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Esophageal Cancer

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

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

SGH+SSH

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairman: Prof. Dr. med. Hermann Einsele

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

www.onkopedia-guidelines.info

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Esophageal Cancer

Date of document: April 2022

Compliance rules:

- Guideline
- Conflict of interests

Authors: Michael Stahl, Salah-Eddin Al-Batran, Markus Borner, Ines Gockel, Lars Grenacher, Holger Hass, Dieter Köberle, Markus Möhler, Rainer Porschen, Ron Pritzkuleit, Holger Rumpold, Marianne Sinn, Martin Stuschke

1 Summary

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

Approximately 30-40% of patients are in principle in a resectable stage at initial diagnosis. Especially in patients with squamous cell carcinoma, comorbidities are frequently prevalent, resulting in limited functional operability. The 5-year survival after resection alone is around 20%. Multimodality approaches improve prognosis in locally advanced tumors; they may also allow organ preservation. After preoperative chemoradiotherapy and complete resection, patients with histologic residual tumor (no pCR) of squamous cell carcinoma or adenocarcinoma (including AEG 1) have an indication for adjuvant immunotherapy (regardless of *PD-L1* status).

For metastatic squamous cell carcinoma, platinum-based chemotherapy remains the treatment of choice despite limited evidence from study results. The use of immune checkpoint inhibitors in combination with chemotherapy is approved in the first-line setting (*PD-L1* CPS ≥ 10) and as monotherapy (regardless of *PD-L1* status) for second-line treatment. For metastatic adenocarcinomas of the esophagus and esophago-gastric junction, personalized therapy approaches (HER-2 positive carcinomas) and immunotherapy in combination with chemotherapy (*PD-L1* CPS ≥ 5) are available in analogy to gastric cancer.

2 Basics

2.1 Definition and basic information

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

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

2.2 Epidemiology

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

In the industrialized countries of Europe, North America and Australia, the incidence of adenocarcinomas has increased in recent decades, now representing 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 up to 100/100,000 individuals [1].

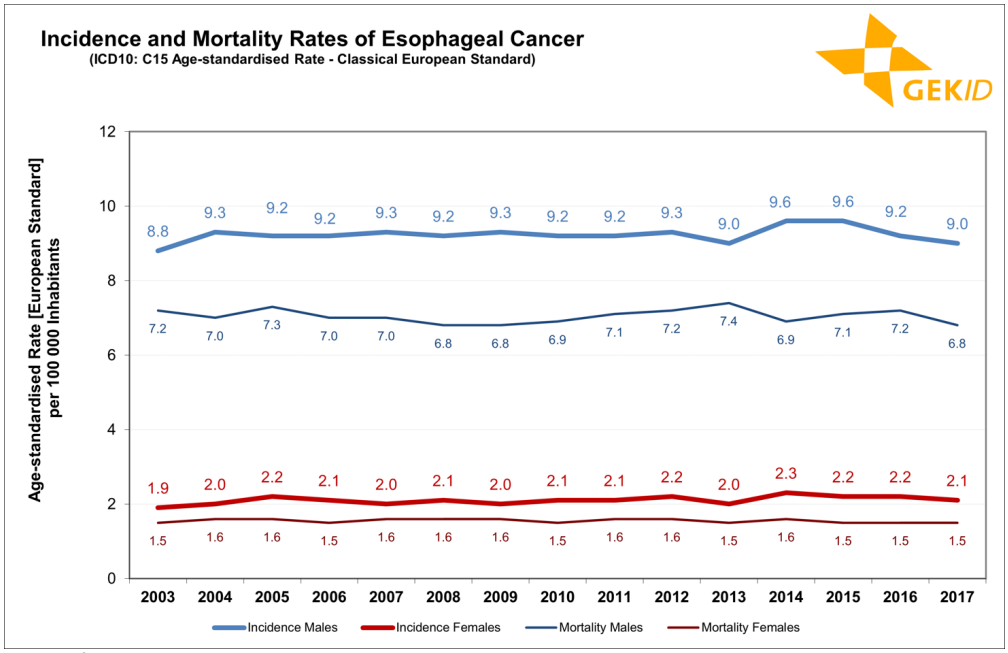
In Germany, approximately 5,500 new cases of esophageal cancer are diagnosed in men and approximately 1,600 new cases in women each year. Esophageal cancer ranks 13th among malignancies in men (2.1% of all cancers) and 8th (3.6%) among cancer-related causes of death; in women, it ranks 22nd (0.7%) and 18th (1.2%), respectively. The median age of onset, 67 years for men, is lower than that for cancer overall (70 years) and 71 years for women, higher than that for cancer overall (69 years). The median age at death is 70 years (men) and 74 years (women) (cancer overall: 75 and 76 years). Approximately 16,000 patients with esophageal cancer 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 50% of all cancers of the esophagus. The proportion of adenocarcinomas, which occur almost exclusively at the esophago-gastric junction, has risen to over 40% 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 among both sexes have been almost constant over the past 15 years. It should be noted that the rates for men are considerably (i.e., factor 3.5) higher than those for women, see Figure 1.

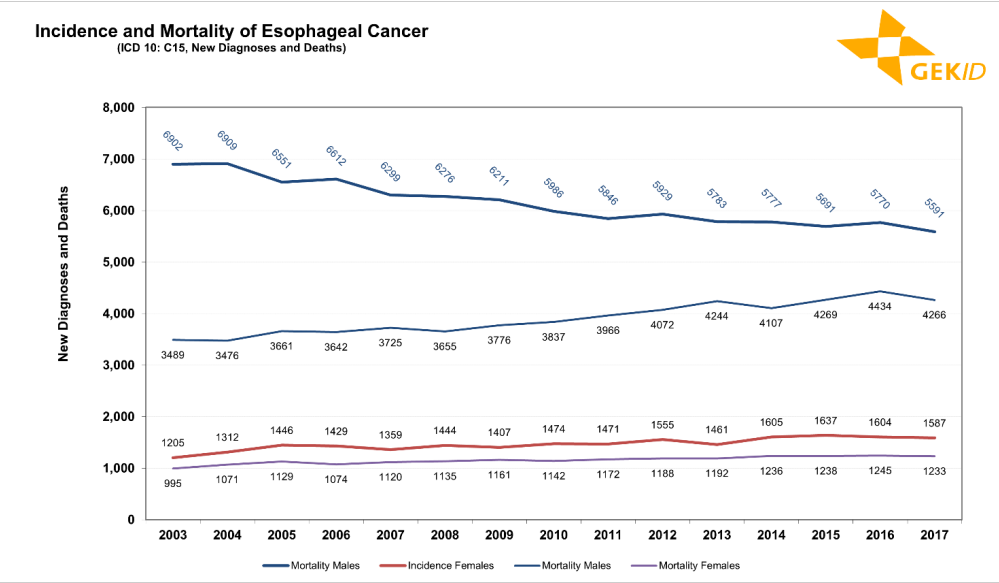
Figure 1: Estimated incidence of esophageal cancer (ICD 10: C15) in Germany



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

Due to the shift in the age structure towards an older society and because the baby boomers have reached the age of highest disease probability, the courses of new cases and deaths differ from the courses of the rates. This shift has a greater absolute effect among men because of the higher probability of disease; in relative terms, the increase is the same for both sexes. Despite constant age-standardized disease rates, the number of cases increased by an average of 1.7% per year over the past 15 years. The situation is similar for the number of deaths. Here, the number increased by an average of 1.7% per year for men and 1.3% per year for women, see Figure 2.

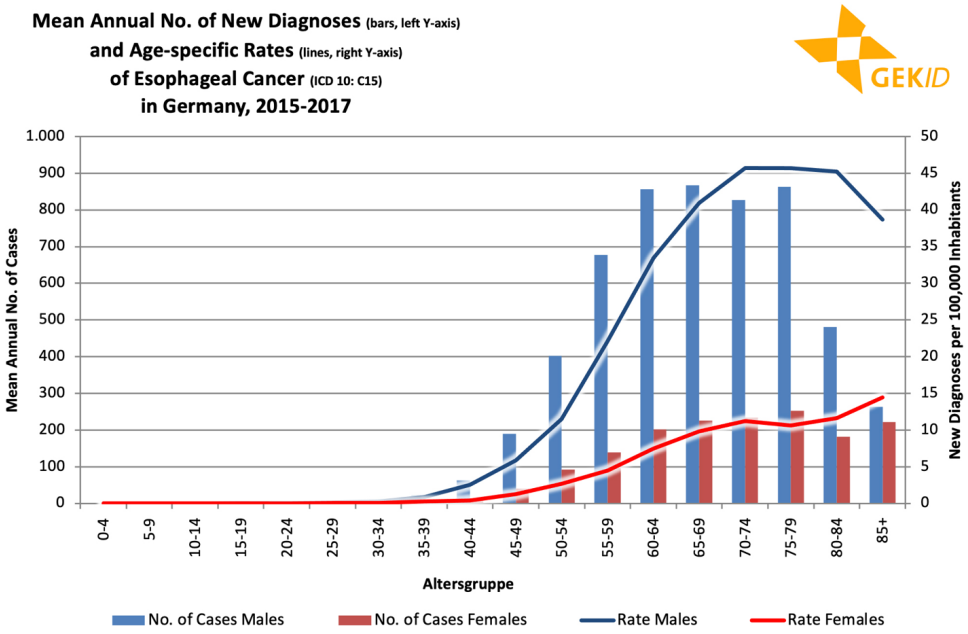
Figure 2: Incidence and mortality of esophageal cancer (ICD 10: C15) in Germany



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

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 then almost constant. 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

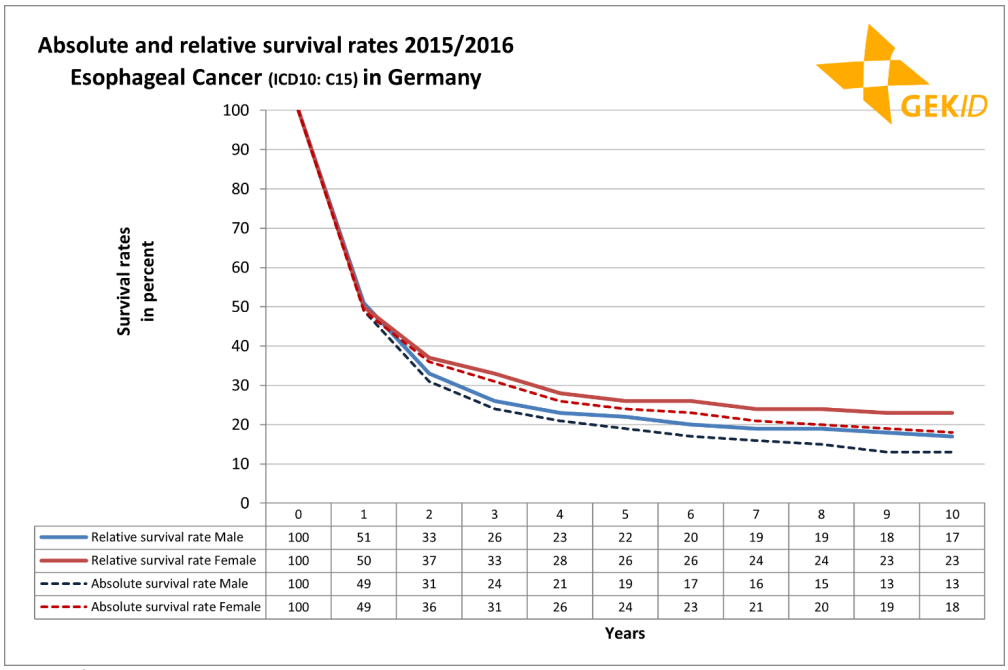


Legend:
Age distribution of esophageal cancer incidence (ICD 10: C15) - age-specific case numbers and rates; source: Center for Cancer Registry Data, database query [2].

