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Esophageal Cancer

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

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Esophageal Cancer

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1 Summary

Esophageal carcinomas account for approx. 1% of all malignant diseases and approx. 2% of all cancer-related deaths in Germany. The distinction between squamous cell and adenocarcinomas is clinically relevant.

Approx. 30-40% of patients are in a principally resectable stage at initial diagnosis. Patients with squamous cell carcinoma in particular often have comorbidities that result in limited functional operability. The 5-year survival with resection alone is around 20%. Multimodal concepts improve the prognosis for locally advanced tumors and can also enable organ preservation. After preoperative chemoradiotherapy and complete resection, there is an indication for the use of adjuvant immunotherapy (regardless of PD-L1 status) in patients with histological tumor residuals (incomplete pathological response) of squamous cell carcinoma or adenocarcinoma (including gastroesophageal junction GEJ/AEG type I).

For metastatic squamous cell carcinoma, platinum-based chemotherapy remains the treatment of choice despite limited evidence. Checkpoint inhibitors are approved either in combination with chemotherapy (pembrolizumab, PD-L1 CPS ≥ 10, nivolumab, PD-L1 TPS ≥ 1%) or as so-called double checkpoint blockade (nivolumab plus ipilimumab, PD-L1 TPS ≥ 1%) in the first line and as monotherapy (nivolumab, regardless of PD-L1 status) in the second line. For metastatic adenocarcinomas of the esophagus and the esophago-gastric junction, personalized treatment 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), in analogy to gastric cancer.

2 Basics

2.1 Definition and basic information

In addition to the histological differentiation between squamous cell and adenocarcinomas, the localization of the tumor is an essential finding for planning diagnosis and treatment. Depending on the location and the positional relationships within the chest, esophageal cancer is divided into cervical and intrathoracic tumors as well as tumors of the esophago-gastric junction (GEJ).

The guideline presented here refers to esophageal carcinomas according to the currently valid 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 clear geographical differences in the general incidence of esophageal carcinomas, but also in the ratio of squamous cell and adenocarcinomas.

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

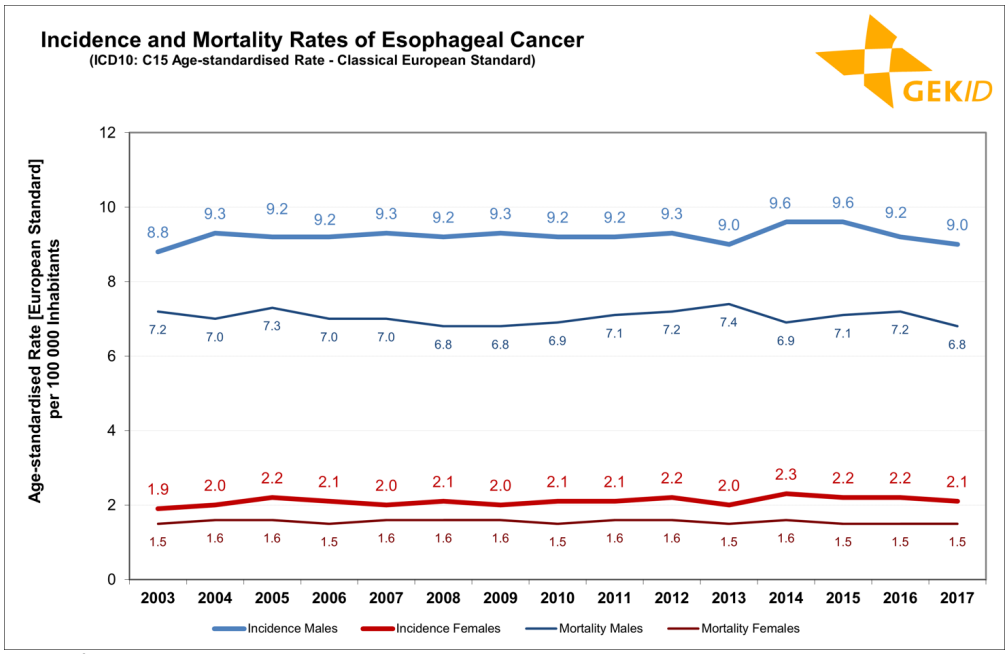
In Germany, around 5,700 new cases of esophageal cancer are diagnosed in men and around 1,850 new cases in women every year. Esophageal cancer is the 13th most common malignant cancer in men (2.2% of all cancers) and the 8th (3.4%) most common cause of cancer-related deaths; in women it ranks 22nd (0.8%) and 18th (1.3%), respectively. The mean age of onset for men (67 years) is lower than for cancer overall (70 years), whereas for women (mean, 71 years) it is 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). Around 16,000 patients with esophageal cancer live in Germany who were diagnosed no more than five years ago, and almost 20,000 patients with a diagnosis in the last 10 years [2].

Squamous cell carcinomas account for around 43% of all esophageal cancers. The proportion of adenocarcinomas, which mainly occur at the lower part of the esophagus and the esophageal-gastric junction, 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 remained almost constant over the last 15 years. It should be noted that the rates for men are considerably higher (by a factor of 3.5) than those for women, see Figure 1.

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

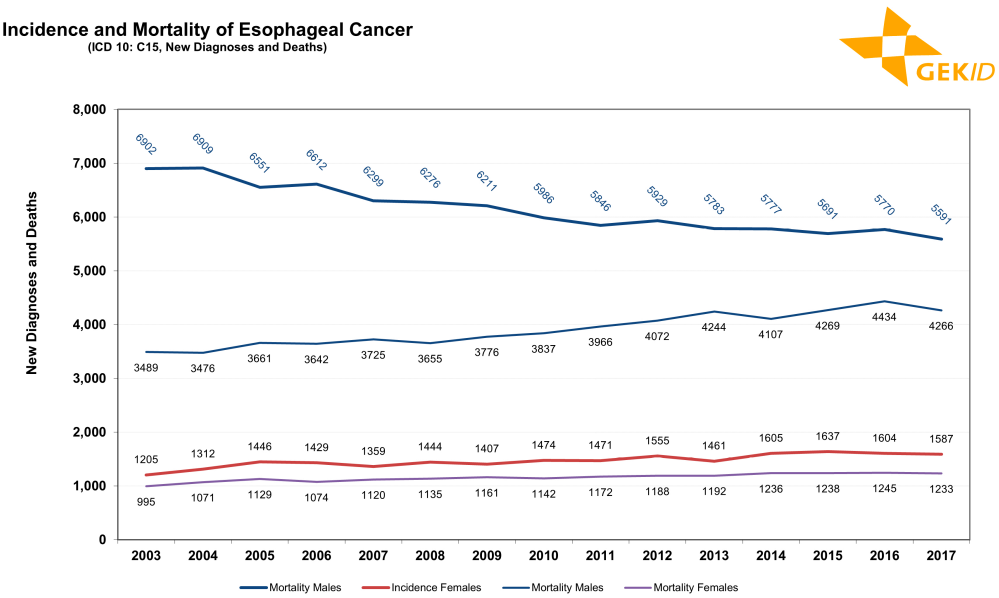


Legend:
Estimated incidence of esophageal cancer (ICD 10: C15) in Germany - age-standardized rates (old European standard); source: Center for Cancer Registry Data, database query [2]

Due to the shift in the age structure towards an older society and because the baby boomers have reached the age of the highest disease probability, the courses of new cases and deaths

differs from the course of rates. This shift has a greater absolute effect on men due to their higher probability of esophageal cancer, but the relative increase is the same for both sexes. Despite constant age-standardized disease rates, the number of cases has increased by an average of 1.7% per year over the last 15 years. The situation is similar for the number of deaths. Here, the number increased by an average of 1.7% per year in men, and by 1.3% per year in women, see Figure 2.

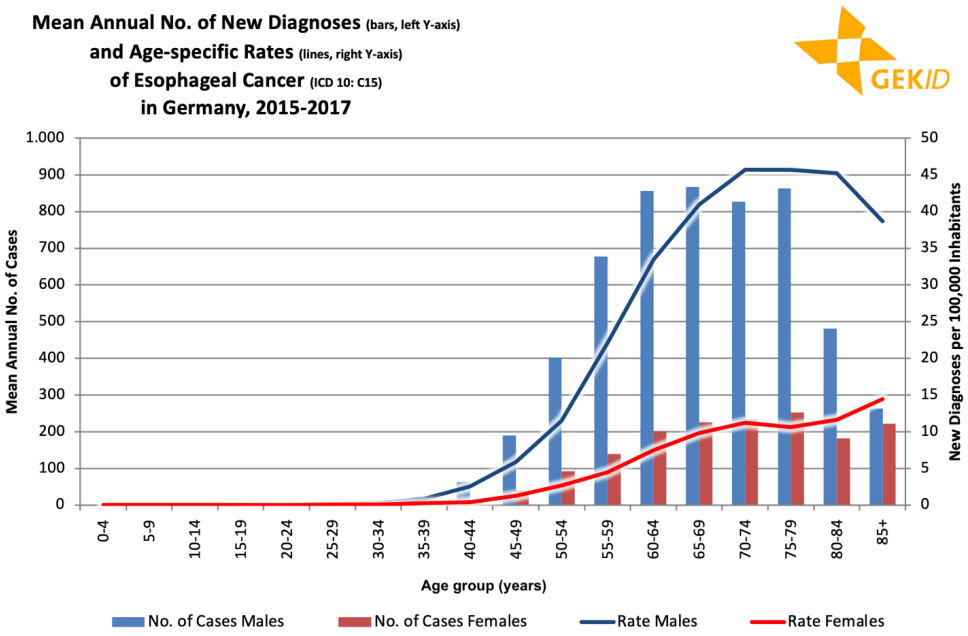
Figure 2: Incidence and mortality of esophageal cancer (ICD 10: C15) in Germany



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

In men, most initial diagnoses are made between 60 and 79 years of age, see Figure 3 (bars). From the age of 40 to 60, the number of new cases increases steadily. The number of cases among 60- to 79-year-olds is almost the same, and the number of cases decreases significantly from the age of 80. In women, the number increases continuously - at a significantly lower level - until the age of 80, and is almost constant after that. The highest risk of disease, see Figure 3 (lines), is found in men between 70 and 85 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.

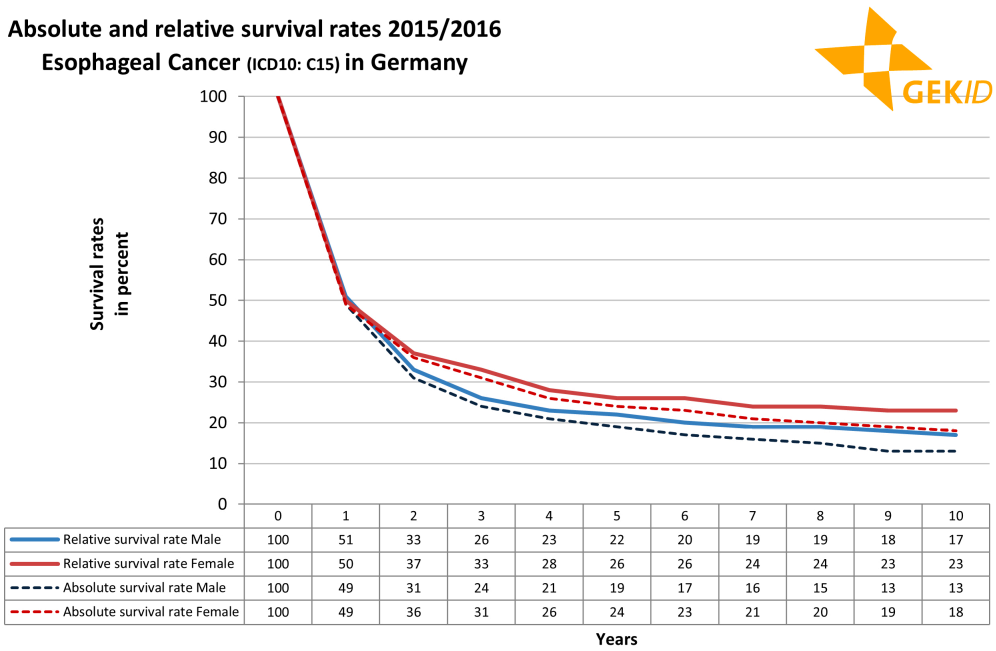
Figure 3: New cases and age-specific rates of esophageal cancer (ICD 10: C15) in Germany



Legend:
Age distribution of the incidence of esophageal cancer (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 in the first year after diagnosis. The small difference between absolute survival rate (percentage of patients who survive 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 sexes.

