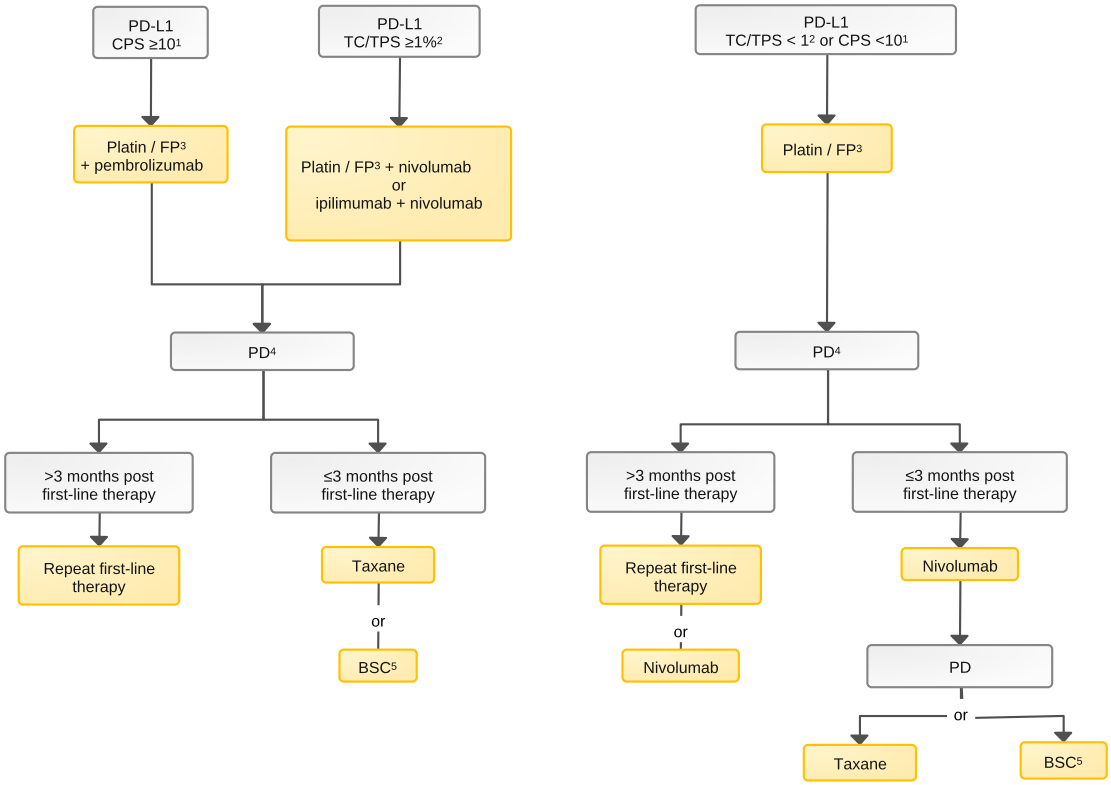
In **preoperative** CRT, chemotherapy with carboplatin and paclitaxel is a standard of care (CROSS trial). It must be kept in mind that the benefit for adenocarcinomas is small and that due to the limited cumulative dose of chemotherapy, there is no detectable effect on the rate of distant recurrences. In addition, the combination of cisplatin and docetaxel is well validated by prospective phase II or phase III trials. Even in the preoperative setting, the addition of an EGFR inhibitor (in this case, cetuximab) does not improve the prognosis of patients. However, a European phase III trial showed a significant improvement in local tumor control [53].

6.1.4 Stage IV (metastatic tumors)

6.1.4.1 Systemic cancer treatment

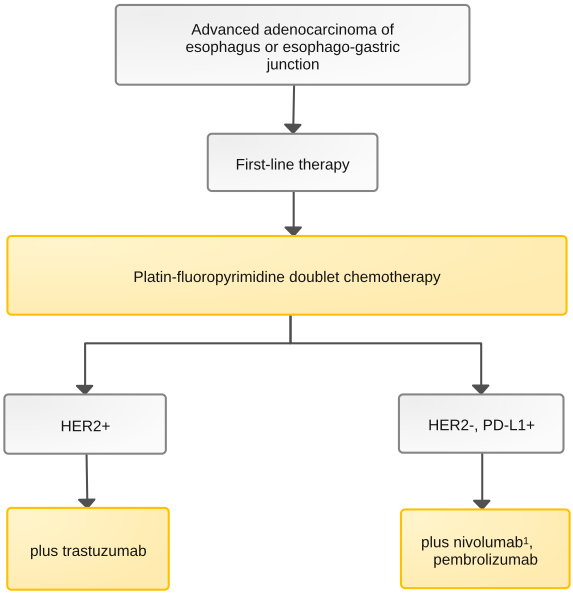
The therapy of metastatic esophageal carcinoma is palliative. The first priority is systemic therapy, supplemented by local therapeutic measures if required. An algorithm for metastatic squamous cell carcinoma is shown in Figure 7 and for metastatic adenocarcinoma in Figure 8, 9, and 10.

Figure 7: Algorithm for the treatment of stage IV esophageal squamous cell carcinoma



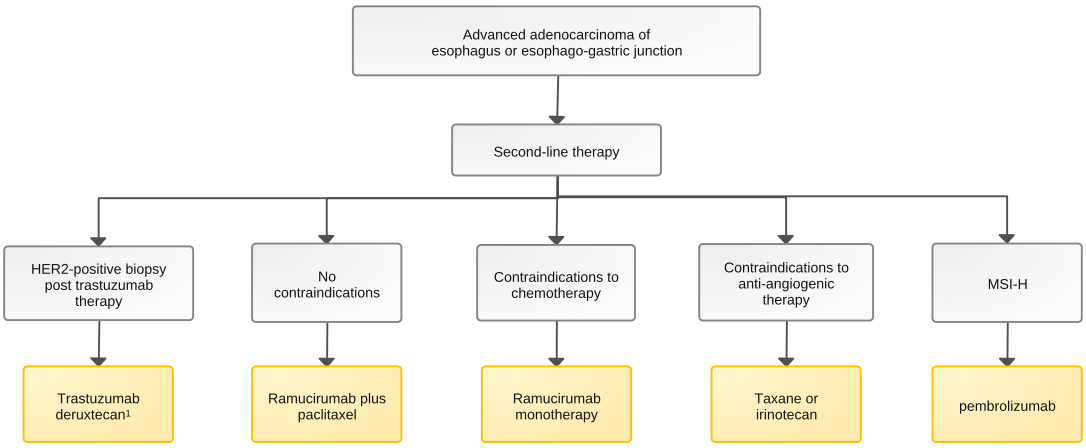
Legend:
Therapy in non-curative intent; Platin – cisplatin or oxaliplatin
[1] CPS - Combined score of PD-L1 expression on tumor cells and immune cell infiltrate
[2] TC or TPS - number of PD-L1 positive tumor cells per 100 tumor cells
[3] FP - Fluoropyrimidine (5-fluorouracil + folinic acid, or capecitabine)
[4] PD - Progressive disease
[5] BSC - Best Supportive Care