The prognosis of patients with esophageal cancer is relatively unfavorable, especially in the first year after diagnosis. About 50% of patients die 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 genders.

Figure 4: Absolute and relative survival rates in patients with esophageal cancer (ICD 10: C15)



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

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

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

2.3 Pathogenesis

Squamous cell carcinomas typically arise from initial mechanical damage, such as 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 of the lower esophagus, the association with chronic acid reflux has been extensively studied and is accepted as a significant risk factor. Metaplasia of the orthotopic squamous epithelium to a cylindrical epithelium results in preneoplastic Barrett's mucosa. The risk of developing carcinoma has long been overestimated. The rate of progression from Barrett's metaplasia to carcinoma is approximately 0.3% (3 per 1000 patients) per year [7]. Case-control studies also show an increased risk of developing adenocarcinoma in smokers. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and statins appears to

reduce the risk of transition from Barrett's carcinoma to invasive adenocarcinoma [8]. However, due to inconsistent data, prophylactic drug treatment cannot be recommended [9].

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

Carcinogenesis of adenocarcinomas not arising from Barrett's mucosa occurs sequentially in analogy to carcinomas of the rest of the digestive tract in multistage processes via precancerous stages. *Low-grade* dysplasia progress to *high-grade* dysplasia and invasive carcinoma. Infection with Helicobacter (H.) pylori could be considered protective for the development of adenocarcinoma of the stomach and gastroesophageal 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 strategies [11].

2.4 Risk factors

Risk factors differ depending on histology and localization. Squamous cell carcinomas are frequently associated with alcohol and nicotine abuse. In contrast, carcinomas of the esophagogastric junction are more frequently associated with obesity and gastroesophageal acid reflux.

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

- Squamous cell carcinoma:
  - Smoking and alcohol, dose-dependent
  - Male gender
  - Tylosis (autosomal dominant dys-/hyperkeratosis of the feet and hands): up to 90% develop squamous cell carcinoma of the esophagus
  - Achalasia
  - Stenosis after chemical burns from alkalis or acids
  - Radiotherapy in 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
  - Stenosis after chemical burns from acids or alkalis

3 Prevention and early detection

3.1 Prevention

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

- Abstaining from excessive alcohol consumption
- Abstaining from tobacco use

- Diet rich of vegetables and fruits
- Treatment of gastroesophageal reflux disease

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

3.2 Early detection

No screening 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 also be difficult to prove due to the low incidence. In some Asian countries, general screening is established due to the high prevalence.

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 and a reduction of cancer-specific mortality are not available [14].

4 Clinical characteristics

4.1 Symptoms

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

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

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis/local findings

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

Since the prognosis of patients with esophageal cancer is closely correlated with local tumor spread and lymph node involvement, the most accurate pretherapeutic staging is critical to guide therapy. The goals of diagnostics are to determine the stage of the disease and to clarify

the patient's ability to tolerate cancer treatment. In this context, the depth of invasion of the tumor (T-category) and its proximity to adjacent structures play a special role, the predictive accuracy of which can be improved by endosonography, see Table 1. Endosonography has the highest accuracy of all methods due to its high local spatial resolution. A recent paper (evidence grade 1b) by Russell et al [17] suggests that consistent EUS tumor staging in esophageal cancer leads to improved survival rates of patients examined by EUS (approximately 3 months superior to the comparison group). Limitations are on the one hand the dependence on the investigator's expertise and on the other hand the limited technical feasibility in case of highly stenosing tumors.

5.2.2 Staging

5.2.2.1 Sonography

B-scan 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. Furthermore, B-scan ultrasonography of the neck can be used as a complementary procedure to exclude cervical lymph node metastases, which are present in 10-28% of patients, especially 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 and is obsolete.

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 performed as a substitute 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)

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

entails the clinical consequence of an expansion of the radiation volume or an expansion of the lymph node dissection.

Note on the reimbursement situation: In 2014, the Federal Joint Committee (G-BA) issued a resolution on outpatient specialized medical care for patients with severe courses of gastrointestinal tumors and tumors of the abdominal cavity: patients with esophageal carcinoma included therein can receive a PET or PET/CT for the detection of distant metastases if such a “§116b” application has been approved.

For response assessment post (radio-) chemotherapy, the usefulness of PET/CT is discussed very 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 setting.

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

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

Table 1: Diagnostics and staging

Investigation	Note
Physical examination	
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation, TSH
Endoscopy upper gastrointestinal tract	Optionally supplemented by chromo-endoscopy
Histology	Histopathological findings with immunohistology
Endoscopic ultrasound (EUS)	For patients with curative therapeutic goal
Computed tomography neck, thorax, abdomen with contrast medium	CT neck for cervical tumors if PET-CT is not performed.
Ultrasound abdomen 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)	Exclusion of distant metastases, surgical planning, radiotherapy planning.
Laryngoscopy; ENT; panendoscopy	For squamous cell carcinomas for surgical planning and exclusion of secondary carcinomas
Bronchoscopy	If anatomically adjacent to the trachea and bronchial system
Risk analysis of important organ functions	Question of functional operability
Screening for malnutrition	Patients at risk for malnutrition
Anesthesiological assessment	Early consultation in curative setting recommended, as many patients have relevant comorbidities.

Legend:
[1]Laparoscopy with cytologic examination of lavage samples helps detecting clinically occult peritoneal metastasis in locally resectable tumors in AEG I and II carcinomas. Detection of macroscopic peritoneal carcinomatosis has immediate implications for treatment planning. Laparoscopically abnormal findings are more frequently found in T3/T4 classified tumors; ENT, Ear-Nose-Throat assessment

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

- Size of the neoplastic lesion in 3 dimensions.
- Graduation of dysplasia or intraepithelial neoplasia according to WHO, if applicable.
- Histological type according to WHO (especially differentiation squamous cell versus adenocarcinoma, other rare types).
- Immunohistochemical information on biomarkers *PD-L1* (as a combined positive score CPS and as a proportion of positive tumor cells TPS), *HER-2* and microsatellite status (both in adenocarcinomas).
- For invasive carcinomas:
  - Degree of differentiation (grading) according to current WHO classification
  - Maximum depth of infiltration: pT1a (mucosa m1, m2, m3, m4), pT1b (submucosa sm1, sm2, sm3) plus depth of infiltration in µm (or higher pT category)
  - Lymphatic vessel and/or venous invasion
- Summarized assessment of LK metastatic risk:
  - Low risk vs. high risk
  - Resection margins with regard to the neoplasia: in the case of ER in toto, circular and basal resection margin; in the case of "piece-meal" ER, basal resection margin, since here the circular resection margin must usually be evaluated histopathologically as “RX”.

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

5.3 Classification

5.3.1 Classification according to localization

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

- Cervical esophagus (C15.0): from the inferior border of the cricoid cartilage to the entry of the esophagus into the thorax (suprasternal fossa), about 18 cm from TR (distal to the maxillary incisors)
- Intrathoracic esophagus
  - Upper thoracic segment (C15.3): from the entry of the esophagus into the thorax to the level of the tracheal bifurcation, approximately 24 cm from TR (distal to the upper incisors).
  - Middle thoracic segment (C15.4): upper half of esophagus between tracheal bifurcation and esophagogastric junction, lower border about 32 cm from TR (distal to maxillary incisors)
  - Lower thoracic segment (C15.5): distal half of esophagus between tracheal bifurcation and esophagogastric junction, lower border is Z line about 40 cm from TR (distal to maxillary incisors), about 8 cm in length and including abdominal esophagus)
- Esophagogastric junction (C16.0): Tumors involving the esophagogastric junction with center within 2 cm above or below and crossing the Z line (Siewert types I and II), synonym AEG (adenocarcinoma of esophago-gastric junction)

- Type I: main tumor in the distal esophagus
- Type II: Main tumor in the cardia of the stomach
- (Type III: adenocarcinoma of the subcardiac stomach, belong to gastric carcinomas).