Figure 4: Absolute and relative survival rates for 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 for 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 about 21% to about 8,500 new cases (2050) can be expected over the next 20 to 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 those resulting from achalasia, radiation therapy or acid or alkali burns, and in combination with toxic carcinogenic substances such as alcohol and nicotine. These carcinogens may also lead to second squamous cell carcinomas in the head and neck region or in the lung [5, 6].

For carcinomas in the distal esophagus, the connection with chronic acid reflux has been extensively studied and is accepted as a significant risk factor. Metaplasia of the orthotopic squamous epithelium into a cylindrical epithelium leads to preneoplastic Barrett's mucosa. The risk of developing carcinoma has long been overestimated. The rate of progression from Barrett's metaplasia to carcinoma is about 0.3% (3 out of 1000 carriers) per year [7]. Case-control studies also show an increased risk of developing adenocarcinoma in smokers. The use of non-steroidal 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 the inconsistent data, prophylactic use of these drugs cannot be recommended [9].

Pathogenetically, transformation of the cylindrical epithelium to cylindrical 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 inactivates this tumor suppressor gene, which is particularly sensitive to the effects of chemical carcinogens [10].

The carcinogenesis of adenocarcinomas not arising from Barrett's mucosa occurs in analogy to the carcinomas of the rest of the digestive tract in multi-stage processes via precancerous stages. Low-grade dysplasia develops into high-grade dysplasia and invasive carcinoma. Infection with Helicobacter (H.) pylori could be considered protective for 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 may also be explained by more intensive surveillance [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 gastro-esophageal acid reflux are more common in carcinomas of the esophago-gastric junction. Nicotine abuse is a common risk factor for the development of cancer.

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

- Squamous cell carcinomas:
  - 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 from alkalis or acids
  - Previous radiotherapy of the neck/thorax area (dose-dependent)
  - History of squamous cell carcinoma of the head and neck or lungs
- Adenocarcinomas:
  - Gastroesophageal reflux disease (GERD): Barrett's esophagus
  - Smoking
  - Obesity
  - Achalasia
  - Stenoses after chemical burns from acids or alkalis

3 Prevention and early detection

3.1 Prevention

The recommendations for the prevention of esophageal cancer refer to the acquired risk factors identified to date [9]:

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

No recommendation can currently 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 approaches 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 be difficult to prove due to the low incidence. In some Asian countries, general screening is being discussed due to their higher burden of esophageal cancer.

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

4 Clinical characteristics

4.1 Symptoms

Early carcinomas are usually asymptomatic. The following symptoms often only occur in locally advanced tumors with obstruction of approx. 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 the primary method for diagnosing esophageal cancer. The aim is to determine the location and extent of the tumor and to detect metaplastic changes in the epithelium of the lower esophagus (Barrett's esophagus). Using high-resolution video endoscopy, it is possible to detect discrete changes in the color, relief and architecture of the mucosa. Endoscopic detection of dysplasia and early carcinomas can be improved by chromo-endoscopy (using Lugol's solution) or by computer-assisted digital procedures (e.g., narrow-band imaging) in the endoscope [15, 16].

As the prognosis of patients with esophageal carcinoma is closely correlated with the local tumor spread and lymph node involvement, a most accurate pre-therapeutic staging is critical to guide therapy. The goals of diagnostic procedures are to determine the stage of the disease and to clarify the patient's ability to tolerate cancer treatment. The depth of invasion of the tumor (T category) and its proximity to adjacent structures play a particularly important role here, the predictive accuracy of which can be improved by endoscopic ultrasound (endosonography), see Table 1. Endosonography has the highest accuracy of available methods due to its high local spatial resolution. Data from Russell et al [17] indicate that consistent EUS tumor staging in esophageal cancer leads to improved survival rates of patients examined by EUS (approx. 3 months longer than the control group). Limitations are on the one hand the depen-

dence on the investigator's skills 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 ultrasound is the initial imaging procedure in staging diagnostics and should be performed as the first procedure to exclude liver metastases. The additional use of contrast-enhanced sonography further increases sensitivity and specificity. Beyond that, B-scan ultrasonography of the neck can be used as a complementary procedure to look for cervical lymph node metastases, which are present in 10-28% of patients, especially if 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)

In patients with newly diagnosed esophageal cancer, MDCT of neck/thorax and abdomen with multiplanar reconstructions and additional wall distention by negative contrast and IV contrast should be performed for primary staging. It is recommended to include the neck in 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 used when CT cannot be performed (contraindications to contrast media) or as a complementary procedure to CT/EUS. MRI is particularly useful in the area of the esophago-gastric junction and for the detection of liver metastases, when liver-specific contrast medium is used. For pulmonary focal findings, it is less accurate than CT.

5.2.2.5 Positron emission tomography (PET/CT)

For locally advanced tumors (cT2-4 and cN+), PET/CT may additionally be used for M-staging for excluding distant metastases if a curative therapy is intended and/or if the PET/CT 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 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 by PET/CT nevertheless entails the clinical consequence of expanding the radiation volume or extending the areas of lymph node dissection.

Note on the reimbursement situation: PET or PET/CT for the detection of distant metastases is included in the outpatient specialist care (ASV) of patients with severe courses of gastrointestinal tumors and tumors of the abdominal cavity.

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

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 patients with frequent comorbidities, including age, nutritional status, comorbidities, cardiopulmonary and hepatic pre-existing conditions (alcohol history, cirrhosis?) or "functional reserve". For patients over 70 years of age, a geriatric assessment is also recommended.

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

Table 1: Diagnostics and staging

Investigation	Remark
Physical examination	
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation, TSH
Endoscopy of the upper gastrointestinal tract	Optionally supplemented by chromo-endoscopy
Histology	Histopathological findings with immunohistology
Endoscopic ultrasound (EUS)	For patients with curative treatment intention
Computed tomography neck, thorax, abdomen with contrast medium	CT neck for cervical tumors, if no PET-CT is performed
Ultrasound abdominen and neck	Complementary to computed tomography, if required
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 to exclude second malignancies
Bronchoscopy	If tumor is adjacent to trachea/bronchial system
Risk analysis of important organ functions	Question of functional operability
Screening for malnutrition	Patients at risk of malnutrition
Anesthesiological assessment	Early consultation recommended in curative setting, as many patients have relevant co-morbidities

Legend:
[1] Laparoscopy helps to detect clinically occult metastasis of the peritoneum in locally resectable tumors with GEJ/AEG-I and GEJ/AEG-II carcinomas. The detection of macroscopic peritoneal carcinomatosis has a direct impact on treatment planning. Laparoscopically conspicuous findings are rarely found in T1/T2 category tumors. ENT, Ear-Nose-Throat assessment

Histopathologic evaluation of resected tissues (endoscopic resection; ER) should contain the following information:

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

- Histological type according to WHO (in particular differentiation between squamous cell versus adenocarcinoma, other rare types)
- Immunohistochemical information on the biomarkers PD-L1 (as combined score CPS and as percentage of positive tumor cells TPS), HER-2 and microsatellite status (both for adenocarcinomas)
- For invasive carcinomas:
  - Degree of differentiation (grading) according to the 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 and/or venous invasion
- Summarized assessment of the risk of LK metastasis:
  - Low risk vs. high risk
  - Resection margins with regard to the neoplasia: for ER in toto, circular and basal resection margin; for "piece-meal" ER, basal resection margin, as the circular resection margin must generally be assessed histopathologically as “RX” here

After neoadjuvant therapy, re-staging should be performed to exclude metastases. If there is clinical evidence of tumor progression during neoadjuvant therapy, symptom-based diagnostic procedures during ongoing therapy 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) and the positional relationships within the chest, a distinction is made according to the current TNM classification 8th edition [22] between carcinomas

- of the cervical esophagus (C15.0): from the lower edge of the cricoid cartilage to the entry of the esophagus into the thorax (suprasternal fossa), about 18 cm from ZR
- of the 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 the esophagus between tracheal bifurcation and esophago-gastric junction, 24 to 32 cm from TR
  - lower thoracic segment (C15.5): distal half of the esophagus between the tracheal bifurcation and the esophago-gastric junction. The lower border is the Z-line about 40 cm from TR
- of the esophago-gastric junction (GEJ) (C16.0): tumors involving the esophago-gastric junction with a center within 2 cm above or below and crossing the Z-line (Siewert types I and II), synonym AEG (adenocarcinoma of the 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 staging/TNM

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

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

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

Classification	Tumor
T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (malignant cells limited by the basement membrane)
T1	Tumor invades the lamina propria or muscularis mucosae or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures such as the aorta, vertebral body or trachea
T4a	Tumor invades the pleura, the pericardium, the azygos vein, the diaphragm or the peritoneum
T4b	Tumor invades the aorta, a vertebral body or the 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 more than 7 regional lymph nodes
M	**Distant metastases**
M0	No distant metastases detected
M1	Distant metastases detected

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 T3	N0, N1 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 of the esophagus - clinical staging according to UICC

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	Each N	M1

5.3.3 Histological subtypes

- Carcinoma in situ (CIS): macroscopically raised or flat epithelial thickening or sunken thinning of the mucosal epithelium, which appears whitish (leukoplakia), reddish (erythroplasia) or unchanged in color (occult type). Solitary in 10-20% and multiple in 80-90%.
- Polypous carcinoma: most common at approx. 60%.
- Diffuse infiltrating carcinoma: approx. 15% of cases.
- Ulcerative carcinoma: in about 25% of cases, the tumor presents as an irregularly bordered hemorrhagic ulcer with raised wall-like edges.
- Varicose carcinoma: This term is used to describe tumors that resemble esophageal varices in their endoscopic and radiographic appearance.

5.3.4 The Cancer Genome Atlas (TCGA) classification

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

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

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

These subtypes have so far had no impact on everyday clinical practice and therapeutic decisions.

6 Therapy

6.1 Treatment structure

Due to the complex treatment options, recommendations should always be discussed and decided on a multidisciplinary basis (multidisciplinary tumor conference).

In addition to tumor-specific factors, patient-specific factors play a special role, as significant comorbidities with potential cardiovascular, pulmonary or hepatic limitations are often present, which make treatment more difficult and can lead to so-called functional inoperability of patients with resectable tumors [11].

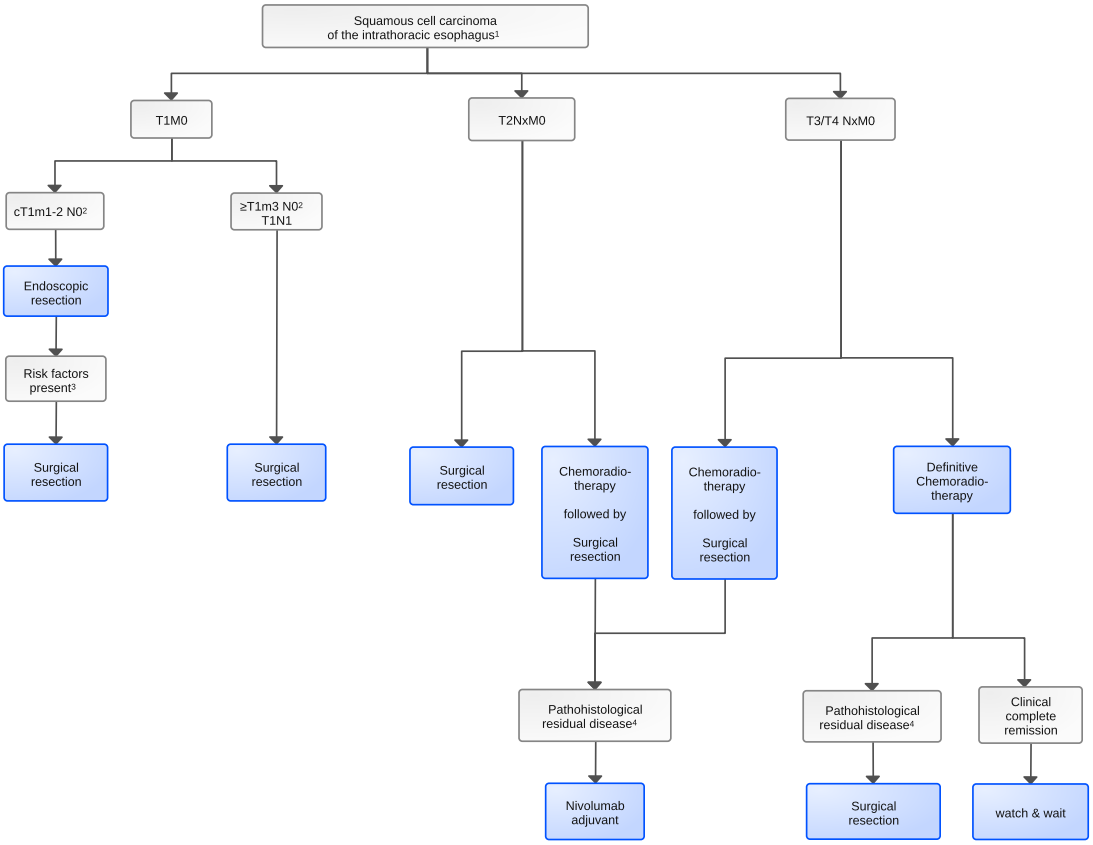
Many patients are in a reduced general performance at the time of diagnosis, and severe malnutrition is particularly common in squamous cell carcinoma. Due to the high metabolic risk, patients should be fed before surgery, even if the operation has to be postponed for this reason. After surgery, (parenteral)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

More than 50% of patients with esophageal cancer are over 65 years old at the time of diagnosis. Nevertheless, there is still little data available on the treatment of patients over 70 years of age. Older British analyses indicate that the advantage of preoperative chemoradiotherapy over surgery alone decreases with age and is no longer significant for patients over 65 years of age. A randomized British study (GO2 study) in metastatic disease proves, at least for older patients with adenocarcinoma, that a primary dose reduction vs. standard dose 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 secondarily in the treatment algorithms.