Figure 8: Algorithm for first-line therapy of advanced adenocarcinoma of the esophagus and esophago-gastric junction



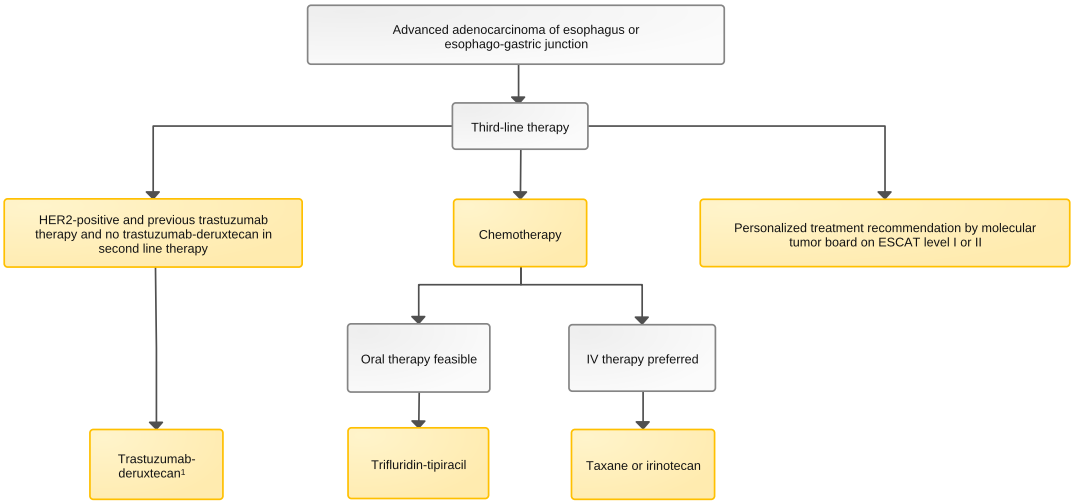
Legend:
therapy in non-curative intent; Platin – cisplatin or oxaliplatin
[1] Nivolumab is approved in Europe for PD-L1 CPS ≥ 5 according to Checkmate-649 trial; pembrolizumab is approved in Europe for adenocarcinoma of the esophagus and esophago-gastric junction for PD-L1 CPS ≥ 10 according to Keynote-590 trial. Positive phase III trial results in PD-L1-positive gastric cancer (CPS) were also reported from Keynote-859

Figure 9: Algorithm for second-line therapy of advanced adenocarcinoma of the esophagus and esophago-gastric junction



Legend:
Therapy in non-curative intent
MSI-H - high microsatellite instability; Taxane – docetaxel or paclitaxel
[1] Since many tumors lose HER2 overexpression after trastuzumab failure, reassessment of HER2 status using a fresh biopsy is recommended prior to second-line T-DXd therapy

Figure 10: Algorithm for third-line therapy of advanced adenocarcinoma of the esophagus and esophago-gastric junction



Legend:
Therapy in non-curative intent
IV – intravenous
Taxane – docetaxel or paclitaxel
[1] According to the Destiny Gastric01 study, re-testing of HER2 status is not mandatory for third-line T-DXd therapy

6.1.4.1.1 Systemic therapy of squamous cell carcinoma

Systemic therapy can prolong survival in patients with non-resectable or metastatic esophageal cancer and is therefore the treatment of choice. In squamous cell carcinoma, this has not been proven by phase III trials. The median overall survival in patients in a good performance status is less than one year in this setting [11]. Nevertheless, palliative chemotherapy is recommended as standard in international guidelines [9].

For the planning of chemotherapy, the performance status of the patient and relevant comorbidities, patient preferences, and the toxicity of the planned therapy must be taken into consideration. Resection of the primary tumor does not improve the prognosis in metastatic disease [46].

In patients with a tumor TPS < 1, combination chemotherapy of cisplatin and 5-FU is considered standard. Addition of EGFR antibodies (panitumumab) does not improve response [58]. For PD-L1 positive tumors, a combination of chemotherapy and checkpoint inhibitor or immunotherapy alone with dual checkpoint inhibition may be used.

Although no comparative data are available, the presumably equally effective combination therapy with FOLFOX can also be recommended instead of cisplatin/FU, due to its lower toxicity. Capecitabine is rarely used instead of 5-FU in esophageal cancer because of the frequent dysphagia.

6.1.4.1.1.2 Immunotherapy

The phase III KEYNOTE-590 trial [55] demonstrated that the combination of chemotherapy and immune checkpoint blockade improved first-line outcomes. In this study, predominantly (73%, n=548) patients with squamous cell carcinoma of the esophagus were included. There was a significant benefit in overall survival for the group of patients with high PD-L1 expression (CPS ≥ 10) of the tumor who received pembrolizumab in combination with cisplatin and 5-FU (HR 0.57; CI 0.43-0.75). In subgroup analyses, patients with PD-L1 positive squamous cell carcinoma benefited in particular. For the group of patients with adenocarcinomas (esophagus

n=110, AEG n=91), the benefit was lower (HR 0.74 (CI 0.54-1.02)). Nevertheless, combined chemo-immunotherapy (platinum + fluoropyrimidine + pembrolizumab) for patients with SCC or AC of the esophagus and high PD-L1 expression (CPS ≥10) was approved in Europe in September 2020.