5.3.2 Stages and TNM

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

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

Table 2: UICC-TNM classification - esophageal cancer

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

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

Stage	T	N	M
I	T1	N0, N1	M0
II	T2 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 2018

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

5.3.3 Histological subtypes

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

5.3.4 The Cancer Genome Atlas (TCGA) Classification

Current studies divide esophageal cancer into three molecular subtypes [21]:

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

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

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

6 Treatment

6.1 Treatment structure

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

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

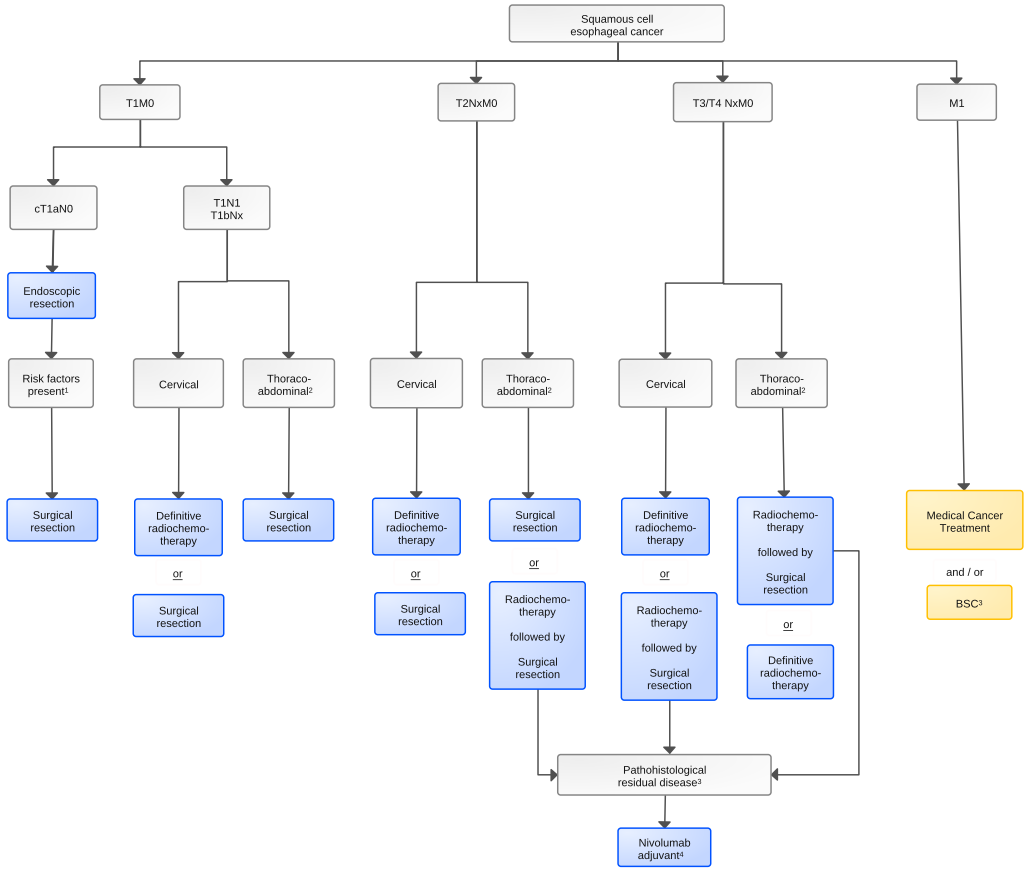
Many patients are in a reduced general performance at diagnosis, and substantial malnutrition is common, especially in patients with squamous cell carcinoma. Due to the high metabolic risk, patients should be fed before surgery, even if surgery has to be postponed because of this. After surgery, (parenteral)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

More than 50% of patients with esophageal cancer are over 65 years of age at diagnosis. However, data on the treatment of patients over 70 years of age are sparse. Older British analyses suggest that the benefit of preoperative chemoradiotherapy compared to surgery alone decreases with age and is no longer significant for patients 65 years and older [119]. A randomized British study in metastatic disease demonstrates, at least for 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.

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

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

Figure 5: Algorithm for primary therapy in squamous cell carcinoma

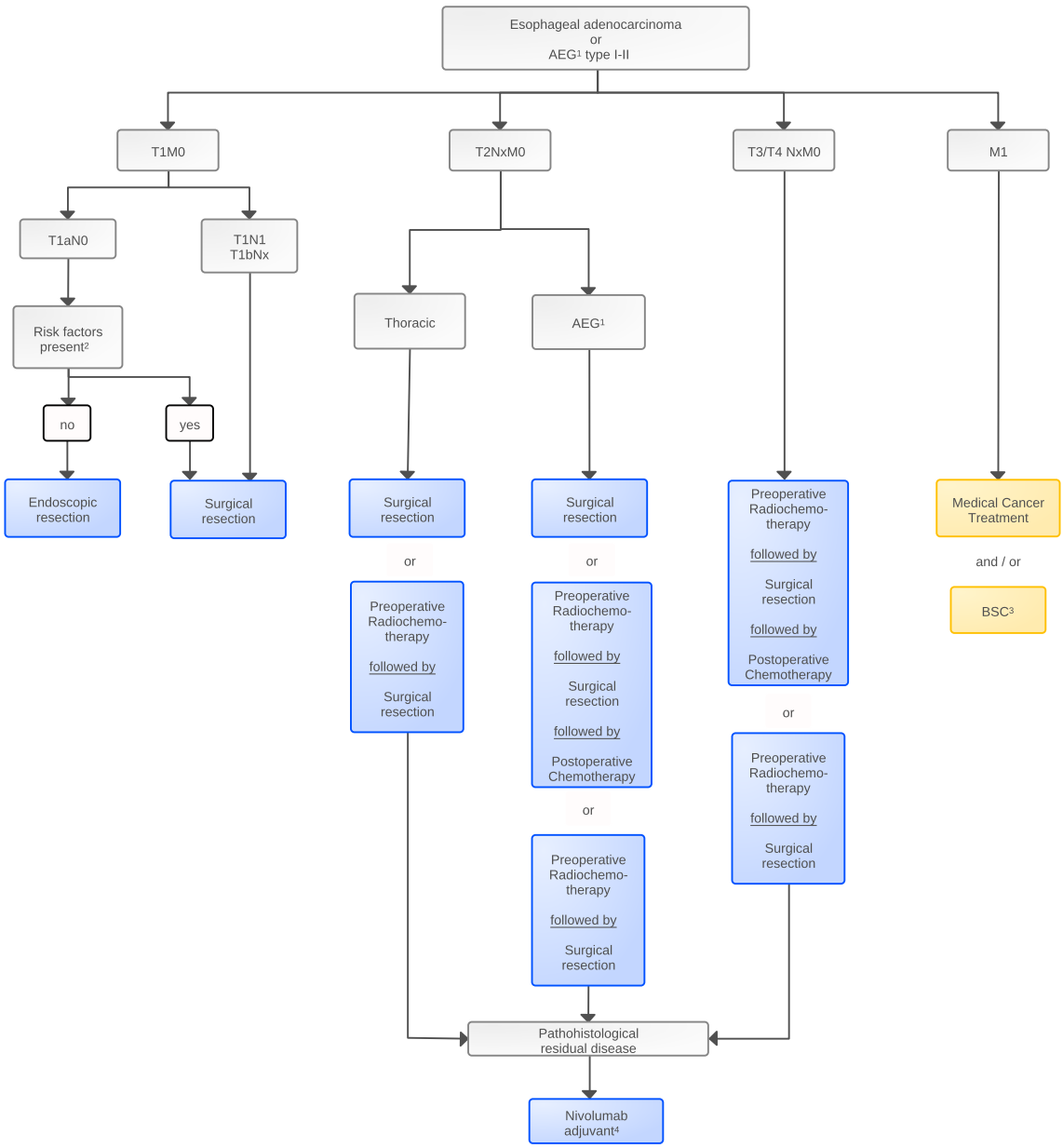


Legend:

therapy with curative intention; therapy with non-curative intention;

[1]Risk factors: ulceration, L1, V1, G3, R1, deep submucosal infiltration,
[2]thoraco-abdominal: more than 16 cm posterior to the tooth row
[3]BSC: best supportive care
[4] in case of pathological residual disease after previous neoadjuvant radiochemotherapy

Figure 6: Algorithm for primary therapy in adenocarcinoma



Legend:

therapy with curative intention; therapy with non-curative intention;

[1] AEG: adenocarcinoma of esophago-gastric junction

[2] Risk factors: ulceration, L1, V1, G3, R1, deep submucosal infiltration, multifocal/non-ablatable Barrett's lesions

[3] BSC: best supportive care

[4] in case of pathological residual disease after previous neoadjuvant radiochemotherapy

6.1.1 T1a M0 (early carcinoma)

Since the likelihood of lymph node metastasis in mucosal esophageal cancer (T1a) is very low (1-2%), mucosectomy by endoscopic resection (ER) is considered the standard of care for category pT1 m1-m3 in early adenocarcinoma and for category pT1 m1-m2 in early squamous cell carcinoma. Here, en bloc resection should be aimed at, thus enabling complete pathohistological assessment of the lateral and basal margins.

The goal of this procedure must be an R0 resection. Endoscopic mucosal resection (EMR / ER) and endoscopic submucosal dissection (ESD) [25] are accepted techniques.

In Europe, EMR is well established. However, only lesions up to max. 15 mm can be completely resected en-bloc. Larger tumors must be resected using the so-called "piece-meal" technique, which increases the risk of incomplete resections. Local relapses or second manifestations occur in up to 30% of Barrett's neoplasms after EMR [26].

Data for ESD are so far available mainly from Asia for squamous cell carcinoma. Here, superiority compared to EMR was shown with regard to en bloc resection rate, curative resection rate, and local recurrence rate. Data from Japan demonstrate that ESD is also possible in principle for Barrett's carcinoma with an R0 resection rate of 85%. However, the value of ESD in adeno-/Barrett's carcinoma has not been conclusively established [27, 28, 29].

In patients with superficial submucosal infiltration of adenocarcinoma and no risk criteria (pT1sm1; <500 µm depth of invasion, for squamous cell carcinoma from T1m3, L0, V0, G1/2, < 20 mm, no ulceration), endoscopic resection may be a sufficient alternative to surgery after multidisciplinary decision.

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

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

After endoscopic resection and histopathological diagnosis of a tumor of category T1m3 (squamous cell carcinoma) or T1b (submucosal tumor extension), surgical resection with systematic lymphadenectomy should be performed. Surgical resection should also always be considered if there is lymphatic or venous invasion (L1, V1), G3 grade of differentiation, or deep submucosal infiltration (> 500 µm) after ER [9].

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

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

6.1.2 T1b-T2 M0

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

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

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

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

Independent from the tumor location in the esophagus and the histology (adenocarcinoma or squamous cell carcinoma), definitive radiochemotherapy is an alternative for patients who are not suitable for surgery due to comorbidities, with the goal of long-term loco-regional tumor

control. For these patients, endoscopic resection may be the treatment of choice for a T1b tumor despite an increased risk of recurrence [9].