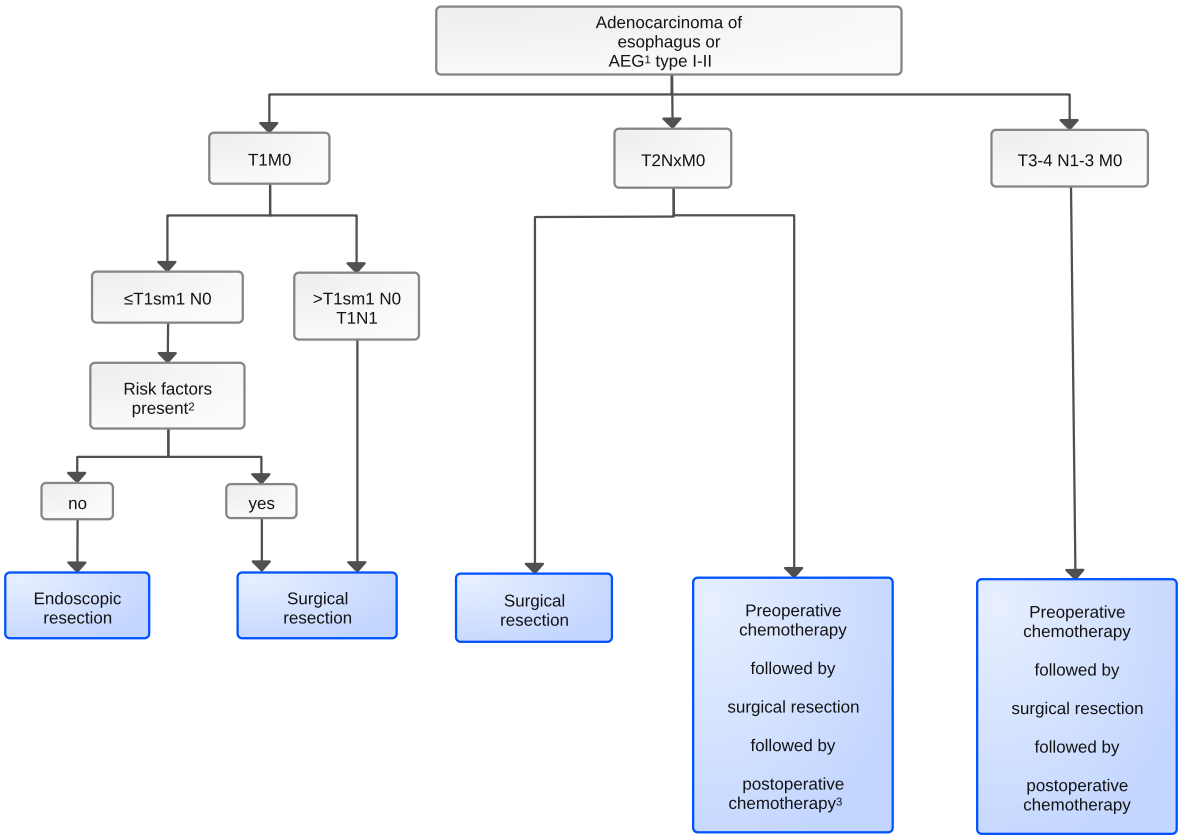
A treatment algorithm for resectable squamous cell carcinomas is shown in Figure 5, for resectable adenocarcinomas in Figure 6, and for metastatic tumors in Figure 7 and Figures 8 to 10.

Figure 5: Algorithm for primary treatment of squamous cell carcinoma



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

Figure 6: Algorithm for primary treatment of adenocarcinoma



Legend:
Therapy with curative intent
[1] AEG: Adenocarcinoma of the esophago-gastric junction (GEJ)
[2] Risk factors: ulceration, L1, V1, G3, R1 basal deep submucosal infiltration, multifocal/non-ablatable Barrett's lesions
[3] Particularly critical indication for postoperative chemotherapy in MSI-high adenocarcinomas

6.1.1 T1a N0 M0 (early carcinoma)

As the probability of lymph node metastasis in mucosal esophageal carcinoma (T1a) is very low at 1-2%, mucosectomy by means of endoscopic resection (ER) is considered the standard treatment for adeno-early carcinoma in the pT1 m1-sm1 category and for squamous early carcinoma in the pT1 m1-m2 category. The aim here should be an en-bloc resection, which allows a complete histological assessment of the lateral and basal margins.

The aim of the procedure must be an R0 resection. Technically, endoscopic mucosal resection (EMR / ER) and endoscopic submucosal dissection (ESD) [24] are available.

EMR is well established in Europe. However, only lesions up to a maximum of 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. For example, up to 30% of Barrett's neoplasms after EMR have relapses or second manifestations [25].

Data for ESD are mainly available from Asian countries for squamous cell carcinoma. Here, superiority was shown with regard to en-bloc resection rate, curative resection rate and local recurrence rate. Data from Japan show that ESD is also possible in principle for Barrett's carcinoma, with an R0 resection being achieved in 85% of cases. However, the value of ESD in adeno-/Barrett's carcinoma has not been conclusively clarified [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.

If the following risk factors are present, surgical resection of the tumor should be performed instead of endoscopic resection [9]:

- Tumor residue at the basal resection margin (R1 basal)
- Multifocal or non-ablative 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 lymphatic or venous invasion (L1, V1), a differentiation grading of G3 or deep submucosal invasion (> 500 µm) is present after ER [9]. In squamous cell carcinoma, definitive chemoradiotherapy is also an alternative to surgical resection. The rate of grade III esophageal stenosis after ER and chemoradiotherapy is around 6%. Some patients require repeated dilatations.

As a local recurrence limited to the mucosa after ER or a previous second carcinoma can be treated again endoscopically with curative intent, regular endoscopic follow-up is indicated. The recommended follow-up intervals are 3 months in the first year and 6 months in the second year. Thereafter, check-ups should be carried out annually.

In Barrett's esophagus, the non-neoplastic Barrett's mucosa should be thermally ablated after successful endoscopic resection, as this can reduce the rate of secondary neoplasia.

6.1.2 T1b-T2 M0 (locally limited tumors)

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

The treatment 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 in the circumference as well as 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 proven for patients with T1b carcinomas regardless of lymph node involvement.

Irrespective of the tumor location in the esophagus and the histology (adeno- or squamous cell carcinoma), definitive chemoradiotherapy is an alternative for patients not suitable for surgery due to comorbidities, with the aim of achieving permanent loco-regional tumor control. For these patients, endoscopic resection may be the treatment of choice for a T1b category tumor despite an increased risk of recurrence [9].

The use of multimodal treatment concepts, as described below for T3/T4 tumors (see Chapter 6.1.3), may already be appropriate for a T2 category tumor, especially in the case of highly suspected or proven lymph node metastases. The recommendation for such a procedure should be discussed on a multidisciplinary basis and the advantages and disadvantages discussed with the patients [27]. In any case, patients with T2 tumors were also included in published randomized studies on perioperative chemotherapy [28] and preoperative chemoradiotherapy [29]. A significant survival benefit has not yet been demonstrated in this subgroup [30, 31].

If preoperative therapy is carried out, care must be taken to ensure that the goal of secondary tumor resection is not compromised. A deterioration in the general condition must be detected early and its cause clarified (toxicity, non-response with persistent or increasing symptoms due

to tumor progression). In these cases, preoperative chemotherapy should be abbreviated if necessary, malnutrition should be treated preoperatively and - if distant metastases have been ruled out - surgery should be brought forward.

6.1.3 T3-T4 M0 (locally advanced tumors)

Both squamous cell and adenocarcinomas of the esophagus/GEJ should be treated as part of multimodal therapy concepts from category cT3. For squamous cell carcinomas, preoperative chemoradiotherapy (CRT) should be carried out in addition to the intended curative resection. Patients with adenocarcinoma of the esophagus or the esophago-gastric junction (GEJ) should receive perioperative chemotherapy [111].

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

After preoperative CRT and surgery, adjuvant immunotherapy with nivolumab for 12 months is recommended for patients with tumors that have not shown pathologically complete remission. This recommendation is based on data from the international phase III CheckMate 577 trial, in which 794 patients were randomized to placebo vs. nivolumab for 1 year after completion of preoperative CRT and recovery from subsequent surgery [33]. The results show that the immunotherapy is easy to administer and does not worsen the patients' quality of life compared to placebo. The primary endpoint was achieved with a significant prolongation of median disease-free survival (prolonged from 11.0 to 22.4 months, p=0.0003, HR 0.69 (CI 0.56-0.86)). In particular, nivolumab 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). The results did not differ between PD-L1-positive (72% of patients) or -negative tumors, whereby only the tumor cells before CRT were considered for the assessment (PD-L1 TPS ≥ 1% or <1%). The disease-free survival in the control arm appears to be short with a median of 11 months.

Although no overall survival data have been reported in the CheckMate-577 study to date, the European Commission granted approval for adjuvant immunotherapy with nivolumab for both histological types in Europe in September 2021, regardless of PD-L1 status. In an update to its statement on esophageal/GEJ cancer, ASCO also issued a strong recommendation for adjuvant therapy with nivolumab after CRT and surgery, if malignant cells were still detectable in the resected tissue [34].

If patients with adenocarcinoma have not been treated perioperatively with FLOT chemotherapy, but preoperatively with chemoradiotherapy according to the CROSS protocol, the recommendation of adjuvant therapy with nivolumab also applies here.

6.1.3.1 Locally advanced squamous cell carcinoma*

*see Figure 5

For cervical (almost always squamous cell) carcinomas of the esophagus, definitive chemoradiotherapy is considered the standard treatment [41]. Only a few centers in Europe perform surgical resection (usually with laryngectomy) for tumors of this location. It should be noted 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 recurrent paresis, so that surgery should not be performed for high-seated esophageal carcinomas.

Definitive radiotherapy alone without chemotherapy, preoperative radiotherapy without chemotherapy or preoperative chemotherapy is at present not recommended for squamous cell carcinoma of the esophagus [35]. Initial data from a Japanese multicenter study (NEXT study) indicate that preoperative chemotherapy improves the prognosis [73]. 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 chemoradiotherapy (41.4 Gy plus 2 courses of cisplatin/5-FU). Of 200 patients in each treatment group, over 98% had squamous cell carcinoma, about 1/3 had cT1 and cT2 tumors. Overall survival was significantly improved compared to cisplatin / 5-FU only by the intensified chemotherapy (survival rate after 3 years 72% vs. 63%, HR 0.68 (0.50-0.92)), but not by the combined CRT (survival rate after 3 years 68% vs. 63%, HR 0.84 (0.63-1.12)). CRT was only superior in terms of histological tumor response (pathological complete response (pCR) 37% with CRT vs. 19% with DCF vs. 2% with CF). The rate of postoperative complications did not differ between the treatment groups. The results of the NEXT study also show that increased pCR rates, as can be achieved with combined CRT, do not necessarily translate into prolonged survival. In Europe, however, preoperative chemotherapy alone for squamous cell carcinoma of the esophagus is not standard.