Results from another phase III trial (CheckMate 648) are available for the first-line treatment of metastatic squamous cell carcinoma [56]. In this three-arm study, a total of almost 1000 patients were randomized to chemotherapy (cisplatin + 5-FU), chemotherapy + nivolumab (240mg every 2 weeks), or nivolumab + ipilimumab (1mg/kg every 6 weeks). The combined primary endpoints were OS and PFS for patients with PD-L1 positive tumors. However, in contrast to the other upper GI tract studies, only tumor cells were evaluated for PD-L1 status in this study (TPS/TC ≥1%). The primary endpoints were met in both experimental arms. With chemotherapy + nivolumab, OS was significantly improved compared to chemotherapy alone (median 15.4 vs. 9.1 months, HR 0.54 (CI 0.37-0.80), p<0.001). OS was also significantly better with double checkpoint blockade than with chemotherapy (median 13.7 vs. 9.1 months, HR 0.64 (CI 0.46-0.90), p=0.001). However, the Kaplan-Meier curves crossed here at baseline, indicating that a proportion of patients had a disadvantage with immunotherapy alone. Evaluation of the data is difficult because of the specific definition of the study population (patients whose tumors are PD-L1 positive by TPS/TC). It is currently unclear which overlaps are between tumors with CPS ≥10 and TPS/TC ≥1%.

A third phase III trial demonstrates the efficacy of immunotherapy in combination with chemotherapy for first-line treatment of advanced squamous cell carcinoma (RATIONALE-306). In this global study, approximately 650 patients were randomized to chemotherapy + placebo (platinum / 5-FU or platinum / paclitaxel) vs. chemotherapy + the PD-1 inhibitor tislelizumab. Overall survival was significantly improved in the tislelizumab group (median OS 17.2 vs. 10.6 months, HR 0.66 (0.54-0.80), p˂0.0001) [89]. The benefit was significant for patients with a PD-L1 score ≥10% (TC/TPS) and for all patients (primary endpoint). However, unlike the above studies, the area with positive tumor cells was assessed here rather than the number of positive cells. The study thus confirms the above data on nivolumab and pembrolizumab. Furthermore, it shows that chemotherapy consisting of platinum + taxane is also improved by the additional immunotherapy. There is currently no approval for tislelizumab for this indication in the EU.

6.1.4.1.1.3 Second-line therapy

Based on data from the ATTRACTION-3 trial, nivolumab is approved in Europe for second-line therapy in advanced squamous cell carcinoma of the esophagus after pretreatment with a combination of a platinum derivative and a fluoropyrimidine, when no checkpoint inhibitor has been given previously. Patients with advanced or recurrent squamous cell carcinoma after therapy with platinum/fluoropyrimidine were randomly assigned to chemotherapy (paclitaxel or docetaxel) or the PD-1 inhibitor nivolumab (240 mg fixed dose) in this phase III trial (ATTRACTION-3) [64]. Approximately half of the patients had PD-L1 positive carcinomas. Regardless of PD-L1 status, overall survival was significantly better with immunotherapy (median 10.9 vs. 8.4 months, HR 0.77 (0.62-0.96), p=0.019). Beyond that, the rate of overall and grade 3-4 adverse events was significantly higher with chemotherapy. Premature discontinuation of therapy occurred in 9% of patients each in both study arms. After 4 months, only 30% of patients in both arms had no tumor progression. The study was in principle also open to "Western" patients. In fact, however, almost exclusively (96%) patients from Asia were included.

A second phase III trial (KEYNOTE-181) was conducted using the PD-1 inhibitor pembrolizumab [65]. In this study, over 60% of the included patients were not from Asia. Patients with squamous cell carcinoma (64%) or adenocarcinoma (including AEG) of the esophagus with progressive disease after first-line chemotherapy were randomized to chemotherapy (paclitaxel, docetaxel, or irinotecan) or pembrolizumab (200 mg fixed dose). Approximately 35% of patients

had highly PD-L1 positive tumors (CPS ≥10%). Intent-to-treat analysis showed no significant difference between treatment groups. Only in patients with highly PD-L1 positive tumors did immunotherapy result in significantly better overall survival (median 9.3 vs. 6.7 months, p=0.0074), Patients with squamous cell carcinoma also trended toward longer survival (median 8.2 vs. 7.1 months). Subgroup analysis showed that mainly Asian patients with PD-L1 positive squamous cell carcinoma benefitted. The study is difficult to interpret because of multiple co-primary endpoints. In the U.S., pembrolizumab was approved in July 2019 based on these data. There is no approval in Europe for this indication.

A review of the approval of immune checkpoint inhibitors in squamous cell carcinoma of the esophagus is presented in the Appendix (German Version only).

6.1.4.1.1.4 Third-line therapy

Older phase II studies indicate the efficacy of taxanes, platin derivatives, or irinotecan for third-line therapy [66]. However, there are no specific approvals for this therapeutic setting. Therefore, treatment decisions have to be made individually and supportive measures are an essential part of treatment.

6.1.4.1.2 Chemotherapy of adenocarcinoma (esophagus and AEG)

Studies in advanced adenocarcinoma (AC) of the upper GI tract have generally included patients with AC of the stomach, esophago-gastric junction, and esophagus. Patients with gastric carcinoma predominate in most studies. Despite the different biology of AC in the aforementioned localizations, systemic therapy for metastatic disease does not differ. Therefore, for advanced disease, the text from the Onkopedia guideline Gastric Cancer was adopted in the following. Text passages that refer exclusively to AC of the stomach are not included here. When “gastric cancer” is addressed below, this guideline on esophageal cancer refers to AC of the esophagus and esophago-gastric junction.

6.1.4.1.2.1 First-line chemotherapy, targeted therapy, and immunotherapy

6.1.4.1.2.1.1 Chemotherapy

Figure 8 shows the algorithm for first-line chemotherapy. The standard of care for advanced gastric cancer is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with advantages regarding the side effect profile for oxaliplatin. This may contribute to a tendency toward better efficacy, especially in older patients (>65 years). Fluoropyrimidines can be administered as infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparably effective to infusional 5-FU. Capecitabine is approved in combination with a platinum derivative and has been tested with both cis- and oxaliplatin in European patients. S-1 is established as the standard of care in Japan and is approved in Europe for initial palliative therapy in combination with cisplatin. Infusional 5-FU should be preferred over oral medications in cases of dysphagia or other feeding problems. In elderly or frail patients, results of phase III GO-2 trial support dose-reduced use of oxaliplatin-fluoropyrimidine chemotherapy to 80% or 60% of the standard dose from the start, resulting in fewer side effects with comparable efficacy [60].