In the case of a tumor of category T2, especially in the case of high suspect or evidence of lymph node metastases, the use of multimodal therapy concepts can be useful, as they are presented below for T3/T4 tumors (see Chapter 6.1.3). The recommendation for such a procedure should be discussed on a multidisciplinary tumor board, and advantages and disadvantages should be shared with the patients [30]. In any case, patients with T2 tumors were also included in published randomized trials of perioperative chemotherapy [31, 32] and preoperative radiochemotherapy [30]. A significant overall survival benefit has not yet been demonstrated in this subgroup [33, 34].

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

6.1.3 T3-T4 M0

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

Preoperative radiochemotherapy showed a survival benefit for both histological subgroups in the CROSS study (median overall survival 49 versus 24 months, HR 0.66, p= 0.003), which, however, was only significant for the squamous cell carcinoma group after long-term follow-up [34]. In this randomized trial, 368 patients (75% of whom had adenocarcinoma) were treated by preoperative radiochemotherapy up to 41.4 Gy and weekly administration of carboplatin and paclitaxel plus subsequent surgery versus surgery alone. The benefit from radiochemotherapy was more pronounced and significant only for patients with squamous cell carcinoma (median overall survival 82 versus 21 months, HR 0.48, p=0.007 vs. adenocarcinoma median overall survival 43 versus 27 months, HR 0.73; p=0.061). Postoperative complications were comparable in both groups [32]. In the assessment of this study, a high patient selection has to be considered. Almost exclusively patients with tumors of the distal esophagus (AEG) in best general condition (84% performance score grade 0 according to WHO) were included as were patients with early tumors (17% category T1 or T2). However, survival rates of more than 40% at 5 years are now possible even in patients with locally advanced carcinomas in multicenter studies after optimized radiotherapy in combination with platinum/taxane-based chemotherapy and surgery.

The benefit of preoperative radiochemotherapy has also been confirmed in meta-analyses [37, 38], so that it can be used equally as a first-line therapy for squamous cell and adenocarcinomas with a tumor ≥T3.

After preoperative RCT and surgery, there was previously no indication for adjuvant therapy. This has changed as a result of the international phase III CheckMate 577 study. The study investigated whether immunotherapy with nivolumab improves survival after chemoradiotherapy and complete surgical resection, if no histopathological complete remission (pCR) has been achieved. In this study, 794 patients were randomized to placebo vs. nivolumab for 1 year after

completion of preoperative chemoradiotherapy and recovery from subsequent surgery [39]. The results show that immunotherapy is feasible and does not worsen patients quality of life compared with placebo. The primary endpoint was met with a significant prolongation of disease-free survival (median of 22.4 vs. 11.0 months, p=0.0003, HR=0.69 (CI 0.56-0.86)). Nivolumab particularly reduced the rate of distant recurrence (29% vs. 39%). Patients with carcinomas of both histologies benefited significantly (HR=0.61 for squamous cell carcinomas, HR=0.75 for adenocarcinomas). Outcome did not differ between *PD-L1* positive (72% of patients) or negative tumors, with only tumor cells before chemoradiotherapy considered for assessment (TPS score ≥ 1% or <1%). DFS in the control arm appears short, with a median of 11 months. In a registry study from the Netherlands published so far only as a congress paper, median OS for patients with residual tumor after CRT without post-treatment was 19.2 months. The unfavorable DFS in the CheckMate 577 study may be due to the high proportion of high-risk patients with absent downsizing (ypT3-4) or persistently positive lymph nodes (ypN+), which was close to 60%. These data are not yet available from the Dutch study.

Although overall survival data have not yet been reported in the CheckMate 577 trial, the European Commission granted approval for adjuvant immunotherapy with nivolumab for both histologic types in Europe in September 2021. ASCO, in an update to its statement on esophageal cancer, also strongly recommended adjuvant therapy with nivolumab after CRT and surgery if malignant cells were still detectable in the resected tumor tissue [40].

6.1.3.1 Squamous cell carcinoma

In patients with squamous cell carcinoma of the upper or middle thoracic esophagus with a good response to radiochemotherapy, the benefit of additional surgery should be critically evaluated. Although additional surgery may improve local tumor control, two randomized trials failed to demonstrate a positive effect on overall survival, and therapy-related mortality is significantly higher with surgery [42, 43, 44]. According to German registry data, hospital mortality in from 2006 to 2013 after complex esophageal surgery was 9.2% in high-volume centers and 12.1% in low-volume centers [45].

On this background, a watch & wait strategy can be recommended in patients with a clinical complete remission 12 weeks post chemoradiotherapy (50.4 Gy radiotherapy dose), documented by CT and endoscopy including biopsies in the former tumor region. Thereafter, short-term controls (every 8 weeks) must be performed in order to preserve the possibility for curation by salvage surgery in case of isolated local tumor progression.

For cervically located (almost always squamous cell) carcinomas of the esophagus, definitive radiochemotherapy is considered the standard therapy [46, 47, 48]. It should be taken into account that resections up to the upper esophageal sphincter are associated with a high complication rate and postoperative disorders such as dysphagia, aspiration risk, and paresis of the N. laryngeus recurrens, so that surgery should not be performed in cases of high-cervically located esophageal carcinoma.

Definitive radiotherapy alone without chemotherapy, preoperative radiotherapy alone without chemotherapy, or preoperative chemotherapy alone is not recommended for squamous cell carcinoma of the esophagus [49]. Study results from Asian and meta-analyses [50, 51] indicating that adjuvant radiotherapy may improve local tumor control and possibly also overall survival should be verified in phase III trial with "Western" patients. Adjuvant radiotherapy (or chemoradiotherapy) is not a standard of care.

6.1.3.2 Adenocarcinomas of the Esophago-Gastric Junction

In patients with adenocarcinomas of the esophago-gastric junction (AEG) of category ≥T3 or N+, perioperative chemotherapy is another evidence-based and well-established therapeutic option. Perioperative chemotherapy consisting of an anthracycline, a platinum derivative, and a fluoropyrimidine (epirubicin, cisplatin, and 5-FU; ECF) has long been considered the standard perioperative therapy based on data from the MAGIC trial [31]. However, more recent data demonstrate that chemotherapy according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) is superior to ECF or a combination of epirubicin, cisplatin, and capecitabine (ECX) in patients with locally advanced AEG (≥cT2 and/or cN+). Perioperative FLOT resulted in a significant prolongation of progression-free (hazard ratio 0.75) and overall survival (HR 0.77 (0.63-0.94), p=0.012). This effect was consistent across all relevant subgroups such as age, histologic subtype, and localization. The rate of perioperative complications was comparable in both arms [32].

Comparative data between preoperative radiochemotherapy and perioperative chemotherapy for locally advanced AEG failed to demonstrate a statistically significant survival benefit with the addition of radiotherapy. However, a single phase III trial [52] indicates that suboptimal preoperative chemotherapy (PLF regimen) can be improved by adding chemoradiotherapy (HR 0.65 (0.42-1.01, p=0.055). In addition, the studies demonstrate improved local tumor control and an increase in the rate of histologically complete remissions and R0 resections with chemoradiotherapy. The systemic therapeutic effect appears to be lower with preoperative radiochemotherapy due to a lower cumulative dose of chemotherapy [49].

In summary, both therapeutic concepts are currently considered equivalent in AEG. In patients with extensive local tumors, preoperative radiochemotherapy may be favored due to the high risk of incomplete resection and local recurrence, otherwise perioperative chemotherapy may be favored [9]. Direct comparison between the two therapeutic modalities is currently being investigated in several phase III trials. However, only one of these trials has the currently accepted standard of perioperative therapy with FLOT in the comparator arm, so that relevant questions will remain unanswered by these trials as well. The suggestion that perioperative chemotherapy may not be effective in patients with signet ring carcinomas or microsatellite unstable (MSI-H) adenocarcinomas is not justified according to recent study results [32].

The treatment of locally advanced adenocarcinomas is currently independent of *HER2* status. For perioperative chemotherapy, phase II data suggest a higher histopathological complete response (pCR) rate in patients treated with the combination of chemotherapy (FLOT) and the anti-*HER2* antibody trastuzumab [54]. However, results from phase III trials are not to be expected in the short term. In the context of combined preoperative chemoradiotherapy (CROSS regimen), the addition of trastuzumab does not improve outcomes [55].

In patients with AEG ≥ stage IB who have received resection without pretreatment (e.g., due to misclassified tumor stage prior to surgery), adjuvant therapy can be administered if there is an increased risk of local recurrence, such as extensive lymph node involvement (pN2-3). However, according to data from an Asian phase III trial, combined radiochemotherapy does not result in a (further) improvement of disease-free survival compared with combination chemotherapy alone (ARTIST2 trial) [56].

After R1 resection, adjuvant radiochemotherapy is recommended because of the high risk of local recurrence [50, 51, 9].