Results from Asian studies and meta-analyses [36, 37] showing that adjuvant radiotherapy can improve local tumor control and possibly also overall survival should be tested in phase III trials with "Western" patients. Adjuvant radiotherapy (or chemoradiotherapy) is not a standard of care.

6.1.3.2 Locally advanced adenocarcinoma of the esophagus/GEJ*

*see Figure 6

6.1.3.2.1 Perioperative therapy

For patients with adenocarcinomas of the esophagus/esophago-gastric junction (GEJ) of category ≥T3 or N+, perioperative chemotherapy is an evidence-based and well-established treatment option and the standard of care. Perioperative chemotherapy consisting of taxane, platinum derivative and a fluoropyrimidine (5-fluorouracil/folinic acid/oxaliplatin/docetaxel, FLOT) is considered standard treatment for patients with locally advanced GEJ (≥cT2 and/or cN+) based on the data of the FLOT-4 study. FLOT led to 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, histological type or localization. The rate of perioperative complications was comparable in both arms [28].

For locally advanced gastroesophageal junction tumors (≥T2 and/or ≥N1), neoadjuvant chemoradiotherapy (CRT) with carboplatin/paclitaxel according to the CROSS protocol has so far also been a treatment option in line with guideline recommendations. Until recently, comparative data between preoperative chemoradiotherapy and perioperative chemotherapy in

locally advanced GEJ could not demonstrate a statistically significant survival benefit from additional radiotherapy. Data from the phase III Neo-AEGIS study show no difference in overall survival (survival rate after 3 years 55% vs. 57%, HR 1.03 (0.77-1.38) between perioperative chemotherapy (90% of patients received epirubicin / platinum / fluoropyrimidine), which is now outdated, and preoperative CRT analogous to the CROSS study [74]. About 80% of the patients had a GEJ of category cT3.

The ESOPEC study is the first head-to-head study to compare both treatment concepts for esophageal adenocarcinomas: perioperative chemotherapy with FLOT versus neoadjuvant CRT according to CROSS. Initial results were presented at ASCO 2024 [111]. The primary endpoint of the study was overall survival. Patients with cT1N+ or cT2-4a, cN0/+, cM0 were included. With a median follow-up of 55 months, the study showed a significant benefit in median overall survival of 66 months with FLOT versus 37 months with CROSS (HR 0.70) and a 3-year survival rate of 57.4% versus 50.7% in the ITT population. Thus, patients treated with FLOT had a 30% lower risk of death after 3 years than those who had received CRT according to the CROSS protocol. This advantage was present for all subgroups, but with a particular effect in T3-4 (HR 0.70) and N+ tumors (HR 0.68). The 3-year progression-free survival was also significantly improved for FLOT in the ITT population (51.6% vs. 35%; HR 0.66, p=0.001). The rate of complete pathological remissions (pCR), defined as ypT0, ypN0, was also clearly improved in favor of neoadjuvant chemotherapy with 16.8% with FLOT compared to 10% with CROSS. Critics note that in the CROSS group, neoadjuvant therapy was only fully administered in 67.7% (even though 98% received the planned 41.4Gy), compared to 87.3% complete administration of neoadjuvant therapy in the FLOT group. Due to the superiority of perioperative chemotherapy over CRT shown in the ESOPEC study, FLOT is considered the standard therapy for locally advanced GEJ tumors. There is no comparison with neoadjuvant CRT according to CROSS, followed by consolidating immunotherapy with nivolumab according to CheckMate 577 for R0 resection without achieving pCR.

The question of the AIO-RACE study is whether a combination of both forms of therapy provides an additional benefit. The current standard of perioperative chemotherapy with FLOT is compared with induction chemotherapy with 2 cycles of FLOT followed by CRT (5-FU/oxaliplatin). The primary endpoint is disease-free survival (DFS). Recruitment was recently completed.

The assumption that perioperative chemotherapy may not be effective in patients with signet ring carcinomas or microsatellite-instable (MSI-H) adenocarcinomas is not justified according to recent analyses [32] demonstrating that perioperative treatment with FLOT is also effective for patients with signet ring carcinoma or MSI-H/dMMR.

6.1.3.2.2 Importance of anti-HER2-directed perioperative therapy

The longest established molecular target structure in gastric carcinoma/GEJ is the HER2 oncogene. Up to 30% of adenocarcinomas of the stomach and esophagus are HER2-positive. The addition of HER2-targeted treatment with trastuzumab to chemotherapy improves overall survival in patients with advanced HER2-positive gastric cancer and GEJ [82]. Treatment of locally advanced adenocarcinomas remains independent of HER2 status. The role of perioperative HER2-directed therapy in resectable disease has not yet been conclusively clarified, but current studies show an increase in efficacy through the additional perioperative use of anti-HER2-targeted therapy.

In the phase II PETRARCA trial, the efficacy of adding HER2-directed therapy with trastuzumab and pertuzumab to perioperative FLOT was studied [39]. pCR rates were significantly higher in patients who received HER2-targeted therapy perioperatively (35% vs. 12%, p=0.02), and R0 resection rates were comparable in both groups (93% vs. 90%). The improved local response

translated into significantly longer disease-free survival and a trend towards better overall survival with anti-HER2 therapy. However, the study was terminated prematurely and the number of cases was small.

In the three-arm phase II INNOVATION trial, patients with resectable HER2-positive gastric cancer or GEJ received either perioperative chemotherapy alone, chemotherapy plus trastuzumab or chemotherapy with dual anti-HER2 therapy with trastuzumab and pertuzumab. The primary endpoint, the major pathological response rate (defined as < 10% vital residual tumor cells), could not be achieved with the combination of chemotherapy plus trastuzumab and pertuzumab. However, compared to chemotherapy alone, there was a significant advantage for the addition of trastuzumab (pathologic major response rate 37% vs. 23%, p=0.099) and not for dual inhibition with trastuzumab and pertuzumab (26% vs. 23%, p=0.378). This could be due to the greater toxicity of the dual inhibition, which led to an increased dose reduction of the concomitant chemotherapy [114]. The follow-up data on survival are still pending.

Despite the emerging increase in efficacy through additional HER2-directed therapies, there is currently no recommendation for anti-HER2 therapy in the context of perioperative therapy for gastric carcinomas and GEJ. Therefore, HER2-targeted therapies in the perioperative treatment of GEJ tumors should currently only be used within clinical trials.

6.1.3.2.3 Value of peri/pre-operative immunotherapy therapy for dMMR/MSI-H GEJ/ AEG tumors

In highly microsatellite-instable (MSI) localized GEJ tumors, retrospective analyses cast doubt on the efficacy of perioperative chemotherapy [120]. However, current data from the DANTE study show that complete and subtotal tumor remissions can also be achieved with FLOT chemotherapy in GEJ tumors of the MSI subtype [120, 72]. Thus, according to the current status, perioperative chemotherapy with the FLOT regimen is still indicated for MSI-GEJ tumors if tumor shrinkage is to be achieved. However, several studies show that the addition of an immune checkpoint inhibitor to neoadjuvant therapy in the case of deficient DNA mismatch repair/MSI leads to significantly better remission rates [119, 122]. In addition, in exploratory subgroup analyses, event-free and overall survival is also significantly improved when perioperative chemotherapy is supplemented with an immune checkpoint inhibitor in MSI-high GEJ tumors [123]. The FFCD-NEONIPIGA phase 2 study shows a high histopathological remission rate after 12 weeks of treatment with nivolumab plus ipilimumab without chemotherapy in resectable MSI cancers [121]. The data require validation in larger and independent cohorts. Nevertheless, preoperative immunotherapy - today most likely in combination with FLOT chemotherapy as tested in the randomized and controlled trials Dante, Keynote-585 and Matterhorn with regard to safety and efficacy - should already be considered in cases of confirmed MSI-high status, regardless of the approval status of the drugs. It is recommended to include patients in studies that use preoperative/perioperative immunotherapy.

6.1.3.2.4 Adjuvant therapy after lack of preoperative therapy

Patients with locally advanced GEJ who have undergone resection without pretreatment (e.g., due to incorrectly low tumor stage prior to surgery) can be treated with adjuvant therapy if there is an increased risk of local recurrence, e.g., 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 plus cisplatin/ capecitabine) does not lead to a (further) improvement in disease-free survival compared to combination chemotherapy alone (cisplatin/capecitabine) (ARTIST2 trial) [40].

Adjuvant CRT is recommended after R1 resection due to the high risk of local recurrence [9, 36, 37]. Alternatively, after R+ resection and subsequent neoadjuvant CRT, adjuvant administration of nivolumab is also covered by the approval (although not included in CM-577) and can be an alternative to radiotherapy in the vulnerable area of the anastomosis, which is often not favored [116, 117, 118].

6.1.3.2.5 Locally inoperable adenocarcinomas of the esophagus/GEJ

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

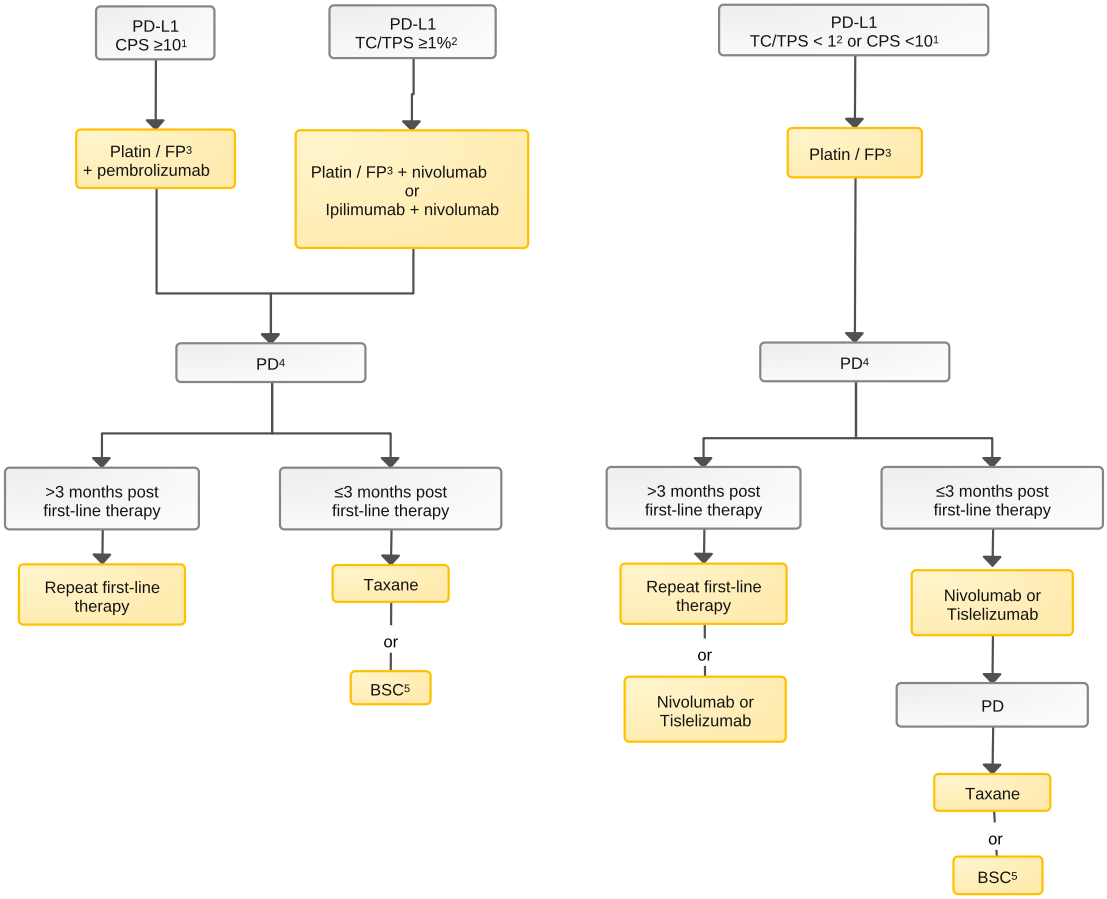
For definitive CRT, a radiation dose of 50.4 Gy should be aimed for. According to mature data from a Dutch phase III study (ARTDECO), higher doses do not improve local tumor control or overall survival in either squamous cell carcinoma or adenocarcinoma [42]. With regard to chemotherapy within CRT, the data available by now favor a combination of platinum and fluoropyrimidine or carboplatin and paclitaxel [43]. A French phase III trial showed comparable efficacy for a combination of oxaliplatin and 5-FU (FOLFOX regimen) compared to the standard combination of cisplatin and 5-FU in conjunction with definitive radiotherapy [44]. The combination of radiotherapy plus carboplatin and paclitaxel, which has been well documented in preoperative therapy, is apparently also suitable for definitive CRT [43], without data from comparative studies being available. The feasibility in combination with 50.4 Gy appears to be better than with cisplatin and FU. The addition of cetuximab showed no increase in efficacy or even negative effects in several studies [45, 46, 47].