The addition of docetaxel to a platinum-fluoropyrimidine combination (three-week DCF regimen) improved radiographic response rates and prolonged overall survival in an older phase III trial, but also resulted in significantly more severe side effects [68]. Other phase II trials examined modified docetaxel-platinum-fluoropyrimidine triplets. Some of these showed reduced toxicity compared with DCF. However, the higher response rate of a triplet does not translate into a prolonged survival in recent trials of effective second-line regimens. In the phase III JCOG1013 trial, patients with advanced gastric cancer received either cisplatin/S-1 or cisplatin/S-1/doc-

etaxel. There were no differences in radiographic response, progression-free survival, or overall survival [69]. Therefore, with increased toxicity and uncertain effects on overall survival, no recommendation can be made for first-line docetaxel/platinum/fluoropyrimidine therapy. The standard is a platinum-fluoropyrimidine doublet. In justified individual cases, for example with vital response pressure of the disease, a therapy start with a platinum/fluoropyrimidine/docetaxel triplet may be indicated.

Irinotecan-5-FU has been compared with cisplatin/5-FU and with epirubicin/cisplatin/capecitabine in randomized phase III trials and showed comparable survival with manageable side effects [59]. Irinotecan-5-FU can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to the scientific evidence, even though irinotecan has no approval in Europe for gastric cancer.

6.1.4.1.2.1.2 HER2-positive gastric cancer

HER2 positivity is defined in gastric cancer 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 [82, 90]. Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer [86]. The recommendation is based on data from the phase III ToGA trial, which showed 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 [96]. Combinations of trastuzumb and oxaliplatin plus fluoropyrimidine produce comparable results to the historical cisplatin-containing ToGA regimen [61, 97].

6.1.4.1.2.1.3 Immunotherapy

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

The Asian phase II/III ATTRACTION-4 trial also showed significant improvement in progression-free survival with nivolumab and first-line chemotherapy, but with no improvement in overall survival compared to first-line chemotherapy alone. The reason for the lack of survival benefit (17.45 vs 17.15 months) is likely that many patients received post-progression therapies including immunotherapy beyond the first line of therapy [98].

The multinational randomized phase III Keynote 859 trial included 1589 patients with advanced incurable gastric cancer. Patients received either platinum-fluoropyrimidine and pembrolizumab or the same chemotherapy and placebo every 3 weeks IV. Overall survival was prolonged in favor of the pembrolizumab group (HR 0.78 [95% CI 0.70-0.87], $p < 0.0001$). The effect was most pronounced in the subgroup with a PD-L1 CPS ≥ 10 (HR 0.64), whereas efficacy was lower for CPS < 10 (HR 0.86) [90]. The results thus complement the positive trial data from the phase III Keynote 590 study, which led to EU approval of pembrolizumab in combination with platinum-fluoropyrimidine chemotherapy for adenocarcinoma of the esophagus and esophagogastric junction [55].

Positive phase III trial data were also presented on two immune checkpoint (PD-1) inhibitors not currently approved in Europe: sintilimab in combination with oxaliplatin and capecitabine improved overall survival in the phase III ORIENT-16 trial [92].

In the phase III Rationale-305 study, tislelizumab prolonged overall survival in combination with platinum-fluoropyrimidine or platinum-investigator-choice chemotherapy in patients with a positive PD-L1 score. This was evaluated according to a scoring system not yet established internationally (so-called Tumor Area Proportion, TAP) [93].

Orient-16 and Rationale-305 have not been fully published to date, but support the overall assessment that PD-1 immune checkpoint inhibitors can improve the efficacy of chemotherapy (depending on PD-L1 expression).

6.1.4.1.2.1.4 Claudin 18.2

Data from the multinational Phase III Spotlight trial were recently presented. These show that in patients with advanced irresectable gastric cancer and tumor claudin18.2 expression in ≥ 75% of tumor cells, zolbetuximab, a chimeric monoclonal IgG1 antibody directed against claudin18.2, in combination with FOLFOX chemotherapy prolongs overall survival (median 18.23 vs. 15.54 months, HR 0.750, p = 0.0053). The main side effects of zolbetuximab are nausea and vomiting, especially in the course of the first applications [99]. The results of the Spotlight trial are largely confirmed by the multinational phase III GLOW trial, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab [100]. It remains to be seen whether the European regulatory authority will grant approval to zolbetuximab in patients with claudin 18.2-positive metastatic and previously untreated carcinoma of the stomach.

6.1.4.1.2.2 Second- and third-line therapy

6.1.4.1.2.2.1 Chemotherapy and anti-angiogenic therapy

Figures 9 and 10 show the algorithm for second- and third-line therapy for patients with advanced gastric cancer. The evidence-based chemotherapy options in this setting are paclitaxel, docetaxel, and irinotecan, which have comparable efficacy with different agent-specific toxicities. Irinotecan may be preferred in the presence of pre-existing neuropathy, however, there is no EU approval. 5-FU/folinic acid plus irinotecan (FOLFIRI) is also occasionally used, but the scientific evidence for it is limited. Ramucirumab plus paclitaxel is the recommended standard therapy in the second line of therapy and is approved in the EU. The addition of the anti-vascular endothelial growth factor receptor-2 (VEGFR-2) antibody ramucirumab to paclitaxel increases tumor response rates and prolongs progression-free and overall survival according to the results of the phase III RAINBOW trial [101]. Already in the phase III REGARD trial, ramucirumab monotherapy showed prolonged survival compared to placebo, albeit with a low radiological response rate [102].

6.1.4.1.2.2.2 Immunotherapy

In the phase III KEYNOTE-061 trial, pembrolizumab monotherapy did not result in a prolonged overall survival compared with chemotherapy [103]. However, an exploratory subgroup analysis recognized a very significant benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric carcinomas [104]. Therefore, PD-1 inhibition is recommended in advanced MSI carcinomas at latest in the second line of treatment. Pembrolizumab has a European approval in this indication based on the KEYNOTE-061 and KEYNOTE-158 trials [105]. Other biomarkers, particularly EBV and tumor mutational burden, are also discussed as predictive factors for PD-1 immune checkpoint inhibitor efficacy [106, 107, 108]. However, the evidence to date is insufficient to support a positive recommendation for immunotherapy based on these biomarkers.