6.1.3.3 Adenocarcinoma of the esophagus

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

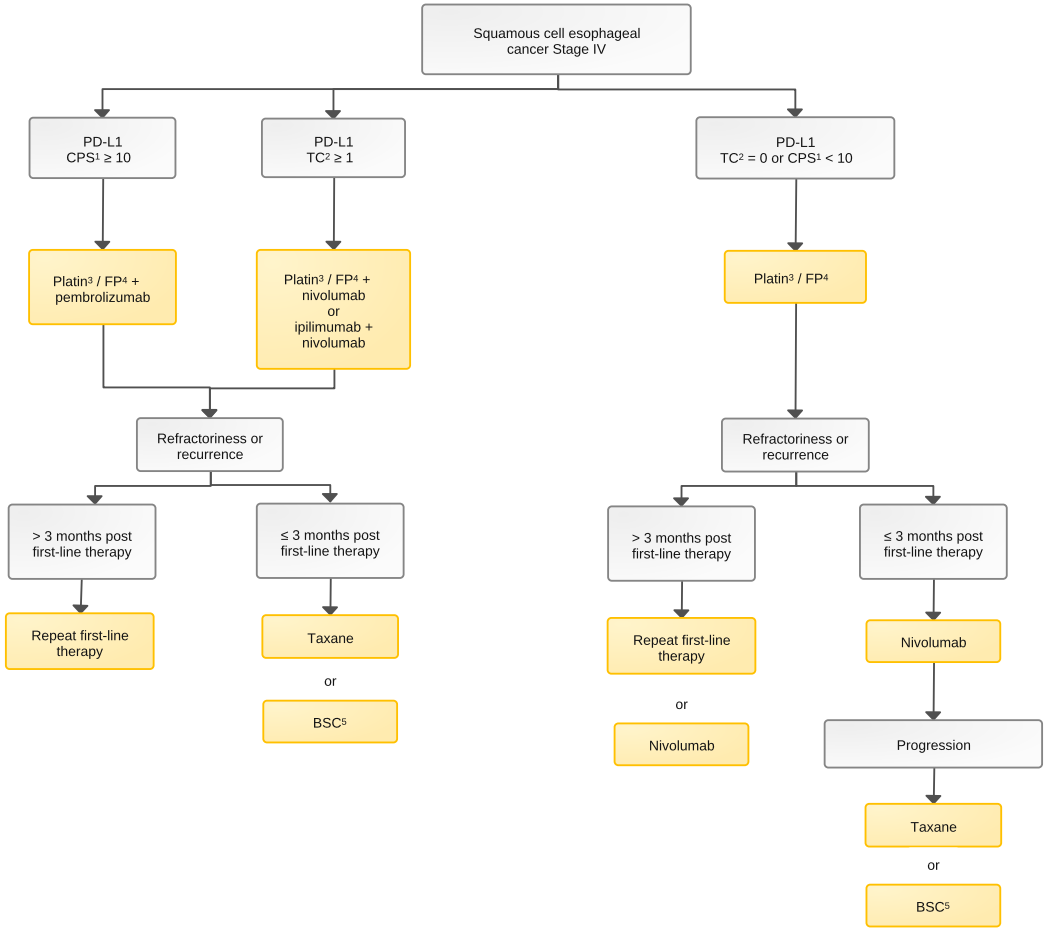
For definitive radiochemotherapy, a radiation dose of 50.4 Gy should be aimed at. Higher doses do not improve local tumor control or overall survival in either squamous cell or adenocarcinoma according to data from a Dutch phase III trial (ARTDECO) [54]. Regarding chemotherapy within combined chemoradiotherapy, data support a combination of platinum and fluoropyrimidine or carboplatin/paclitaxel, associated with low toxicity [61]. A French phase III trial showed comparable efficacy for a combination of oxaliplatin and 5-FU (FOLFOX regimen) versus the standard combination of cisplatin and 5-FU in combination with definitive radiotherapy [63]. The combination of radiotherapy plus carboplatin and paclitaxel, which is well proven in preoperative therapy, appears also suitable for definitive radiochemotherapy [62], however, data from comparative studies are lacking. The tolerability in combination with 50.4 Gy radiotherapy is reported to be better than for the cisplatin/FU-based radiochemotherapy. The addition of cetuximab did not increase efficacy and even had negative effects in several studies [64, 65, 66]. In preoperative radiochemotherapy, carboplatin plus paclitaxel is a standard of care (CROSS trial). It must be kept in mind that the benefit is lower for adenocarcinomas and that due to the limited duration of chemotherapy, there is no proven impact on the rate of distant recurrences. In addition, the combination of cisplatin and docetaxel is well validated by prospective phase II or phase III trials. In the preoperative setting, the addition of an EGFR inhibitor (in this case, cetuximab) does not improve the prognosis of patients. However, a European phase III trial showed a significant improvement in local tumor control [67].

6.1.4 Stage IV (M1)

6.1.4.1 Systemic cancer treatment

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

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



Legend:

Therapy in non-curative intention;

[1]CPS - Combined Positive Score of PD-L1 positive tumor cells and immune cell infiltrate

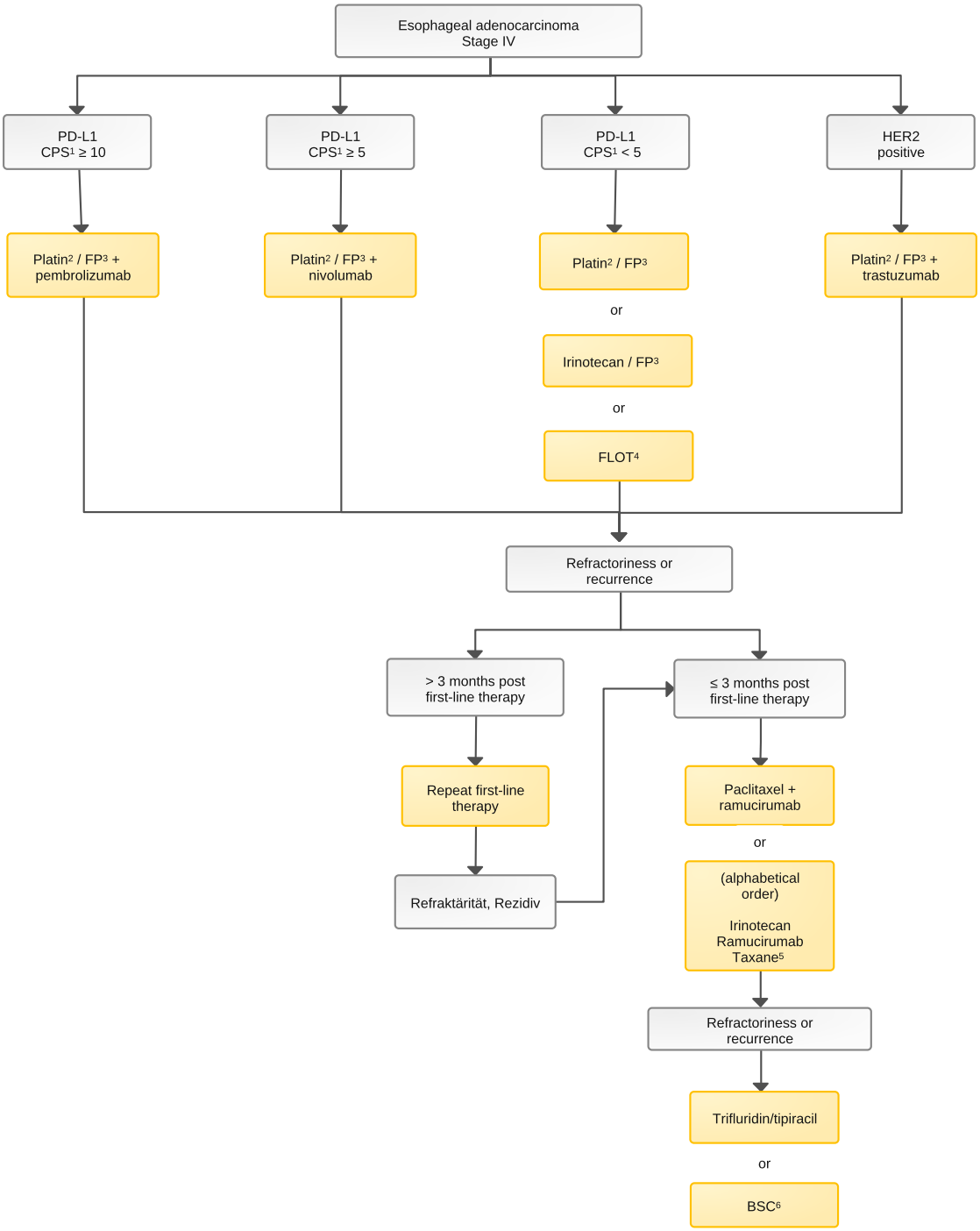
[2]TC - Number of PD-L1 positive tumor cells as a percentage of all tumor cells

[3]Platin: cisplatin or oxaliplatin

[4]FP: fluoropyrimidine

[5]BSC: best supportive care

Figure 8: Algorithm for the treatment of stage IV esophageal adenocarcinoma



Legend:

Therapy in non-curative intention;

[1]CPS - Combined Positive Score of PD-L1 positive tumor cells and immune cell infiltrate

[2]Platin: cisplatin or oxaliplatin

[3]FP: fluoropyrimidine

[4]FLOT - 5-FU, folinic acid, oxaliplatin, docetaxel

[5]Taxane - docetaxel or paclitaxel

[6]BSC: best supportive care

6.1.4.1.1 Premises

Systemic therapy can prolong survival in patients with stage IV esophageal cancer and is therefore the treatment of choice. In squamous cell carcinoma, this has not been proven by phase III

trials, however, palliative chemotherapy is recommended as standard of care in international guidelines [9].

For the planning of chemotherapy, the general performance of the patient and relevant comorbidities, patient 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 situation [61].

6.1.4.1.2 First-line therapy

6.1.4.1.2.1 Immunotherapy

The phase III KEYNOTE-590 trial [69] demonstrated that the combination of chemotherapy and immune checkpoint blockade improves first-line outcomes. In this study, predominantly (73%, n=548) patients with squamous cell carcinoma of the esophagus were treated. There was a significant benefit in overall survival for the group of patients with high tumor *PD-L1* expression who 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 carcinomas benefited in particular. For the group of patients with adenocarcinomas (esophagus n=110, AEG n=91), the benefit was less pronounced (HR 0.74 (CI 0.54-1.02)). Combined chemo-immunotherapy (platinum + fluoropyrimidine + pembrolizumab) for patients with SCC or AC of the esophagus and high *PD-L1* expression (CPS ≥10) was approved in Europe in September 2020.

Results from another phase III trial (CheckMate 648) are available for the first-line treatment of metastatic esophageal squamous cell carcinoma [70]. In this three-arm study, a total of nearly 1000 patients were randomized to the 3 treatment groups of chemotherapy (cisplatin + 5-FU), chemotherapy + nivolumab (240mg every 2 weeks), or nivolumab + ipilimumab (1mg/kg every 6 weeks). The common primary endpoints were OS and PFS for patients with *PD-L1* positive tumors. However, in contrast to the other upper GI tract studies, only tumor cells were evaluated for *PD-L1* status in this study (TPS ≥1%). The primary endpoints were met in both experimental arms. With chemotherapy + nivolumab, OS was significantly improved compared to chemotherapy alone (median 15.4 vs. 9.1 mo, HR 0.54 (CI 0.37-0.80), p<0.001). OS was also significantly better with double checkpoint blockade than with chemotherapy (median 13.7 vs. 9.1 mo, HR 0.64 (CI 0.46-0.90), p=0.001). Appraisal of these data is difficult because of the specific definition of the study population (patients whose tumors are positive for TPS). It is currently unclear what the overlaps are between tumors with CPS ≥10 and TPS ≥1%. Combined chemo-immunotherapy (platinum + fluoropyrimidine + nivolumab) or combined checkpoint-inhibition (nivolumab + ipilimumab) for patients with SCC of the esophagus and *PD-L1* expression (TPS ≥1) was approved in Europe in March 2022.