6.1.4 Stage IV (metastatic tumors)

6.1.4.1 Systemic cancer treatment

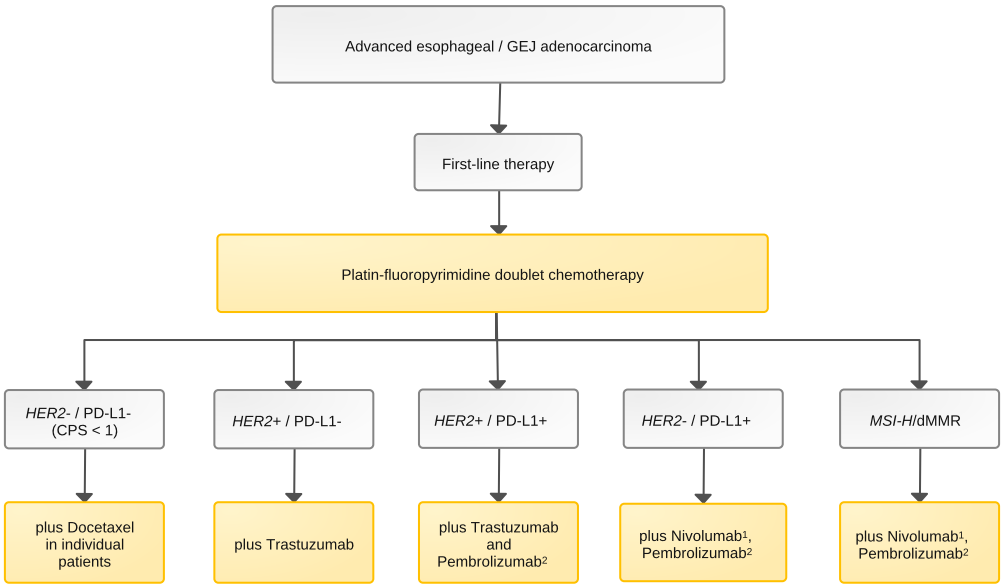
The treatment of metastatic esophageal/GEJ cancer is palliative. Systemic therapy is the first priority, supplemented by local therapy measures if indicated. An algorithm for metastatic squamous cell carcinoma is shown in Figure 7 and for metastatic adenocarcinoma in Figure 8 to 10.

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



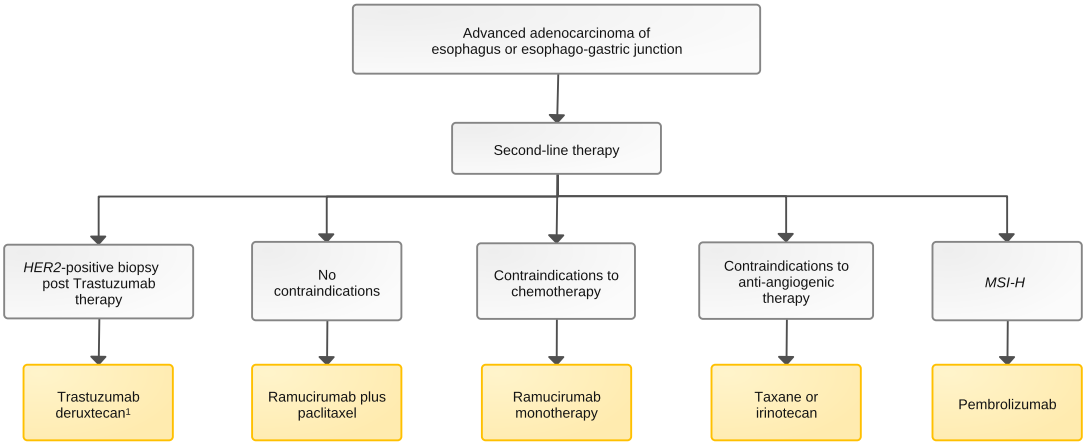
Legend:
Therapy with non-curative intention
[1] Combined score from tumor cells and immune cell infiltrate
[2] Indicates the ratio of PD-L1-positive stained tumor cells in relation to all vital tumor cells (%)
[3] Fluoropyrimidine (5-fluorouracil plus folinic acid or capecitabine)
[4] progressive disease
[5] best supportive care

Figure 8: Algorithm for first-line treatment of advanced adenocarcinoma of the esophagus/GEJ



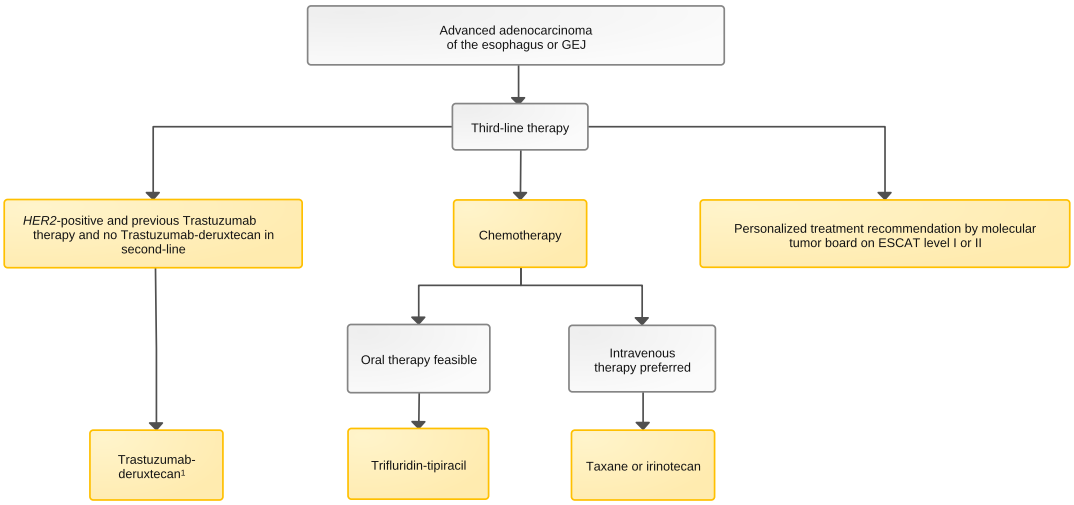
Legend:
Therapy with non-curative intention
1 Nivolumab is approved in Europe for PD-L1 CPS ≥ 5 based on results of the Checkmate-649 study;
2 Pembrolizumab is approved in Europe for adenocarcinomas of the esophagus with PD-L1 CPS ≥ 10 based on the KEYNOTE -590 study and for HER2-negative and HER2-positive adenocarcinomas of the stomach and esophago-gastric junction with PD-L1 CPS ≥ 1 based on the KEYNOTE 859 study and KEYNOTE 811 study.

Figure 9: Algorithm for second-line treatment of advanced adenocarcinoma of the esophagus/GEJ



Legend:
Therapy with non-curative intention
1 Since tumors can lose their HER2 overexpression after trastuzumab failure, it is recommended to re-check the current HER2 status using a fresh biopsy before T-DXd therapy in the second line

Figure 10: Algorithm for third-line treatment of advanced adenocarcinoma of the esophagus/GEJ



Legend:
Therapy with non-curative intention
[1] According to the Destiny Gastric01 study, a re-examination of the HER2 status is not mandatory for third-line T-DXd therapy

6.1.4.1.1 Chemotherapy for squamous cell carcinoma

When planning chemotherapy, the patient's general performance and relevant comorbidities, the patient's preference and the toxicity of the planned therapy must be taken into account. Resection of the primary tumor does not improve the prognosis in the metastatic setting [41].

For patients with PD-L1 negative tumors (TPS < 1), a combination chemotherapy of cisplatin and 5-FU is considered standard. The addition of EGFR antibodies (panitumumab) does not improve the response [51]. For PD-L1 positive tumors, a combination of chemotherapy and checkpoint inhibitor or immunotherapy alone using dual checkpoint inhibition can 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 due to the frequent prevalence of dysphagia.

6.1.4.1.1.1 First-line therapy

The KEYNOTE-590 phase III trial [48] showed that the combination of chemotherapy and immune checkpoint blockade improves the results of first-line therapy. In this study, the majority (73%, n=548) of patients treated had squamous cell carcinoma of the esophagus. There was a significant advantage in overall survival for the group of patients with high PD-L1 expression (CPS ≥ 10) of the tumor, who had received pembrolizumab in addition to 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, GEJ n=91), the benefit was lower (HR 0.74 (CI 0.54-1.02)). Nevertheless, the combined chemo-immunotherapy (platinum plus fluoropyrimidine plus pembrolizumab) for patients with SCC or AC of the esophagus and high PD-L1 expression (CPS ≥10) was approved in Europe in September 2020.

A second phase III trial (CheckMate 648) is available for the first-line treatment of metastatic squamous cell carcinoma [49]. In this three-arm study, a total of almost 1000 patients were randomized into the 3 treatment groups: chemotherapy (cisplatin plus 5-FU), chemotherapy plus nivolumab (240 mg every 2 weeks) or nivolumab plus ipilimumab (1 mg/kg every 6

weeks). OS and PFS were defined as common primary endpoints 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 (TC ≥1%). The primary endpoints were met in both experimental arms. With chemotherapy plus nivolumab, OS was significantly improved compared to chemotherapy alone (median 15.4 vs. 9.1 mo, HR 0.54 (CI 0.37-0.80), p<0.001). The OS was also significantly better with double checkpoint blockade than with chemotherapy (median 13.7 vs. 9.1 mo, HR 0.64 (CI 0.46-0.90), p=0.001). However, the Kaplan-Meier curves crossed at the beginning, which means that some of the patients were at a disadvantage due to immunotherapy alone.

A third phase III trial has demonstrated the efficacy of immunotherapy in combination with chemotherapy in the first-line treatment of advanced squamous cell carcinoma (RATIONALE-306). In this global study, around 650 patients were randomized to chemotherapy plus placebo (platinum / 5-FU or platinum / paclitaxel) vs. chemotherapy plus the PD-1 inhibitor tislelizumab. Tislelizumab is a humanized IgG4 mAb with high affinity and binding specificity to PD-1. Overall survival was significantly improved in the group with tislelizumab (mOS 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% and for all patients (primary endpoint). Unlike in the above-mentioned studies, however, the area with positive tumor cells (TAP score) rather than the number of positive cells was evaluated here. The study therefore confirms the above-mentioned data on nivolumab and pembrolizumab. It also shows that chemotherapy consisting of platinum plus taxane is improved by the additional immunotherapy. An application for an extension of the marketing authorization for tislelizumab in this indication has been submitted to the EMA.

6.1.4.1.1.2 Second-line therapy

Based on the data from the ATTRACTION -3 and RATIONALE 302 studies, both nivolumab and tislelizumab have been approved for second-line treatment of advanced squamous cell carcinoma of the esophagus after prior treatment with a combination of a platinum derivative and a fluoropyrimidine in Europe for patients to whom no checkpoint inhibitor has previously been administered.

In the phase III trial ATTRACTION-3, patients with advanced or recurrent squamous cell carcinoma after treatment with platinum/fluoropyrimidine were randomly assigned to chemotherapy (paclitaxel or docetaxel) or the PD-1 inhibitor nivolumab (240 mg fixed dose) [56]. About half of the patients had PD-L1 positive carcinomas. Regardless of PD-L1 status, overall survival was significantly longer with immunotherapy (median 10.9 vs. 8.4 months, HR 0.77 (0.62-0.96), p=0.019). In addition, the rate of side effects (overall and of severity grades 3-4) was significantly higher with chemotherapy. Premature treatment discontinuation occurred in 9% of patients in both study arms. After 4 months, only 30% of patients in both arms showed no tumor progression. In principle, the study was also open to "western patients". In fact, however, almost exclusively (96%) patients from Asia were recruited.