6.1.4.1.2.2.3 Her2-targeted therapy

Studies evaluating trastuzumab, lapatinib, and trastuzumab emtansine in the second-line treatment of patients with HER2-positive carcinoma were negative efficacy [62, 109, 110, 111, 112]. Therefore, these drugs should not be used in gastric carcinoma outside of clinical trials. A ran-

domized phase II trial showed an improvement in tumor response rate and overall survival for the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) compared with standard chemotherapy in patients with pretreated HER2-positive advanced gastric cancer efficacy [99]. Inclusion criteria in the Destiny-Gastric01 study were at least two prior lines of therapy, prior treatment with a platinum derivative, a fluoropyrimidine, and trastuzumab, and previously confirmed HER2 positivity. Patients were recruited exclusively in East Asia. The results of Destiny-Gastric01 were largely confirmed in the nonrandomized phase II Destiny-Gastric02 trial, which included non-Asian patients in the second line of therapy. Mandatory was platinum-fluoropyrimidine-trastuzumab pretreatment and confirmed HER2 positivity of the tumor in a recent re-biopsy before initiating T-DXd therapy [94].

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

We recommend, according to the classically established HER2 diagnostic criteria, to check the HER2 status prior to therapy with T-DXd, especially if use in second-line therapy is planned, where a valid alternative with paclitaxel-ramucirumab is available. This recommendation is based on the inclusion criteria of the Destiny-Gasictr02 trial and the knowledge that loss of HER2 status occurs in approximately 30% of gastric cancers during first-line therapy with trastuzumab efficacy [111].

There is initial evidence of efficacy of T-DXd in low HER2 expression [95]. However, data are not yet sufficient to recommend its use.

6.1.4.1.2.2.4 Third-line therapy

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 group, in the third-line cohort, and in the fourth-line cohort [67]. Therefore, if oral therapy is feasible, trifluridine-tipiracil (FTD/TPI) should be used; alternatively, if intravenous therapy is preferred, irinotecan or a taxane can be given if not already used in a previous line of therapy. As shown above, T-DXd is a very effective third-line therapy for HER2-positive carcinoma after trastuzumab pretreatment. Nivolumab also proved to be effective; however, the data from the ATTRACTION-3 trial were obtained exclusively in Asian patients [64], so that nivolumab in the third line of treatment in patients with advanced gastric carcinoma does not have EMA approval and therefore cannot be recommended.

Following the recommendation of a molecular tumor board, a non-approved therapy option may also be preferred in justified cases, especially 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 efficacy [113].

6.1.4.1.2.2.5 Surgery for metastatic adenocarcinoma

The randomized phase III REGATTA trial showed that gastrectomy in addition to chemotherapy for metastatic disease did not confer a survival benefit compared with chemotherapy alone [54]. International data indicate that surgical therapy for oligometastasis is increasingly perceived as a treatment option. 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 [114]. The potential prognostic benefit of resections for oligometastatic gastric cancer is currently being evaluated in randomized phase III trials (RENAISSANCE [74], NCT0257836 and SURGIGAST, NCT03042169).

In a Delphi process, a definition for oligometastasis was determined in a European expert group (OMEC). According to this definition, oligometastasis can be defined as the following phenotypes: 1 to 2 metastases in either liver, lung, retroperitoneal lymph nodes, adrenal glands, soft tissue or bone [115].

6.1.4.1.2.2.6 Supportive therapy and nutrition

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

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 reduced survival [117]. A change in body composition with impaired muscular capacity was also shown to be prognostically unfavorable in patients with advanced gastric cancer [118]. 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 [119].

From this, it can be concluded that screening for nutritional status should be performed in all patients with advanced gastric cancer (for example, using Nutritional Risk Screening, NRS) [120] and expert nutritional counseling and co-supervision should be offered if nutritional deficiency is evident.

Dysphagia in proximal gastric cancer can be improved with radiotherapy or stent insertion [121]. Single-dose brachytherapy is the preferred option at some centers and results in longer-lasting symptom control and fewer complications than stent insertion. Stenting is needed for severe dysphagia and especially in patients with limited life expectancy, as the effects of the stent are immediate, whereas radiotherapy improves dysphagic symptoms only after approximately 4-6 weeks [122]. If radiotherapy or a stent are not an option, enteral nutrition via nasogastric, naso-jejunal, or percutaneously placed feeding tubes may provide relief [123]. The indication for parenteral nutrition follows generally accepted guidelines.

6.2 Treatment modalities

6.2.1 Resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for resection of early carcinomas. Techniques include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [22]. ER 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 post-treatment. Thereafter, controls should be carried out annually.

Local recurrences after ER of early carcinoma may be treated endoscopically, if purely mucosal involvement (rT1aN0M0) is present again. A (limited) surgical approach is an alternative.

6.2.1.2 Esophagectomy, lymphadenectomy and reconstruction procedures

Resection of the primary tumor including the regional lymph nodes is a central element of curative therapy. The goal of surgery is to achieve an R0 situation.

In standard surgical techniques, a safety distance of 2-4 cm is aimed for. Depending on the location, the following surgical techniques should be chosen:

- Middle and distal esophageal tumors and AEG I: transthoracic subtotal esophagectomy with tubular gastric elevation and high-intrathoracic anastomosis (if necessary, with extension orally with total esophagectomy and cervical anastomosis).
- AEG type II: transthoracic esophagectomy with tubular gastric elevation or transhiatal extended gastrectomy with distal esophageal partial resection, then Roux-Y reconstruction (currently comparing techniques in German phase III trial, “Cardia Study”).
- In cases of long-sectional involvement of both the distal esophagus and proximal stomach, total esophago-gastrectomy may be indicated. This usually requires reconstruction using a colonic interposition device.
- Esophagectomy and reconstruction should be performed minimally invasively or in combination with open techniques (hybrid technique) if there are no contraindications for this [9].