Another phase III study, the three-arm CheckMate 649 [71] trial, included adenocarcinomas of the stomach, AEG, and esophagus (total n=2031; stomach 70%, AEG 16%, esophagus 14%). For the primary endpoint, overall survival, only patients whose tumor had a positive *PD-L1* status (CPS ≥ 5) were evaluated (n=955). For the comparison of chemo- and chemo-immunotherapy, results showed significantly improved OS with the addition of nivolumab to FOLFOX or XELOX (median 14.4 vs. 11.1 months, HR 0.71, p<0.0001). Based on these data, approval was granted in Europe in October 2021 for esophago-gastric AC with positive *PD-L1* status (CPS ≥ 5) and negativity for *HER2.* From subgroup analyses, the question arises to what extent patients with AEG benefit from immunotherapy. Furthermore, due to the small number of patients (n=114), conclusions regarding signet ring carcinoma are limited.

The comparison between chemotherapy and double checkpoint blockade (ipilimumab 3mg/kg + nivolumab 1 mg/kg) was terminated prematurely due to high toxicity [71]. Here, even for patients with *PD-L1* positive tumors, there was no difference in OS (HR 0.89; p=0.23) and increased mortality in the immunotherapy group during the first 12 months of therapy. In addi-

tion, the rate of severe toxicities was higher with this therapy than with chemotherapy. Therefore, chemotherapy-free combined immunotherapy is not indicated for metastatic esophagogastric AC.

6.1.4.1.2.2 Squamous cell carcinoma

The median overall survival in stage IV patients in a good general condition is less than one year [11]. To assess the benefit of systemic therapy, no data from randomized phase III trials are available to demonstrate prolonged survival. Due to the lack of evidence, many recommendations are made by analogy with head and neck squamous cell carcinomas.

Combination chemotherapy of cisplatin and 5-FU is considered standard. The addition of anti-*EGFR* antibodies (panitumumab) does not improve response [72]. Although no comparative data are available, the presumably equally effective combination therapy with FOLFOX can also be recommended because of its lower toxicity. Capecitabine is rarely used in place of 5-FU for esophageal cancer because of frequently present dysphagia.

6.1.4.1.2.3 Adenocarcinoma

For the assessment of available data, it must be taken into account that in many studies on gastric cancer, patients with AEG – typically as a smaller subgroup - were also included and treated. Therefore, the recommendations for adenocarcinomas of the esophagus are analogous to those of the Onkopedia guideline Gastric cancer.

Prior to initiating therapy, *HER2* status as well as PD-L1 expression should be reviewed as these biomarkers impact treatment options.

6.1.4.1.2.3.1 Carcinomas without HER2 expression

Doublet chemotherapies based on platinum and a fluoropyrimidine are the recommended standard. Triplet combinations probably achieve a higher remission rate, but they more often lead to higher-grade toxicity: this holds true for the combination with docetaxel [73] or epirubicin [74]. The decision between doublet or triplet therapy must be made taking into account general condition, age, comorbidities, patient wishes, and individual disease course. If a docetaxel-containing triple combination is indicated (patient under 65 years of age, good performance score, high urgency of swift remission), the FLOT regimen (docetaxel, oxaliplatin, 5-FU/folinic acid) achieves at least comparable efficacy with better tolerability compared to DCF (docetaxel, cisplatin, 5-FU) [75]. For patients with PD-L1 positive carcinomas (CPS ≥ 5) see chapter 6.1.4.1.2.1.

In both doublet and triplet therapies, cisplatin and oxaliplatin were shown to be equivalent therapeutic options, each associated with well-known compound-specific side effect profiles [76]. The same holds true for capecitabine and intravenous 5-FU [77]. The combination of oral S-1 and cisplatin shows comparable efficacy with an improved toxicity profile [78], and S1 is also easier to swallow than capecitabine. However, S1 is poorly established in Europe and is only approved in combination with cisplatin [79].

The combination of irinotecan and 5-FU/folinic acid (FOLFIRI) was shown to be equally effective as cisplatin-based doublet or triplet therapy in randomized trials [80]. Irinotecan also appears to be similarly effective to cisplatin when combined with capecitabine [81].

Patients of higher age

A pooled analysis from phase 3 trials comparing patients ≥ 70 years with younger patients showed no differences in response rates and survival. However, there is no indication for older patients ≥ 65-70 years to receive intensified first-line chemotherapy with a docetaxel-containing triplet combination. Moreover, a randomized phase III trial from the United Kingdom demon-

strates that in elderly or "unfit" patients, a primary dose reduction of chemotherapy with capecitabine and oxaliplatin to 60% of the standard dose can be given. This was less likely to result in an objective response, while in terms of survival, dose-reduced therapy was non-inferior and global quality of life improved [82]. In general, the use of a geriatric assessment to detect and specifically address comorbidities, cognitive impairment, and malnutrition is recommended in this age group, see Geriatric Oncology Knowledge Base.

6.1.4.1.2.3.2 Carcinomas with HER2 expression

Approximately 20% of AEG are *HER2*-positive and benefit from the addition of trastuzumab to chemotherapy with cisplatin and a fluoropyrimidine. In the ToGA study, a randomized phase III trial, this resulted in a significant improvement of response rate, progression-free survival, and overall survival (median overall survival 13.8 versus 11.1 months, HR 0.74; p = 0.0046) [76]. This effect was particularly pronounced for patients with *HER2* overexpression (IHC 3+) or *HER2* amplification (IHC 2+ as well as positive fluorescence in situ hybridization (FISH) (median overall survival 16.0 versus 11.8 months; HR 0.65). This combination is now the recommended standard of care.

Data are now available from prospective phase 2 and retrospective case-control studies indicating that first-line trastuzumab therapy is also effective in combination with oxaliplatin + fluoropyrimidine chemotherapy (FOLFOX), so that this triplet therapy can also be recommended, when there is an appropriate contraindication to cisplatin-based chemotherapy [83, 84, 85].

Other HER2-targeted therapeutics have so far shown no additional benefit in first-line therapy and should therefore not be used outside clinical trials. This applies to lapatinib [86, 87], trastuzumab emtansine (TDM-1) [88] and pertuzumab.

Preliminary results indicate that the addition of an immune checkpoint inhibitor to chemotherapy + trastuzumab may further improve outcomes in *HER2*-positive carcinomas. In the phase III KEYNOTE-811 trial [89], pembrolizumab (200mg every 3 weeks) was used. This increased the objective treatment response rate from 52% to 74% regardless of PD-L1 status, and the tumor control rate was as high as 96%. In the randomized phase II INTEGA trial (AIO-STO-0217), a high tumor response rate was also observed with FOLFOX/trastuzumab + nivolumab (56% in the overall group, 67% in patients with PD-L1 positive tumors (CPS ≥5)). The median survival time reached 21.8 months [90]. In the comparator group without chemotherapy (ipilimumab + trastuzumab + nivolumab), the results were less positive (tumor control for *PD-L1* CPS ≥5 only 33%, median OS for the overall group 16.4 months).

6.1.4.1.3 Second-line therapy

6.1.4.1.3.1 Squamous cell carcinoma - second-line therapy

A phase III trial (ATTRACTION-3) randomized patients with advanced or recurrent esophageal squamous cell carcinoma after therapy with platinum/fluoropyrimidine to either chemotherapy (paclitaxel or docetaxel) or the PD-1 inhibitor nivolumab (240 mg fixed dose every 2 weeks) [91]. Approximately half of the patients had *PD-L1* positive carcinomas. Regardless of *PD-L1* status, overall survival was significantly better with immunotherapy (median 10.9 vs. 8.4 months, HR 0.77 (0.62-0.96), p=0.019). The rates of overall and grade 3-4 adverse events were significantly higher with chemotherapy. Premature treatment discontinuation occurred in 9% of patients in both study arms, and after 4 months, only 30% of patients in both arms were free from tumor progression. In principle, the study was also open to "Western patients". In fact, however, almost exclusively (96%) patients from Asia were included. Nevertheless, based on these study data, nivolumab was approved in Europe in October 2020 for advanced squamous

cell carcinoma of the esophagus and is thus available for second-line therapy after pretreatment with a combination of platinum and fluoropyrimidine.

A second phase III trial (KEYNOTE-181) was conducted with the PD-1 inhibitor pembrolizumab [92]. In this study, over 60% of the patients included were not from Asia. Patients with squamous cell carcinoma (64%) or adenocarcinoma (including AEG) of the esophagus after progression despite first-line chemotherapy were randomized to chemotherapy (paclitaxel, docetaxel, or irinotecan) or pembrolizumab (200 mg fixed dose every 3 weeks). Approximately 35% of patients had *PD-L1* highly-positive tumors (combined score ≥10%). The intent-to-treat analysis showed no significant difference between treatment groups. Only in patients with *PD-L1* highly-positive tumors did immunotherapy result in significantly better overall survival (median 9.3 vs. 6.7 months, p=0.0074), Patients with squamous cell carcinoma also tended towards longer survival (median 8.2 vs. 7.1 months). Subgroup analysis shows that mainly Asian patients with *PD-L1* positive squamous cell carcinoma benefitted. The study is difficult to interpret because of multiple co-primary endpoints. In the U.S., pembrolizumab was approved in July 2019 based on these data. There is no approval in Europe for this indication.

Older phase II studies indicate efficacy in principle of taxanes, platinum derivatives, or irinotecan in second- and third-line therapy [93].

Supportive measures are an important focus in this treatment situation.

6.1.4.1.3.2 Adenocarcinoma - second-line therapy

Approximately 40% of patients are able to tolerate second-line therapy after tumor progression under first-line palliative therapy [84]. Randomized phase III studies show an improvement in survival time and quality of life for patients with a good general performance (ECOG 0-1) by the use of second-line therapy. This effect was also demonstrated in a meta-analysis. Data are available for monotherapy with irinotecan, paclitaxel, and docetaxel, and for ramucirumab. A randomized phase 3 study showed a comparable benefit from irinotecan and paclitaxel.