A second phase III trial (RATIONALE 302) was conducted with the PD-1 inhibitor tislelizumab [112]. Tislelizumab therapy prolonged overall survival (OS) in patients with esophageal cancer compared to chemotherapy according to investigator's choice (docetaxel, paclitaxel, irinotecan) by a median of 2.3 months (8.6 months versus 6.3 months (p=0.0001) and reduced the risk of death by 30%. In PD-L1 positive patients (TAP ≥ 5), tislelizumab therapy prolonged the median OS by 3.5 months and reduced the risk of death by 46%. In addition to the response rates (20.3% vs. 9.8%), the response duration was also longer with tislelizumab (7.1 months) compared to chemotherapy (4.0 months).

At 6.7%, the discontinuation rate due to treatment-related adverse events was lower with tislelizumab than with chemotherapy (13.8%). In the RATIONALE 302 study, the proportion of

non-Asian patients was 21%. Tislelizumab has been approved in Europe since 2023 for second-line therapy after platinum pre-treatment, regardless of PD-L1 expression.

An overview of the approval of immune checkpoint inhibitors in squamous cell carcinoma of the esophagus is presented in the appendix.

6.1.4.1.1.3 Third-line therapy

Older phase II studies indicate the efficacy of taxanes, platinum derivatives or irinotecan in third-line therapy [57]. However, there are no specific approvals for this treatment situation. Treatment decisions must therefore be made on an individual basis and supportive measures must be included in the treatment.

6.1.4.1.2 Chemotherapy for adenocarcinoma of the esophagus/GEJ

Studies of advanced adenocarcinoma (AC) in the upper GI tract have generally included patients with AC of the stomach, esophago-gastric junction and esophagus. In most studies, patients with gastric carcinoma were predominant. Despite the different biology of AC in the aforementioned localizations, the systemic therapy for metastatic disease does not differ. The text from the Onkopedia guideline on gastric cancer was therefore adopted for advanced disease. Sections referring exclusively to gastric adenocarcinoma are not included here.

6.1.4.1.3 First-line chemotherapy, targeted therapy and immunotherapy

6.1.4.1.3.1 Chemotherapy

Figure 8 shows the algorithm for first-line chemotherapy. The standard for advanced gastric carcinoma and GEJ is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with advantages in terms of the side-effect profile for oxaliplatin. This can contribute to a tendency towards better efficacy, especially in older patients (>65 years). Fluoropyrimidines can be administered as an infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are as effective as infused 5-FU. Capecitabine is approved in combination with a platinum derivative and has been tested with both cis- and oxaliplatin in Europeans. S-1 is established as the standard of care in Japan and is approved in Europe for initial palliative therapy in combination with cisplatin [60]. Infused 5-FU should be preferred over oral drugs in cases of dysphagia or other feeding problems. In elderly or frail patients, the results of the phase III GO2 study support the dose-reduced use of oxaliplatin-fluoropyrimidine chemotherapy (to 80% or 60% of the standard dose from the outset), which resulted in fewer side effects but comparable efficacy [53].

The addition of docetaxel to a platinum/fluoropyrimidine combination (three-week DCF regimen) improved the radiologic response rate and prolonged overall survival in an older phase III trial, but at the same time led to significantly increased side effects [59]. Further phase II trials investigated modified docetaxel/platinum/fluoropyrimidine triplets. A recently presented, but not yet fully published, French investigator-initiated phase III study showed significantly prolonged progression-free survival and significantly prolonged overall survival for a platinum-fluoropyrimidine-docetaxel triplet (modified FLOT, called TFOX) compared to the doublet FOLFOX. The median overall survival was improved from 12 to 15 months (HR 0.76 95% CI 0.62-0.93; p=0.008) [115]. It should be noted that all patients were docetaxel-naïve and that these effects were not observed in patients over the age of 65, in patients with an ECOG performance status worse than 0 and in Lauren intestinal-type carcinomas. Toxicity rates were found to be increased in several aspects (hematologic, gastrointestinal, neurologic) with mFLOT/TFOX. Nev-

ertheless, the time to deterioration of quality of life was significantly prolonged in the mFLOT/T-FOX group. With increased toxicity and uncertain effects on overall survival, it is therefore not possible to make a general recommendation for first-line therapy with docetaxel-platinum-fluoropyrimidine. mFLOT/TFOX triplet chemotherapy is an individually usable regimen for patients with high remission pressure, docetaxel-naïve and without the option of biomarker-supported targeted or immunotherapy. The standard remains a platinum-fluoropyrimidine doublet.

Irinotecan-5-FU was compared with cisplatin-5-FU and with epirubicin-cisplatin-capecitabine in randomized phase III trials and showed comparable survival times with manageable side effects [52]. Irinotecan-5-FU can therefore be regarded as a treatment alternative to platinum-fluoropyrimidine doublets according to the scientific evidence, even though irinotecan is not approved for gastric and esophageal cancer in Europe.

6.1.4.1.3.2 HER2-positive gastric carcinoma/GEJ

HER2 positivity in gastric cancer is defined as the presence of protein expression with immunohistochemistry score [IHC] 3+ or IHC 2+ and simultaneous gene amplification by in situ hybridization [ISH] HER2/CEP17 ratio ≥2.0. HER2 diagnostics should be quality-controlled [71, 77]. Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric/GEJ cancer [72]. The recommendation is based on the results of the phase III ToGA study, which showed a higher response rate and longer survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy versus chemotherapy alone with the above-mentioned selection criteria; the additional trastuzumab side effects are minor and manageable [82]. Combinations of trastuzumab and oxaliplatin plus fluoropyrimidine lead to comparable results to the original cisplatin-containing ToGA regimen [54, 83].

Based on the randomized phase III KEYNOTE -811 trial [124], the EMA approved the combination of pembrolizumab plus trastuzumab and chemotherapy for first-line treatment for HER2-positive advanced gastric or esophago-gastric (GEJ) adenocarcinoma with PD-L1 expression of CPS ≥ 1 in September 2023 (Figure 6). 698 patients with HER-2 positive advanced carcinoma of the stomach or GEJ were randomized between platinum, fluoropyrimidine, trastuzumab with pembrolizumab or placebo. In the 85% of patients whose tumors showed PD-L1 overexpression (PD-L1 CPS ≥1), progression-free survival was significantly prolonged in the pembrolizumab arm (HR 0.70; 95% CI 0.58-0.85). The co-primary endpoint of overall survival was also achieved. The final OS result is expected at ESMO 2024. Patients with PD-L1 negative tumors did not benefit from the addition of pembrolizumab. Pembrolizumab should therefore now be added to the chemo-trastuzumab combination for HER2 and PD-L1-positive tumors.

6.1.4.1.3.3 Immunotherapy

The phase III CheckMate 649 study investigated the addition of nivolumab to chemotherapy (capecitabine-oxaliplatin or 5-FU/folinic acid-oxaliplatin) in patients with previously untreated gastric, GEJ or esophageal adenocarcinoma [50]. The study included patients regardless of tumor PD-L1 status; the dual primary endpoints were overall survival and progression-free survival. Approximately 60% of the study population had tumors with a PD-L1 CPS ≥ 5. Nivolumab plus chemotherapy resulted in 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 trial ATTRACTION-4 also showed a significant improvement in progression-free survival with nivolumab and first-line chemotherapy, although there was no demonstrable improvement in overall survival compared to first-line chemotherapy alone. The reason for the lack of survival benefit (>17 months in both arms) is probably that many patients received post-progression therapies including immunotherapy beyond the first line of therapy [84].

The multinational randomized phase III KEYNOTE-859 trial included 1589 patients with advanced incurable gastric/GEJ cancer [76]. Patients received either platinum-fluoropyrimidine and pembrolizumab or the same chemotherapy and placebo every 3 weeks i.v. 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 particularly pronounced in the subgroup with a PD-L1 CPS ≥ 10 (HR 0.64), while the efficacy was lower with CPS < 10 (HR 0.86) [76]. The results thus complement the positive results from the phase III KEYNOTE-590 study, which led to EU approval of pembrolizumab in combination with platinum-fluoropyrimidine chemotherapy for adenocarcinomas of the esophagus and GEJ [48].

Positive phase III study data were also presented for two immune checkpoint PD1 inhibitors not yet approved in Europe for GEJ: Sintilimab in combination with oxaliplatin and capecitabine improved overall survival in the phase III ORIENT-16 study [78]. 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 (so-called Tumor Area Proportion, TAP) that has not yet been established internationally [79].

6.1.4.1.3.3.1 Microsatellite-instable tumors

Due to the convincing efficacy of PD-1/PD-L1 inhibitors in carcinomas with DNA mismatch repair deficiency (microsatellite-instable type), all patients with MSI-high diagnosed gastric carcinomas or adenocarcinomas of the GEJ should already be administered one of the approved PD-1 immune checkpoint inhibitors first-line. The subgroup analyses in all pivotal studies (CheckMate-649, KEYNOTE-859) and also in the studies that could not be used for approval (e.g., KEYNOTE-062) are convincingly positive for the administration of an immune checkpoint inhibitor plus chemotherapy. Whether the additional administration of chemotherapy can generally be abandoned in this setting is uncertain according to current data and should be further examined in studies.

6.1.4.1.3.3.2 Claudin 18.2

Data from the multinational phase III Spotlight study showed that in patients with advanced irresectable gastric/GEJ cancer and tumor claudin18.2 expression in ≥ 75% of tumor cells (documented in up to 38% of tumors), zolbetuximab, a chimeric monoclonal anti-claudin18.2-targeted IgG1 antibody in combination with FOLFOX chemotherapy prolonged overall survival (median 18.23 vs. 15.54 months, HR 0.750, p=0.0053) [113]. The main side effects of zolbetuximab are acute nausea and vomiting, especially during the first applications [99]. Antiemetic triple prophylaxis, consisting of 5-HT3 receptor antagonist (RA), NK1-RA and dexamethasone, should therefore be used prior to administration. An infusion duration of 2-4 hours can also reduce the incidence of nausea and vomiting.

The results of the Spotlight study are largely confirmed by the multinational phase III GLOW study, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab [86].

The European Medicines Agency is expected to approve zolbetuximab in patients with claudin 18.2-positive metastatic and previously untreated carcinoma of the stomach/GEJ shortly. A positive CHMP vote by the EMA was granted on July 26, 2024.

6.1.4.1.4 Second- and third-line therapy

6.1.4.1.4.1 Chemotherapy and anti-angiogenic therapy for adenocarcinoma of the esophagus/GEJ

Figures 9 and 10 show the algorithm for second- and third-line therapy for patients with advanced adenocarcinoma of the esophagus/GEJ, corresponding to the recommendations for gastric carcinoma. The evidence-based chemotherapy options in this setting are paclitaxel, docetaxel and irinotecan, which have comparable efficacy with different drug-related toxicities. Irinotecan can be used preferentially in the case of pre-existing neuropathy, even if it still does not have EU approval. 5-FU/folinic acid irinotecan (FOLFIRI) is also occasionally used, but the scientific evidence for this is limited. Ramucirumab plus paclitaxel is the recommended standard for second-line therapy and is approved in the EU. The addition of the anti-vascular endothelial growth factor receptor-2 (VEGFR-2) antibody ramucirumab to paclitaxel increased the tumor response rate and prolonged progression-free and overall survival according to the results of the phase III RAINBOW study [87]. In the phase III REGARD trial, ramucirumab monotherapy already showed a prolonged survival time compared to placebo, albeit with a low radiologic response rate [88].

6.1.4.1.4.2 Immunotherapy

In the phase III KEYNOTE-061 trial, pembrolizumab monotherapy did not show prolonged overall survival compared to chemotherapy [89]. However, an exploratory subgroup analysis recognized a very clear benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric and GEJ carcinoma [90]. PD-1 inhibition is therefore recommended for advanced MSI-H cancers 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 [91]. Other biomarkers, in particular EBV and tumor mutation burden, are also discussed as predictive factors for the efficacy of PD-1 immune checkpoint inhibitors [92- 94]. However, the evidence is not yet sufficient for a positive recommendation for immunotherapy in the presence of these biomarkers.

6.1.4.1.4.3 Her2-directed therapy

Studies investigating trastuzumab, lapatinib and trastuzumab emtansine in the second line of treatment in patients with HER2-positive carcinomas were negative [55,95-98]. These drugs should therefore not be used in esophageal/GEJ adenocarcinoma, as in gastric carcinoma, outside of clinical trials.