The extent of lymphadenectomy is based on tumor location. Cervical, thoracic and abdominal fields are distinguished. Two-field lymphadenectomy is the method of choice. Depending on the location of the primary tumor, cervical + thoracic or thoracic + abdominal peritumoral lymph node dissection is performed, which must include the accompanying lymphatic drainage area.

For TNM classification, the histopathological analysis of at least 7 lymph nodes is required, and usually more than 20 lymph nodes are removed. Retrospective studies suggest an improvement in prognosis associated with the resection of at least 23 regional lymph nodes [70, 71].

The operation should be performed at a specialized center (high-volume center) [72, 73], because the higher surgical and perioperative expertise ("failure to rescue") reduces the perioperative mortality and improves the long-term prognosis of the patients. For certification as an esophageal center according to the German Cancer Society, at least 20 resections of esophageal carcinomas per year are required. For the future, a demand of the Joint Federal Committee B-GA defines a number of at least 26 complex procedures per year for a center to be approved for surgery of esophageal cancer.

If, in contrast to the diagnosis made in the obligatory intraoperative frozen section, an R1 resection is found postoperatively in the histological workup, the conditions for a second, extended resection are usually unfavorable. Because of the high local recurrence risk, adjuvant CRT should therefore be recommended here [40, 41].

6.2.1.3 Resection of metastases

As yet, there is no proven benefit for palliative resection of primary tumor or metastases of esophageal cancer in patients with stage IV esophageal cancer. Therefore, resection should not be performed. If metastases are discovered during curative-intended surgery, which are completely resectable (without risk), they can be resected in individual cases. According to the German perioperative AIO FLOT-3 study, patients with good response to 6-8 cycles of intensive chemotherapy (such as FLOT) had better 5-year survival after resection of residual metastases. Patients with synchronous limited metastasis or peritoneal carcinomatosis should therefore be presented to a high-volume center to assess secondary resectability, preferably in the prospec-

tive randomized phase III RENAISSANCE / FLOT-5 trial currently active in Germany (NCT02578368). This study evaluates whether induction chemotherapy plus metastasectomy improves prognosis in limited metastatic AEG or adenocarcinoma of the stomach compared with continuation of palliative chemotherapy without surgery [74].

6.2.2 Radiotherapy

6.2.2.1 Neo-/adjuvant chemoradiotherapy

Neoadjuvant chemoradiotherapy (CRT) is standard of care for locally advanced (category cT3/T4) squamous cell carcinoma and adenocarcinoma of the esophagus. In randomized trials, preoperative doses of 41.4 to 54 Gy were administered in 22 to 28 fractions. Weekly administrations of carboplatin (AUC 2) and paclitaxel (50 mg/m²) [75] or cisplatin (30mg/m^2) and docetaxel (60mg/m^2) have been established as partners for combined CRT, in addition to the original standard of cisplatin and 5-fluorouracil given every 3 to 4 weeks.

Neoadjuvant CRT is a therapeutic option for patients with a category T2 tumor, especially if lymph node metastases are present. Its use as an alternative to primary resection should be discussed multidisciplinarily and recommended in individual cases.

In patients with R1 resection, retrospective studies suggest that adjuvant CRT may improve survival [76]. In this case, CRT should be performed according to definitive CRT protocols. The clinical target volume includes residual tumor (if present), the anastomoses, and the affected lymph node areas. Intensity-modulated radiotherapy should be used to optimize sparing of adjacent normal tissues, particularly heart and lungs [77, 78].

6.2.2.2 Definitive chemoradiotherapy

For high-seated (cervical) esophageal cancer, definitive CRT is the method of first choice, thereby avoiding otherwise frequent postoperative complications such as dysphagia and aspiration, and mutilating surgery (laryngectomy). CRT results in long-term survival rates of 17-55% [79, 80]. It has been shown in various studies to be superior to radiotherapy alone, which is therefore only used for palliative intent in esophageal cancer.

Definitive CRT is also a treatment alternative for tumors that are considered unresectable after multidisciplinary discussion and for patients with functional inoperability or those who decline surgical therapy.

Results of a randomized phase III trial from the Netherlands (ARTDECO trial) showed no benefit in terms of local tumor control with a total radiation dose increased above 50.4 Gy in patients with intrathoracic esophageal cancer receiving simultaneous chemotherapy with carboplatin/paclitaxel. This study aimed to demonstrate an improvement in local tumor control from 50% to ≥ 65% by increasing the total dose to the primary tumor from 50.4 Gy to 61.6 Gy, applied in 28 fractions in both treatment arms. Local tumor control rates (the primary endpoint) were significantly better than expected at 71% and 73% at 3 years in both the standard and dose-escalated arm, respectively. In this study, 62% of patients had squamous cell carcinoma and 38% had adenocarcinoma [47]. The study report demonstrates the high quality of study conduct and analysis. Accordingly, a total dose of 50.4 Gy should be considered the standard for definitive CRT of intrathoracic esophageal carcinomas, with simultaneous carboplatin/paclitaxel chemotherapy. For tumor localization in the cervical esophagus, higher total doses up to 66 Gy in conventional fractionation with 1.8 Gy per fraction are recommended, based on single-institution treatment series, in accordance with the recommendations of the current NCCN guideline on esophageal cancer (version 4.2023). The larger randomized trials used total radiation

doses of 60-66 Gy in conventional fractionation with concurrent chemotherapy with cisplatin/5-FU or other cisplatin-containing combinations to compare neoadjuvant CRT + subsequent surgery with definitive CRT without surgery for squamous cell carcinoma of the esophagus [42]. Significant differences in overall survival were not observed between treatment arms. Exploratory analysis of the FFCD 9102 trial showed a dose-effect relationship when comparing patients treated conventionally up to 66 Gy with those treated hypofractionated up to 45 Gy [124]. Therefore, for simultaneous chemotherapy with cisplatin/5-FU, total radiation doses of 50-60 Gy are recommended as a therapeutic corridor for definitive CRT. However, if salvage surgery appears to be an option for patients, depending on their general performance and tumor spread, the total dose for radiotherapy should be limited to 50 Gy-55 Gy in conventional fractionation with 1.8-2.0 Gy per fraction, according to the FREGAT group data [125], as an increase in postoperative complications was observed with higher total doses of preoperative radiation.