Ramucirumab, a monoclonal antibody targeting *VEGFR-2,* prolonged survival when given as monotherapy (median survival 5.2 months versus 3.8 months, HR 0.776; p=0.047) [94], and its efficacy appears comparable to mono-chemotherapy. In combination with paclitaxel, ramucirumab was more effective than paclitaxel alone in the second-line setting (median survival 9.6 months versus 7.4 months, HR 0.807; p=0.017) [95].

As an alternative to initiating second-line therapy with the above drugs, patients who experience progression more than 3 months after the end of first-line therapy may be re-exposed to the same drug combination [91].

For HER2-positive carcinomas, there has been no indication for continued *HER2* blockade after first-line chemotherapy + trastuzumab. All studies on this topic were negative. In a non-randomized phase II study, trastuzumab-deruxtecan in the 2nd line could still showed objective remissions in 38% of patients at the ESMO Congress 2021, if it was histopathologically confirmed that the tumors were still *HER2*-positive after first-line therapy [96]. A phase III trial has been activated.

6.1.4.1.4 Third-line therapy

6.1.4.1.4.1 Squamous cell carcinoma - third-line therapy

Beyond second-line therapy, there are no approved drugs available. Therapeutic decisions must be made on an individual basis.

6.1.4.1.4.2 Adenocarcinomas - third-line therapy

Currently, only the oral fluoropyrimidine trifluridine in a fixed combination with tipiracil (TAS-102) is approved in Europe in this indication (at least 2 pretreatments). In a phase III trial conducted worldwide, 507 patients (80% of whom were from Europe) were randomized (TAS-102 vs. placebo), 145 of whom had AEG [97]. TAS-102 significantly prolonged PFS (0.2 months, HR 0.57 (0.47-0.70), p<0.0001) and OS (2.1 months, HR 0.69 (0.56-0.85), p<0.001). In a planned subgroup analysis, the outcome for patients with AEG was less favorable (HR for OS 0.75) than for gastric cancer (HR 0.67). Serious adverse events occurred in 78% of patients with TAS-102, but did not lead to treatment discontinuation more frequently than with placebo (13% vs. 17%). These were predominantly hematologic toxicity, worsening general condition, pulmonary embolism, and gastrointestinal adverse events (loss of appetite, nausea, dysphagia, vomiting). Time to deterioration of general condition was significantly prolonged by TAS-102.

Immunotherapy with checkpoint inhibitors is also an emerging treatment option for AEG. In a phase III study from the Asian region, nivolumab led to an increase in progression-free survival (hazard ratio 0.60; median 0.2 months) and overall survival (hazard ratio 0.63; median 1.2 months) in patients with gastric cancer or AEG after failure of at least 2 prior therapies. The remission rate was 11.2% [98].

Similar results were obtained in a phase II study with pembrolizumab in 259 Caucasian patients. 11.6% of patients achieved partial or complete remission [99]. Median progression-free survival was 2 months, and median overall survival was 5.6 months. The response rate was higher in patients with *PD-L1* positive carcinomas and especially in patients with evidence of high microsatellite instability (MSI-H), although with a very small number of patients (n=7). Nevertheless, MSI-H is currently the only predictive factor for the use of immunotherapy after first line treatment in AEG.

In Switzerland and Japan, nivolumab is approved for the treatment of adult patients with advanced or recurrent adenocarcinoma of the stomach or AEG after two or more prior systemic therapies. There is currently no approval in other European countries.

6.2 Treatment modalities

6.2.1 Resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for resection of early carcinomas. Techniques include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [22]. ER is performed as an en-bloc resection. It allows complete histologic evaluation of the lateral and basal margins.

The recommended endoscopic control intervals are 3 months in the first year and 6 months in the second year. Thereafter, controls should be carried out annually.

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

6.2.1.2 Esophagectomy, lymphadenectomy and reconstruction procedures

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

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

- Middle and distal esophageal tumors and AEG I: transthoracic subtotal esophagectomy with tubular gastric elevation and high-intrathoracic anastomosis (if necessary, with extension orally with total esophagectomy and cervical anastomosis).
- AEG type II: transthoracic esophagectomy with tubular gastric elevation or transhiatal extended gastrectomy with distal esophageal partial resection, then Roux-Y reconstruction (currently comparing techniques in a German phase III trial, “Cardia study”).
- In cases of long-sectional involvement of both the distal esophagus and proximal stomach, total esophago-gastrectomy may be appropriate. 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 for this [9].

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

For TNM classification, the histopathological analysis of at least 7 lymph nodes is required, and usually more than 20 lymph nodes are removed. Retrospective studies suggest an improvement in prognosis associated with the resection of at least 23 regional lymph nodes [100, 101].

Surgery should be performed at a specialized center (high-volume center) [102, 103], because the higher surgical and perioperative expertise ["failure to rescue") reduces perioperative mortality and improves the long-term prognosis of patients. For certification as an esophageal cancer center according to the German Cancer Society, at least 20 resections of esophageal cancer per year are required.

If, in contrast to the diagnosis made in the obligatory intraoperative frozen section, an R1 resection is found postoperatively in the histological workup, the conditions for a second, extended resection are usually unfavorable. Because of the high local recurrence risk, adjuvant radiochemotherapy should therefore be recommended [50, 51].

6.2.1.3 Resection of metastases

Currently, there is no evidence-based benefit from palliative resection of primary tumor or metastases in patients with stage IV esophageal cancer. Therefore, resection should not be performed. If metastases are discovered during curative surgery that are completely resectable (without risk), they can be resected in individual cases. By now there is no consensus on how to deal with so called oligo-metastatic disease (intraabdominal lymph nodes +/- one organ involved, no more than 3 metastases). 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 significantly better 5-year survival after resection of residual metastases. Patients with synchronous limited metastasis or peritoneal carcinomatosis should be offered presentation to a high-volume center to check for secondary resectability. A recently initiated prospective randomized phase 3 trial in Germany (FLOT-5, NCT02578368) is evaluating whether induction chemotherapy plus metastasectomy improves prognosis in limited metastasis of AEG (or adenocarcinoma of the stomach) compared with continuation of palliative chemotherapy [104].

6.2.2 Radiotherapy

6.2.2.1 (Neo)adjuvant radiochemotherapy

Neoadjuvant radiochemotherapy is standard of care for locally advanced (category cT3/T4) squamous cell carcinoma and adenocarcinoma of the esophagus. In randomized trials, preoperative doses of 41.4 to 54 Gy were administered in 22 to 28 fractions. Weekly administrations of carboplatin (AUC 2) and paclitaxel (50 mg/m²) [105] or cisplatin (30mg/m2) and docetaxel (60mg/m2) have been established as partners for combined chemoradiotherapy, as an alternative to the original standard of cisplatin and 5-fluorouracil every 3 to 4 weeks.

Neoadjuvant radiochemotherapy is a therapeutic option for patients with a category T2 tumor, especially if lymph node metastases are present or detected. Its use instead of primary resection should be discussed in the multidisciplinary tumor board on a case-to-case basis.

In patients with R1 resection, retrospective studies suggest that adjuvant radiochemotherapy may improve survival [106]. In this case, radiochemotherapy should be performed as in the case of definitive radiochemotherapy. The clinical target volume includes residual tumor (if present), the anastomoses, and the affected lymph node stations. Intensity-modulated radiotherapy should be used to optimize sparing of surrounding normal tissues, particularly the heart and lungs [107, 108].

6.2.2.2 Definitive radiochemotherapy

For high-seated (cervical) esophageal cancer, definitive radiochemotherapy is the method of first choice, in order to avoid frequent postoperative complications such as dysphagia and aspiration, and mutilating surgery (laryngectomy). It leads to long-term survival rates of 17-55% [109, 110], and has been shown in various studies to be superior to radiotherapy alone [111], the latter being therefore only used for palliative treatment in esophageal cancer.

Definitive radiochemotherapy is also an alternative therapy for tumors that are considered unresectable after multidisciplinary discussion, as well as for patients with functional inoperability or patients who decline surgical treatment.

Recent data from the Netherlands (ARTDECO trial) showed no benefit in local tumor control with total radiation doses above 50.4 Gy in patients with intrathoracic esophageal carcinoma and concurrent chemotherapy with carboplatin / paclitaxel. This study aimed to demonstrate an improvement in local tumor control from 50% to at least 65% by increasing the total dose to the primary tumor from 50.4 Gy to 61.6 Gy in each of 28 fractions. Local tumor control rates (the primary endpoint) were significantly better than expected at 71% and 73% at 3 years in the standard and dose escalation arms, respectively. In this study, 62% of patients had squamous cell carcinoma and 38% had adenocarcinoma [61].

As this trial had a high quality of the study conduct and analysis, **a total dose of 50.4 Gy should be considered the standard for definitive chemoradiation of intrathoracic esophageal carcinomas** with simultaneous chemotherapy with carboplatin/paclitaxel.

For tumor localization in the cervical esophagus, higher total doses of up to 66 Gy in conventional fractionation with 1.8 Gy per fraction are recommended after single-institution treatment series, in accordance with the recommendations of the current NCCN guideline on esophageal cancer version 4.2020.

Larger randomized trials comparing neoadjuvant radiochemotherapy and surgery with definitive radiochemotherapy for squamous cell carcinoma of the esophagus used total radiation

doses of 60-66 Gy in conventional fractions along with concurrent chemotherapy with cisplatin/5-FU or other cisplatin-containing combinations [42, 44], however, without significant differences in outcomes between treatment arms. Also, exploratory analysis of the FFCD 9102 trial showed a dose-effect relationship when comparing patients treated conventionally to 66 Gy with those treated hypofractionated to 45 Gy. Overall, for simultaneous chemotherapy with cisplatin/5-FU, total radiation doses of 50-60 Gy are recommended as a therapeutic corridor for definitive radiochemotherapy. However, if salvage surgery appears to be an option for the patients depending on their general condition and tumor spread, the total dose for radiotherapy should be limited to 50 Gy - 55 Gy in conventional fractionation with 1.8 - 2.0 Gy per fraction according to the FREGAT group data, as an increase in postoperative complications was observed at higher total doses.

Previously, the most commonly used chemotherapy in combination with radiotherapy was the combination of cisplatin and 5-FU [11], but combined radiochemotherapy with FOLFOX is considered equivalent [63]. Definitive chemoradiotherapy using carboplatin/paclitaxel or cisplatin/paclitaxel is also a first-line option with low toxicity and comparable long-term treatment outcomes and is increasingly used. Randomized trials comparing the efficacy and toxicity of the combination of cisplatin/5-FU with carboplatin/paclitaxel are ongoin.