A randomized phase II trial showed an improvement in tumor response rate and overall survival for the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) compared to standard chemotherapy in patients with previously treated HER2-positive advanced gastric/GEJ cancer [85]. Prerequisites for inclusion in the Destiny-Gastric01 study were at least two previous lines of therapy, previous treatment with a platinum derivative, a fluoropyrimidine and trastuzumab as well as previously confirmed HER2 positivity. The study was recruited exclusively in East Asia. The results of Destiny-Gastric01 were largely confirmed in the non-randomized phase II Destiny-Gastric02 study, which included non-Asian patients in the second line of therapy. A platinum-fluoropyrimidine-trastuzumab pre-treatment and confirmed HER2 positivity of the tumor in a recent re-biopsy were mandatory before initiating T-DXd therapy [80]. The EU approval includes the following indication for 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 checking the Her2 status according to the classic established HER2 diagnostic criteria before treatment with T-DXd, especially if use in the second line of therapy is planned, where a valid alternative with paclitaxel-ramucirumab is available. This recommendation is based on the inclusion criteria of the Destiny-Gastric02 study and the knowledge that loss of HER2 status occurs in approx. 30% of gastric carcinomas/GEJ during first-line treatment with trastuzumab [97].

Early study results indicate the efficacy of T-DXd in tumors with low HER2 expression [81]. However, these are not yet sufficient to recommend its use in this setting.

6.1.4.1.4.4 Third-line therapy for adenocarcinoma of the esophagus/GEJ

In the treatment of patients with advanced gastric/GEJ carcinoma in the third line and beyond, the best evidence is available for trifluridine-tipiracil (FTD/TPI) based on the phase III TAGS trial. The median overall survival with FTD/TPI versus placebo was significantly improved in the overall group, in the third-line and in the fourth-line cohort [58].

If oral therapy is feasible, trifluridine-tipiracil (FTD/TPI) should therefore be used; alternatively, if intravenous therapy is preferred, irinotecan or a taxane can be given, if not already used in a previous line of therapy. As shown above, T-DXd is a very effective third-line therapy for HER2-positive carcinomas after trastuzumab pre-treatment. Nivolumab also proved to be effective; however, the data of the ATTRACTION-3 study were obtained exclusively in Asian patients [56], so that nivolumab does not have EMA approval for third-line treatment in patients with advanced gastric carcinoma/GEJ and therefore cannot be recommended.

Following the recommendation of a molecular tumor board, an unapproved treatment option may also be preferable in selected 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 [99].

6.1.4.2 Supportive care and nutrition

It is recommended that all patients with advanced esophageal/GEJ cancer undergo regular nutritional and symptom screening using suitable instruments and that appropriate supportive therapies be derived from this. A study from China showed that the early integration of supportive palliative care is effective and suggests a survival benefit in patients with advanced gastric/GEJ cancer [101].

Weight loss is a multifactorial phenomenon and may be due to digestive tract obstruction, malabsorption or hypermetabolism. Clinical data show that weight loss of ≥10% before chemotherapy or ≥3% during the first cycle of chemotherapy is associated with reduced survival times [102]. A change in body composition with a reduction in muscle quality was also found to be prognostically unfavorable in patients with advanced gastric/GEJ cancer [103]. 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/GEJ carcinoma [104]. From this it can be deduced that all patients with advanced esophageal/GEJ cancer should be screened for nutritional status (e.g., using Nutritional Risk Screening, NRS) [105] and, if there are indications of nutritional deficiency, professional nutritional advice and co-care should be offered.

Dysphagia in patients with adenocarcinoma of the esophagus or GEJ can be improved by radiotherapy or stent insertion [106]. Single-dose brachytherapy is the preferred option at some centers and results in longer-lasting symptom control and fewer complications than stent placement. Stenting is needed for severe dysphagia and especially in patients with limited life expectancy, as the effects of stenting are immediate, whereas radiotherapy takes about 4-6 weeks to improve dysphagia [107]. If radiotherapy or a stent is not an option, enteral nutrition using a naso-gastric, naso-jejunal or percutaneously placed feeding tube can provide relief [108]. The indication for parenteral nutrition follows the generally recognized guidelines.

6.2 Treatment modalities

6.2.1 Resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for the resection of early carcinomas. Techniques include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [26]. ER is performed as an en-bloc resection. It allows a complete histologic assessment of the lateral and basal margins.

The recommended endoscopic control intervals are 3 months in the first year and 6 months in the second year. Thereafter, check-ups should take place annually.

Local recurrences after ER of an early carcinoma can be treated endoscopically if a purely mucosal involvement (rT1aN0M0) is present again. A (limited) surgical procedure 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 aim of surgery is to achieve an R0 situation (oral, aboral and circumferential).

A safety margin of 2-4 cm is aimed for in standard surgical techniques. Depending on the location, the following surgical techniques should be chosen:

- Tumors of the middle and distal esophagus and GEJ/AEG I: abdomino-thoracic subtotal esophagectomy with tube gastric pull-up and high intrathoracic anastomosis (if necessary, with extension to the oral side in the case of total esophagectomy with cervical anastomosis).
- GEJ/AEG type II: abdomino-thoracic esophagectomy with sleeve gastrectomy vs. transhiatal extended gastrectomy with distal partial esophageal resection, then reconstruction according to Roux-Y (currently comparing the techniques in the German-Dutch phase III CARDIA study).
- A total esophago-gastrectomy may be necessary in the case of extensive involvement of both the distal esophagus and the proximal stomach. This usually requires reconstruction using a colonic interposition.
- Esophagectomy and reconstruction should be performed minimally invasively or in combination with open techniques (hybrid technique) if there are no contraindications [9]

The extent of lymphadenectomy depends on the location of the tumor. A distinction is made between cervical, thoracic and abdominal lymph node fields. Lymphadenectomy of two anatomic areas (abdominal and thoracic) is the method of choice. Depending on the location of the primary tumor, a cervical plus thoracic or thoracic plus abdominal peritumoral lymph node dissection, including the corresponding lymphatic drainage area, is required.

For the correct TNM classification of esophageal cancer, at least 7 lymph nodes must be assessed, while usually more than 20 lymph nodes are removed. Retrospective studies suggest an improvement in prognosis if 23 or more lymph nodes are resected [61, 62].

Surgery should be performed at a specialized center (high-volume center) [63, 64], because the higher surgical and perioperative expertise ("failure to rescue") reduces perioperative mortality and improves the long-term prognosis of patients. At least 20 resections of esophageal

carcinomas per year are required for certification as an esophageal center according to the German Cancer Society (DKG). Since early 2022, the Federal Joint Committee (G-BA) has defined a number of at least 26 oncological esophagectomies per year as the minimum volume for a center that is allowed to operate on esophageal cancer in the future.

If an R1 resection is diagnosed postoperatively by histological work-up, in contrast to the diagnosis made during the obligatory intraoperative frozen section, the conditions for a second, extended resection are generally unfavorable. Due to the high risk of local recurrence, adjuvant chemoradiotherapy should therefore be recommended in this setting [36, 37].

6.2.1.3 Resection of metastases

As yet, there is no unequivocal benefit for the palliative resection of primary tumors or metastases of stage IV esophageal/GEJ carcinoma. Resection should therefore not be performed. If metastases that are completely resectable (without risk) are discovered during the curative-intent surgery, these can be resected in individual cases. According to the German perioperative AIO FLOT-3 study, patients with a good response to 6-8 cycles of intensive chemotherapy (such as FLOT) had a better 5-year survival after resection of residual metastases than patients with more extensive metastases [100]. Patients with synchronous limited metastasis or peritoneal carcinomatosis should therefore be presented at a high-volume center to decide on secondary surgical resectability. Initial results of the prospective randomized phase III study RENAISSANCE / FLOT-5 were presented at ASCO 2024 [65]. This study evaluated whether induction chemotherapy plus metastasectomy improves the prognosis of limited metastatic GEJ or gastric adenocarcinoma compared to the continuation of palliative chemotherapy without surgery. First-line standard of care (SOC) versus 4 cycles of neoadjuvant chemotherapy with FLOT followed by surgical resection of primary tumor and metastases were compared. The primary endpoint was overall survival (OS) in the ITT population. After recruitment of 183 patients (141 of whom were randomized) stopped due to slow recruitment. 20% of the included patients had only retroperitoneal lymph node metastases (RPLN), 58% had only organ metastases and 22% had both. In the surgical arm (=Arm A) (ITT), 91% of patients underwent surgery and the R0 resection rate (primary) was 82%. The 30-day and 90-day mortality rates in the surgical population were 3% and 8%, respectively. At least 4 additional cycles of chemotherapy after surgery or after randomization were given to 42% of patients in Arm A vs. 71% of pat. in Arm B (chemotherapy alone arm). The primary endpoint of overall survival was not met due to increased early mortality in the surgery arm, resulting in crossing survival curves at approximately 24 months. Subgroup analyses showed that patients with only retroperitoneal lymph node metastases seemed to benefit most from the surgical approach (median OS 30 vs. 17 months; 3-year survival 45% vs. 19%). Patients who did not respond to chemotherapy (median OS 13 vs. 22 months) and patients with peritoneal carcinomatosis (median OS 12 vs. 19 months) had a detrimental effect. The RENAISSANCE/FLOT-5 study is the first prospective study on the question if patients with limited metastatic disease have a favorable survival that is independent of surgical therapy. The results of this study suggest that, with the exception of patients with retroperitoneal lymph node metastasis, a multimodal approach including surgical resection should be discouraged. Patients with regional lymph node metastases only can be offered surgical resection of the primary tumor and lymph node metastases as an individualized approach after responding to systemic therapy. The German S3 guidelines [9] provide the following consensus-based recommendation: in selected cases of limited metastasis, resection of the primary with resection or ablation of metastases can be performed after consensus in the tumor board in patients with good response to primary systemic therapy, provided that all tumor manifestations can be completely removed.

6.2.2 Radiotherapy

6.2.2.1 Neo-/adjuvant chemoradiotherapy

Neoadjuvant CRT is standard for locally advanced (category cT3/T4) squamous cell carcinoma of the esophagus. In randomized studies, doses of 41.4 to 54 Gy in 22 to 28 fractions were administered preoperatively. Concomitant weekly carboplatin (AUC 2) and paclitaxel (50 mg/m²) [66] or cisplatin (30mg/m^2) and docetaxel (60mg/m^2) are accepted partners for CRT, besides the original standard of cisplatin and 5-fluorouracil every 3 to 4 weeks.

Neoadjuvant CRT is a treatment option for patients with a T2 category tumor, especially if lymph node metastases are suspected or proven. Its use instead of primary resection should be discussed on a multidisciplinary basis and recommended in individual cases.

In patients with R1 resection, retrospective studies suggest that adjuvant CRT can improve survival [67]. After neoadjuvant CRT, treatment should be completed with adjuvant nivolumab analogous to Checkmate-577 in the event of an incomplete response (R1). According to the current approval, there is also the option of adjuvant nivolumab administration for R+ resected tumors after neoadjuvant CRT, which should be considered as an alternative to radiotherapy of the anastomosis.

RCT should be carried out in the same way as definitive CRT. 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 the sparing of surrounding normal tissue, especially heart and lungs [68].

6.2.2.2 Definitive chemoradiotherapy

Definitive CRT is the method of first choice for high-resectable (cervical) esophageal carcinomas in order to avoid frequent postoperative complications such as dysphagia or recurrent aspiration and mutilating operation (laryngectomy). It leads to long-term survival rates of 17-55 % [69, 70]. Various studies have shown it to be superior to radiotherapy alone, which is therefore only used for symptomatic relief in esophageal carcinoma.

Definitive CRT is also an alternative approach for patients with tumors deemed inoperable after multidisciplinary discussion and for co-morbid patients with functional inoperability or patients who refuse surgical treatment.