Previously, the most commonly used chemotherapy in combination with radiotherapy was cisplatin and 5-FU [11], but now combined CRT with FOLFOX is considered equivalent [49]. Definitive CRT using carboplatin/paclitaxel or cisplatin/paclitaxel is also a first-line option with low toxicity and comparable long-term treatment outcomes. Randomized trials comparing the efficacy and toxicity of the combination of cisplatin/5-FU with carboplatin/paclitaxel have not been published to date.

6.2.3 Systemic cancer treatment

6.2.3.1 Perioperative chemotherapy

Perioperative chemotherapy is a well-established standard therapy for adenocarcinomas of the esophago-gastric junction for tumors with a category cT3 or higher (see also Onkopedia guideline on gastric cancer). A direct comparison between perioperative chemotherapy and neoadjuvant CRT is only available for AEG. The results are inconclusive (see chapter 6.1.3). From the Neo-AEGIS study, there are no differences in survival between perioperative chemotherapy with EC(O)F(X) / FLOT and preoperative CRT according to the CROSS protocol (chapter 6.1.3.2). However, in this study only about 10% of the patients received the standard therapy with FLOT, so that the comparator goup of perioperative chemotherapy in this study was suboptimally treated.

On the basis of the UK-MRC MAGIC trial, a combination of epirubicin, cisplatin, and 5-FU (ECF), 3 cycles of 3 weeks each preoperatively and 3 cycles postoperatively, was long considered the standard of care because it resulted in an improvement of 5-year survival from 23% to 36% compared with surgery alone. Comparable results are available for the combination of cisplatin and 5-FU (2 cycles corresponding to 8 weeks of preoperative treatment). The FLOT regimen (5-FU, folinic acid, oxaliplatin, docetaxel) showed a significantly higher histopathologic response rate (15.6% vs. 5.8%), improved progression-free survival (hazard ratio 0.75; median 12 months), and significantly improved overall survival (HR 0.77; p=0.012) in a randomized phase III trial compared with ECF/ECX [28]. With also lower toxicity rates, FLOT is therefore the standard therapy in the perioperative concept.

Current data indicate that the response to preoperative chemotherapy does not determine the choice of postoperative chemotherapy, neither with regard to its implementation nor to intensification or swichting of drug. Only in the case of tumor progression under preoperative therapy should it not be continued postoperatively. Whether early response evaluation by PET-CT after 1 course of preoperative chemotherapy with cisplatin/5-FU can change this situation has not yet been clarified. Of interest are the results of a randomized phase II trial (DOCTOR) [81], in which treatment for patients without metabolic tumor response was escalated to either docetaxel, cisplatin, 5-FU (DCF) or DCF + radiotherapy. Over 90% of patients with AC of the esophagus or

AEG subsequently underwent surgery. Additional radiotherapy appears to improve both progression-free survival (at 3 years, 46% vs. 29%) and overall survival (at 5 years, 46% vs. 31%).

In individual cases (understaging), adjuvant chemotherapy alone may be justified [83], if no therapy was or could be given preoperatively. This is particularly relevant in cases of extensive lymph node metastasis (pN2-3). In these exceptional situations, adjuvant chemotherapy with oxaliplatin and a fluoropyrimidine can be recommended for a total duration of 6 months according to the Korean CLASSIC study [83, 84].

Monotherapy with an oral fluoropyrimidine for 12 months is no longer considered the standard of care, even in Asia, on the basis of the ARTIST2 trial [85].

6.2.3.2 Palliative chemotherapy

This is the therapy of choice for metastatic tumors or, in exceptional cases, an option for symptomatic treatment in patients with locally advanced esophageal cancer in whom neither resection nor radiotherapy can be applied [86].

An overview of the various therapeutic options can be found in Chapter 6.1.4.1 Drug-based tumor therapy and on the individual substances in the next Chapter 6.2.3.3.

6.2.3.3 Systemic tumor treatment - substances

6.2.3.3.1 Capecitabine and S1 (tegafur/gimeracil/oteracil)

Capecitabine and S1 are oral fluoropyrimidines that are metabolized in the body to 5-FU. In comparative clinical trials, they are as effective as 5-FU. They can be used in place of 5-fluorouracil for palliative therapy if there is adequate swallowing function. In combination with platinum derivatives, remission rates up to 45% are achieved. Serious side effects (grade 3/4) occurring in more than 5% of patients in pivotal studies are diarrhea and hand-foot syndrome (very rare for S1). Prior to capecitabine or S1-containing chemotherapy, a mutation in the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded.

6.2.3.3.2 Cisplatin

Platinum derivatives are among the most effective single substances. In combination with other cytostatic drugs, cisplatin is part of the treatment standard of 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 shifts, and diarrhea.

6.2.3.3.3 Docetaxel

Docetaxel belongs to the taxanes and is an effective combination partner of fluoropyrimidines and platinum derivatives in perioperative and palliative therapy; it is a component of the FLOT regimen. Severe side effects (grade 3/4) include infection, nail changes, taste disturbances, stomatitis, and diarrhea. Burdensome side effects (grade 2) include alopecia. Particularly distressing is polyneuropathy, some of which is irreversible. Common side effects such as nausea/

vomiting and allergic reactions can be prevented by adequate supportive therapy, see Onkopedia Antiemesis.

6.2.3.3.4 5-Fluorouracil

5-Fluorouracil is used in almost all drug treatment protocols for patients with esophageal cancer. Its efficacy is increased by combination with folinic acid. An alternative is oral therapy with capecitabine, see Chapter 6.2.3.3.1. 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 including neutropenia and neutropenic fever. Mutations in the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to 5-FU-containing chemotherapy.

6.2.3.3.5 Irinotecan

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

6.2.3.3.6 Nivolumab

Nivolumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. It is approved as monotherapy for second-line treatment of esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy regardless of PD-L1 status. Typical mild (grade 1-2) adverse events in the pivotal study were rash (11%), diarrhea (10%), and loss of appetite (7%); severe (grade 3-4) adverse events were pyrexia (2%) and interstitial lung disease (2%).

6.2.3.3.7 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 perioperatively recommended FLOT regimen and the standard of palliative first-line regimens FOLFOX and FLO, respectively.

6.2.3.3.8 Paclitaxel

Paclitaxel belongs to the taxanes and is effective as monotherapy in second-line palliative therapy or in combination with cisplatin/5-FU/folinic acid (Gastro-Tax) in first-line palliative therapy. Severe side effects (grade 3/4) include infection, stomatitis and diarrhea, and allergic reactions to the contained solvent, Cremophor. Burdensome side effects include alopecia. Particularly dis-

tressing is polyneuropathy, some of which is irreversible. Common side effects such as allergic reactions can be partially prevented by adequate supportive therapy.

6.2.3.3.9 Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. In the phase III KEYNOTE-590 trial [55] of first-line treatment in metastatic esophageal cancer, pembrolizumab + chemotherapy significantly increased response rates, prolonged progression-free and overall survival, and increased survival at 2 years in comparison with chemotherapy alone. Pembrolizumab is indicated in combination with platin- plus fluoropyrimidine-based chemotherapy for first-line treatment of locally advanced, non-resectable, or metastatic, HER2-negative adenocarcinoma of the esophago-gastric junction in adults with a PD-L1-positive (CPS ≥ 10) tumor, and also as a monotherapy for the treatment of MSI-H or dMMR gastric cancer after at least one line of pretreatment. Characteristic side effects with pembrolizumab are immune-mediated, particularly autoimmune phenomena. More common side effects include hypothyroidism/hyperthyroidism, loss of appetite, fatigue, diarrhea, nausea, rash, and asthenia.

6.2.3.3.10 Ramucirumab

Ramucirumab is a VEGF receptor2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab leads to significant prolongation of progression-free survival, prolongation of overall survival, and an increase in remission rate compared to paclitaxel monotherapy. In patients ineligible for paclitaxel therapy, ramucirumab monotherapy versus placebo also results in prolongation of progression-free survival and overall survival. The only grade 3/4 serious adverse event 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%).

6.2.3.3.11 Trastuzumab

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

6.2.3.3.12 Trastuzumab deruxtecan (T-DXd)

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

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

6.2.3.3.13 Trifluridine/Tipiracil (FTD/TPI)

The combination preparation FTD/TPI consists of the nucleoside thymidine analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil (TPI). The molar ratio of trifluridine/tipiracil is 1 : 0.5 (exact mass ratio: 1 : 0.471). TF is phosphorylated intracellularly by the enzyme thymidine kinase to monophosphate (TF-MP) and subsequently by the enzyme thymidylate kinase to di- (TF-DP) and triphosphate (TF-TP). TF-TP is incorporated into the DNA as a false 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 the thymidine nucleotides and is thus vital for DNA synthesis by maintaining sufficient amounts of thymidine. Trifluridine/tipiracil proved superior to placebo in the third line of treatment of metastatic gastric cancer, prolonging overall survival (HR 0.69; $p<0.001$) and was satisfactorily tolerated: Grade ≥3 adverse events occurred in 267 (80%) patients in the trifluridine/tipiracil group and in 97 (58%) in the placebo group.

6.2.4 Adequate nutrition

The majority of patients have already advanced tumors at the time of first diagnosis, often resulting in symptomatic stenoses. Combination chemotherapy can rapidly improve these symptoms in two thirds of patients. Other patients need local palliative measures due to dysphagia. The use of self-expanding metal stents (SEMS) for rapid relief of dysphagia has become a standard of care. In symptomatic tumor stenosis, high-dose intraluminal brachytherapy or percutaneous radiotherapy may be offered in addition to SEMS, depending on the overall prognosis. The choice of palliative therapy depends on the localization and extent of the primary, the severity of symptoms, and prior therapy. Data on preoperative therapy for locally advanced adenocarcinoma of the esophagus and AEG also show that chemotherapy leads to improvement or normalization of swallowing function in two thirds of patients with high-grade dysphagia (dysphagia grade 0 or 1).

If endoscopic hemostasis is not applicable in patients with tumor bleeding, palliative radiotherapy can be offered (hypofractionated, e.g., 5 x 3 Gy). It is the treatment of choice especially in cases of chronic oozing hemorrhage. If available, angiographic embolization may be useful. Palliative resection can only be considered as ultima ratio.

7 Rehabilitation

Esophageal cancer itself, but also its treatment by surgery, chemotherapy and/or radiotherapy, often leads to significant somatic sequelae, such as weight loss to tumor cachexia, postopera-

tive malnutrition, chemotherapy-induced polyneuropathy, and general weakness or (chronic) fatigue syndrome.

As a result of these side effects and the malignancy itself, there is also often a high psychological burden and a corresponding need for psycho-oncological support.

Targeted rehabilitative measures are therefore necessary. These should be started as soon as possible after completion of the primary therapy as part of follow-up rehabilitation.

When selecting the rehabilitation facility, the approval of this facility for esophageal cancer patients by the funding agencies (pension insurance, health insurance) is a mandatory prerequisite; in addition, the patient's right of choice and wish according to the German §9 SGB IX should be taken into account.

During rehabilitation, in addition to general therapy services (sports/physio/occupational therapy), comprehensive nutritional counseling should be provided, patients should be trained in a teaching kitchen, and there should be the option of administering all scientifically recognized diets - from normal whole foods to complete parenteral nutrition.

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). Further socio-medical questions as well as the possibly required care for patients should be clarified during the rehabilitation.

All patients should be offered psycho-oncological care.

8 Follow-up

8.1 Control examinations during treatment

During ongoing chemotherapy, the patient's general condition and vital bodily functions should generally be checked once a week. Imaging procedures, preferably by means of computer tomography, are also regularly indicated in order to detect an unfavorable disease course in time, not to expose patients to ineffective therapies for an unnecessarily long time, and to ensure the chance of switching to effective treatment alternatives.

8.2 Follow-up post curative treatment

There are no prospective data on the basis of which a specific follow-up regimen can be recommended. The focus should be on clinical control and treatment of therapy-related complaints; regular endoscopic and imaging examinations may be considered. In past and ongoing studies, the regimen in Table 5 has become established.

Table 5: Structured follow-up for patients after curative therapy

Investigation	Months after completion of therapy													
	(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
Laboratory Blood count and serum routine	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging: 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 the supporting professional societies.