Results of a randomized phase III trial from the Netherlands (ARTDECO trial) showed no benefit in terms of local tumor control with simultaneous chemotherapy using carboplatin / paclitaxel with a total radiation dose of more than 50.4 Gy in patients with intrathoracic esophageal carcinoma. 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 in 28 fractions in both arms. The local tumor control rates as the primary endpoint were significantly better in both arms than expected, at 71% and 73% after 3 years in the standard and dose escalation arms, respectively. In this study, 62% of patients had squamous cell carcinoma and 38% had adenocarcinoma [42]. Accordingly, a total dose of 50.4 Gy should be regarded as the standard for definitive chemoradiation therapy of intrathoracic esophageal carcinomas with simultaneous chemotherapy using carboplatin/paclitaxel. If the tumor is located in the cervical esophagus, higher total doses of up to 66 Gy in conventional fractionation with 1.8 Gy per fraction based on single-institutional treatment series are recommended in accordance with the recommendations of the current NCCN guideline on esophageal cancer, version 4.2024. The larger randomized trials used total radiation doses of 60-66 Gy in conventional fractionation with simultaneous chemotherapy with cisplatin/5-FU or other cisplatin-containing combinations to

compare neoadjuvant CRT plus subsequent surgery with definitive CRT without surgery for squamous cell carcinoma of the esophagus [38]. Significant differences in overall survival were not observed between treatment arms. The exploratory analysis of the FFCD 9102 trial showed a dose-effect relationship when comparing patients treated conventionally with up to 66 Gy to those treated hypofractionated with up to 45 Gy [109]. 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 condition and tumor spread, the total dose of radiotherapy should be limited to 50-55 Gy in conventional fractionation with 1.8-2.0 Gy per fraction according to the data of the FREGAT group [110], because an increase in postoperative complications was observed with higher total doses of preoperative radiation.

The previous most commonly used chemotherapy in combination with radiotherapy was cisplatin and 5-FU [11], but CRT with concurrent FOLFOX is now considered equivalent [44]. Definitive CRT using carboplatin/paclitaxel or cisplatin/paclitaxel is also a first-choice option with low toxicity and comparable long-term treatment results. Randomized studies 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 Palliative chemotherapy

This is the treatment of choice for metastatic tumors or, in exceptional cases, an option for symptomatic treatment in patients with locally advanced esophageal/GEJ cancer in whom neither resection nor radiotherapy can be performed [72].

6.2.3.2 Drug used for systemic treatment

6.2.3.2.1 -Fluorouracil

5-Fluorouracil is used in almost all forms of systemic tumor therapy for patients with esophageal cancer. Its efficacy is increased by combining it with folinic acid. An alternative is oral therapy with capecitabine, see chapter 6.2.3.2.2. 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. A mutation in the four most important gene loci of dihydropyrimidine dehydrogenase (DPD) must be excluded before 5-FU-containing chemotherapy.

6.2.3.2.2 Capecitabine and S1

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

6.2.3.2.3 Cisplatin

Platinum derivatives are among the most effective single agents. In combination with other cytostatic drugs, cisplatin is part of the standard drug regimen for esophageal cancer. 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 imbalances and diarrhea.

6.2.3.2.4 Docetaxel

Docetaxel is a taxane. It is an effective combination partner of fluoropyrimidines and platinum derivatives in perioperative and palliative therapy and is part of the FLOT regimen. Severe side effects (grade 3 / 4) include infections, nail changes, taste disturbances, stomatitis and diarrhea. Alopecia (grade 2) is one of the most troublesome side effects. Polyneuropathy, some of which is irreversible, is particularly burdensome. Common side effects such as nausea/vomiting and allergic reactions can be prevented by adequate supportive care, see Onkopedia Antiemesis.

6.2.3.2.5 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with fluoropyrimidines, remission rates up to 40% can be observed. FOLFIRI is comparably effective to cisplatin-based therapies in terms of progression-free survival and overall survival. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the pivotal studies, are diarrhea, nausea/vomiting, neutropenia and neutropenic fever. The substance can also be administered as monotherapy on a weekly, bi-weekly or tri-weekly basis.

6.2.3.2.6 Nivolumab

Nivolumab is a monoclonal anti-PD-1 antibody and belongs to the class of immune checkpoint inhibitors. It is approved as a monotherapy for second-line treatment of squamous cell carcinoma of the esophagus 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) side effects were pyrexia (2%) and interstitial lung disease (2%).

6.2.3.2.7 Oxaliplatin

This platinum derivative is effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line therapy for stage IV esophageal cancer, remission rates up to 45% have been reported. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the pivotal studies, are nausea/vomiting, diarrhea, mucositis and polyneuropathy. Oxaliplatin is part of the recommended perioperative FLOT regimen and the standard of palliative first-line therapy FOLFOX or FLO.

6.2.3.2.8 Paclitaxel

Paclitaxel is a taxane. Paclitaxel is effective as monotherapy or in combination with ramucirumab in palliative second-line therapy or in combination with cisplatin/5-FU/folinic acid (Gastro-Tax) in palliative first-line therapy. Severe side effects (grade 3 / 4) include infections, stomatitis and diarrhea and allergic reactions to the solvent cremophor. Alopecia is one of the most troublesome side effects. Polyneuropathy, some of which is irreversible, is particularly burdensome. Common side effects such as allergic reactions can be partially prevented by adequate supportive care.

6.2.3.2.9 Pembrolizumab

Pembrolizumab is a monoclonal anti-PD-1 antibody and belongs to the class of immune checkpoint inhibitors. In the phase III KEYNOTE-590 trial [48] , first-line treatment of metastatic esophageal cancer using pembrolizumab plus chemotherapy led to a significant increase in the response rate, a prolongation of progression-free and overall survival and an increase in the survival rate after 2 years compared to chemotherapy alone. Pembrolizumab is indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-negative adenocarcinoma of GEJ in adults with PD-L1-expressing tumors (CPS ≥ 10) and as monotherapy for the treatment of gastric carcinoma with MSI-H or with a dMMR after at least one prior therapy. Characteristic side effects with pembrolizumab are immune-mediated, in particular autoimmune phenomena. More common side effects are hypothyroidism/hyperthyroidism, loss of appetite, fatigue, diarrhea, nausea, rash and asthenia.

6.2.3.2.10 Ramucirumab

Ramucirumab is a VEGF receptor 2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab leads to a significant prolongation of progression-free survival, an increase in overall survival and an increase in the remission rate compared to paclitaxel monotherapy. In patients who are not suitable for paclitaxel therapy, monotherapy with ramucirumab also leads to a prolongation of progression-free survival and overall survival compared to placebo. The only severe grade 3 / 4 adverse event that occurred in more than 5% of patients receiving ramucirumab monotherapy was arterial hypertension. More frequent side effects in combination therapy were fatigue (12%), neuropathy (8%) and abdominal pain (6%).

6.2.3.2.11 Tislelizumab

Tislelizumab is a humanized IgG4 mAb with high affinity and binding specificity against PD-1 specifically designed to minimize binding to FcγR on macrophages. The binding surface of tislelizumab to PD-1 largely overlaps with that of PD-L1, resulting in a complete blockade of the PD-1/PD-L1 interaction (>99%).

Tislelizumab prolonged overall survival in combination with platinum-fluoropyrimidine or platinum-investigator choice chemotherapy in the phase III RATIONALE 305 trial (adenocarcinoma) and in the phase III RATIONALE 306 trial (squamous cell carcinoma) [75]. The effect was dependent on a positive PD-L1 score in patients with adenocarcinoma (RATIONALE 305), while it was independent of PD-L1 expression in patients with squamous cell carcinoma (RATIONALE 306). This expression was evaluated according to a scoring system (so-called Tumor Area Proportion,

TAP score) that has not yet been established internationally. RATIONALE -305 [79] and -306 [75] support the overall assessment that PD-1 immune checkpoint inhibitors can improve the efficacy of chemotherapy (depending on PD-L1 expression).

6.2.3.2.12 Trastuzumab

Trastuzumab is a monoclonal antibody that specifically interferes with the HER2 receptor and has been approved for the treatment of patients with HER2 overexpression or gene amplification. In HER2-positive gastric/GEJ cancer, trastuzumab in combination with a fluoropyrimidine and cisplatin leads to an increase in overall survival compared to chemotherapy alone. Severe side effects (grade 3 / 4) are rare.

6.2.3.2.13 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 linked to DXd, an exatecan derivative and topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 8 DXd molecules are bound to each antibody molecule. T-DXd is used as monotherapy for the treatment of adult patients with advanced HER2-positive gastric/GEJ adenocarcinoma who have received a prior trastuzumab-based 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 administered as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity occurs. The initial dose should be given as a 90-minute intravenous infusion. If the previous infusion was well tolerated, T-DXd can subsequently be given as a 30-minute infusion. If the patient shows infusion-related symptoms, the infusion rate of T-DXd must be reduced or the infusion interrupted. If severe reactions to the infusion occur, T-DXd should be permanently discontinued. Particular attention should be paid to the possible occurrence of pulmonary toxicity in terms of interstitial lung disease or pneumonitis. It should also be noted that trastuzumab deruxtecan has a moderate to high acute and delayed emetogenic potential. We therefore recommend the use of prophylaxis with 3 antiemetics (dexamethasone, 5-HT3 antagonist, NK-1 antagonist).

6.2.3.2.14 Trifluridine/Tipiracil (FTD/TPI; TAS-102)

The fixed drug combination FTD-TPI consists of the nucleoside thymidine analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil (TPI). The molar ratio of trifluridine/tipiracil is 1:0.5 (exact mass ratio: 1:0.471). TF is phosphorylated intracellularly by the enzyme thymidine kinase to monophosphate (TF-MP) and subsequently by the enzyme thymidylate kinase to di- (TF-DP) and triphosphate (TF-TP). TF-TP is incorporated into the DNA as a defective component. This incorporation results in long-lasting DNA damage and DNA strand breaks. TF-MP, in turn, binds covalently to thyrosine-146 in the active site of the enzyme thymidilate synthetase (TS, also thymidilate synthase) and inhibits its activity. TS is responsible for the conversion of uracil nucleotides to the thymidine nucleotides and is thus vital for DNA synthesis by maintaining sufficient amounts of thymidine. FTD-TPI proved superior to placebo in the third line of treatment of metastatic gastric cancer, prolonging overall survival (HR 0.69; $p < 0.001$)

and was satisfactorily tolerated: Grade ≥ 3 adverse events occurred in 267 (80%) patients in the trifluridine/tipiracil group and in 97 (58%) in the placebo group.

6.2.4 Securing adequate nutrition

The majority of patients already have advanced tumors at the time of diagnosis and therefore often have symptomatic tumor stenosis. This symptomatology can be rapidly improved in two thirds of patients with combination chemotherapy. Other patients require local palliative measures due to dysphagia. The use of self-expanding metal stents (SEMS) for rapid relief of dysphagia has become established as standard therapy. In the case of symptomatic tumor stenosis, high-dose intraluminal brachytherapy or percutaneous radiotherapy can be offered in addition to SEMS, depending on the prognosis. The choice of palliative therapy depends on the localization and extent of the primary tumor, the severity of the symptoms and previous therapy. Data on preoperative therapy for locally advanced adenocarcinoma of the esophagus and GEJ also show that chemotherapy leads to an improvement or normalization of swallowing ability in 2/3 of patients with high-grade dysphagia.

If tumor bleeding cannot be stopped endoscopically, palliative radiotherapy can be offered (hypofractionated, e.g., 5 x 3 Gy). This is the treatment of choice particularly for chronic hemorrhage. If available, trans-arterial embolization may be useful. Palliative resection should only be considered as a last resort.

7 Rehabilitation

Esophageal/GEJ carcinoma itself, but also its treatment by means of surgery, systemic therapy and/or radiotherapy often leads to considerable somatic sequelae such as weight loss up to tumor cachexia, postoperative maldigestion, chemotherapy-induced polyneuropathy and general weakness up to a (chronic) fatigue syndrome.

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

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

When selecting the rehabilitation facility, the approval of the clinic for esophageal/GEJ cancer patients by the health insurance (pension insurance, health insurance) is a mandatory requirement. In addition, the patient's right of wish and choice according to §9 SGB IX should be taken into account.

During rehabilitation, in addition to the general therapy options (sports/physio/occupational therapy), comprehensive nutritional advice should be provided, patients should be trained in a teaching kitchen and there should be the possibility 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 long-term care should be clarified during rehabilitation.

All patients should be offered psycho-oncological support.

8 Follow-up

8.1 Surveillance during treatment

During ongoing chemotherapy, the patient's general performance and vital body functions should usually be checked once a week. Imaging procedures, preferably using computed tomography, are also regularly indicated in order to detect an unfavorable course of the disease in time and 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 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 the treatment of therapy-related complaints; regular endoscopic and imaging examinations may be considered. In past and ongoing studies, the regimen shown in Table 5 has been established.

Table 5: Structured follow-up and surveillance after curative therapy

Procedure	**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 indicated, 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 responsible Medical Societies.