6.2.3 Systemic cancer treatment

6.2.3.1 Perioperative chemotherapy

Perioperative chemotherapy is a well-established standard therapy for adenocarcinomas of the esophago-gastric junction with a category T3 or higher (see also Onkopedia Gastric Cancer, S3-Guideline of Adenocarcinomas of the Stomach and AEG Tumors 2019 [9]). A direct comparison between perioperative chemotherapy and neoadjuvant radiochemotherapy is only available for AEG. The results are inconclusive (see chapter 6.1.3)

On the basis of the UK MRC MAGIC trial, a combination of epirubicin, cisplatin, and 5-FU (ECF 3 cycles every 3 weeks each preoperatively and postoperatively) was long considered the standard of care, because it resulted in an improvement of 5-year survival from 23% to 36% compared with surgery alone [28]. Comparable results are available for the combination of cisplatin and 5-FU (2 cycles corresponding to 8 weeks of preoperative treatment duration). The FLOT regimen (5-FU, leucovorin, oxaliplatin, docetaxel) showed a significantly higher histopathologic complete response (pCR) rate (15.6% vs. 5.8%), improved progression-free survival (hazard ratio 0.75; median 12 months), and significantly improved overall survival (HR 0.77; p=0.012) in a randomized phase III trial compared with ECF/ECX [29]. Being also less toxic, FLOT is therefore the new standard therapy in the perioperative treatment approach.

Current data indicate that the response to preoperative chemotherapy does not determine the choice of postoperative chemotherapy, neither with regard to its implementation nor to intensification or drug switching. Only in the case of tumor progression under preoperative therapy should it not be continued postoperatively. Whether early response evaluation by PET-CT after 1 course of preoperative chemotherapy with cisplatin/5-FU might be beneficial in this situation, has not yet been clarified. Of interest are the results of a randomized phase II trial (DOCTOR) [112] in which treatment for patients without metabolic tumor response was escalated to either docetaxel, cisplatin, 5-FU (DCF) or DCF plus radiotherapy. Over 90% of patients with adenocarcinoma of the esophagus or AEG subsequently received surgery. The addition of radiotherapy appears to improve both progression-free survival (at 3 years, 46% vs. 29%) and overall survival (at 5 years, 46% vs. 31%).

In individual cases (understaging), adjuvant chemotherapy may be justified [112] if no therapy was or could be performed preoperatively. This is particularly true in cases of extensive lymph node metastasis (pN2-3). In these exceptional situations, adjuvant chemotherapy with oxaliplatin and a fluoropyrimidine can be justified for a total duration of 6 months according to the Korean CLASSIC study [114, 115].

The alternative using an oral fluoropyrimidine for 12 months is no longer considered standard, even in Asia, on the basis of the ARTIST2 trial [116].

6.2.3.2 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 cancer in whom neither resection nor radiotherapy can be administered [117, 118].

An overview of the various therapeutic options can be found in chapter 6.1.4.1 (Systemic cancer treatment), and on individual substances in the next chapter 6.2.3.3.

6.2.3.3 Systemic cancer treatment - substances

6.2.3.3.1 Capecitabine and S1

Capecitabine and S1 (tegafur/gimeracil/oteracil) are oral fluoropyrimidines metabolized in the body to 5-FU. In comparative clinical trials in esophago-gastric adenocarcinomas, they are as effective as 5-FU. They can be used in place of 5-fluorouracil in palliative therapy if there is sufficient swallowing function. In combination with platinum derivatives, remission rates up to 45% are achieved. Severe side effects (grade 3 / 4) occurring in more than 5% of patients in pivotal studies are diarrhea and hand-foot syndrome (very rare for S1). Before starting therapy with fluoropyrimidines a blood test to recognize mutation in specific allels of the DPYD-gen shall be performed to avoid overdose in patients with hampered metabolisation capacity.

6.2.3.3.2 Cisplatin

Platinum derivatives are among the most effective single substances. In combination with other cytostatic drugs, cisplatin is part of the standard of care. In palliative therapy, cisplatin in combination with fluoropyrimidines achieves remission rates of up to 30%. Drug-related severe side effects (grade 3/4) include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte shifts, and diarrhea.

6.2.3.3.3 Docetaxel

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

6.2.3.3.4 5-Fluorouracil

5-Fluorouracil is used in almost all forms of drug therapy for patients with esophageal cancer. Its efficacy is increased by combination with folinic acid. An alternative is the oral application of capecitabine or S-1, see chapter 6.2.3.3.1. Severe side effects are diarrhea and stomatitis. Patients with functionally relevant polymorphisms of 5-FU degradation genes have an increased risk of severe side effects including neutropenia and neutropenic fever, so before starting therapy with fluoropyrimidines a blood test to recognize mutation in specific allels of the DPYD-gen shall be performed.

6.2.3.3.5 Irinotecan

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

6.2.3.3.6 Nivolumab

Nivolumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. It is approved as combination therapy with platinum / fluoropyrimidine or ipilimumab for first-line treatment of esophageal squamous cell carcinoma with positive score of PD-L1 (TPS ≥ 1%) as well as monotherapy for second-line treatment of esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy regardless of *PD-L1* status. Moreover Nivolumab is indicated in combination with FOLFOX chemotherapy in advanced esophago-gastric adenocarcinoma. Characteristic side effects with nivolumab are immune-mediated, particularly autoimmune phenomena. More common side effects include hypothyroidism/hyperthyroidism, loss of appetite, fatigue, diarrhea, nausea, rash, and asthenia. Typical mild (grade 1-2) adverse events in the pivotal study were rash (11%), diarrhea (10%), and loss of appetite (7%); severe (grade 3-4) adverse events were pyrexia (2%) and interstitial lung disease (2%).

6.2.3.3.7 Oxaliplatin

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

6.2.3.3.8 Paclitaxel

Paclitaxel belongs to the taxanes and is effective as monotherapy or combined with the VEGFR-inhibitor ramucirumab in second-line palliative therapy. Moreover, it has shown efficacy in combination with cisplatin/5-FU/folinic acid (Gastro-Tax study) in first-line palliative therapy. Severe

side effects (grade 3/4) include infection, stomatitis and diarrhea, and allergic reactions to the contained solvent, Cremophor. Burdensome side effects include alopecia. Particularly distressing is polyneuropathy, which can be irreversible. Common side effects such as allergic reactions can be partially prevented by appropriate supportive medication.

6.2.3.3.9 Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. In the phase III KEYNOTE-590 trial [69] on first-line treatment of metastatic esophageal cancer, pembrolizumab + chemotherapy compared with chemotherapy significantly increased response rates, prolonged progression-free and overall survival, and increased survival at 2 years in patients with PD-L1 positive carcinomas (CPS ≥ 10). Characteristic side effects with pembrolizumab are immune-mediated, particularly autoimmune phenomena. More common side effects include hypothyroidism/hyperthyroidism, loss of appetite, fatigue, diarrhea, nausea, rash, and asthenia.

1. *Ramucirumab*

Ramucirumab is a VEGF receptor2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab significantly prolongs progression-free survival, prolongs overall survival, and increases remission rates compared to paclitaxel monotherapy. In patients ineligible for paclitaxel therapy, ramucirumab monotherapy versus placebo also results in prolongation of progression-free survival and overall survival. The only grade 3/4 serious adverse event that occurred in more than 5% of patients on ramucirumab monotherapy was arterial hypertension. More common adverse events in combination therapy were fatigue (12%), neuropathy (8%), and abdominal pain (6%).

6.2.3.3.10 Trifluridine/Tipiracil (TAS102)

Since the beginning of September 2019, the oral cytostatic drug trifluridine/tipiracil (TAS102) has been approved as monotherapy for metastatic gastric and adenocarcinomas of the esophageal junction, provided that patients had already received at least two lines of systemic therapy. Approval is based on the international TAGS phase 3 trial. Grade ≥3 adverse events occurred in 267 (80%) patients in the trifluridine/tipiracil group and in 97 (58%) in the placebo group. Clinically relevant grade ≥3 neutropenias (34%) and anemias (19%).

6.2.3.3.11 Trastuzumab

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

6.2.4 Securing adequate nutrition

The majority of patients have already advanced tumors at the time of first diagnosis, often resulting in symptomatic stenoses. Combination chemotherapy can rapidly improve these symptoms in two thirds of patients. Other patients need local palliative measures due to dysphagia. The use of self-expanding metal stents (SEMS) for rapid relief of dysphagia has become

a standard of care. In symptomatic tumor stenosis, high-dose intraluminal brachytherapy or percutaneous radiotherapy may be offered in addition to SEMS, depending on the overall prognosis. The choice of palliative therapy depends on the localization and extent of the primary, the severity of symptoms, and prior therapy. Data on preoperative therapy for locally advanced adenocarcinoma of the esophagus and AEG also show that chemotherapy leads to improvement or normalization of swallowing function in two thirds of patients with high-grade dysphagia (dysphagia grade 0 or 1).

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

7 Rehabilitation

Esophageal cancer itself, but also its treatment by surgery, chemotherapy and/or radiotherapy, often leads to significant somatic sequelae, such as weight loss to tumor cachexia, postoperative malnutrition, chemotherapy-induced polyneuropathy, and general weakness or (chronic) fatigue syndrome.

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

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

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

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

Rehabilitation facilities should be able to continue systemic cancer treatment, if required.

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 the rehabilitation.

All patients should be offered psycho-oncological support.

8 Follow-up

8.1 Control examinations during treatment

During ongoing chemotherapy, the patient's general condition and vital bodily functions should generally be checked once a week. Image procedures, preferably by means of computer tomography, are also regularly indicated in order to detect negative developments 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 treatment of therapy-related complaints; regular endoscopic and imaging examinations may be considered. In past and ongoing studies, the regimen in T able 5 has become established.

Table 5: Structured follow-up and aftercare for curative therapy

Investigation	**Months after completion of therapy**													
	(3)	6	(9)	12	(15)	18	(21)	24	(30)	36	(42)	48	54	60
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Blood count and serum routine	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging: Ultrasound or if necessary CT thorax/ abdomen/ pelvis	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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11 Links

Self-help groups

15 Authors' Affiliations

Prof. Dr. med. Michael Stahl
Evang. Huyssens-Stiftung
Kliniken Essen-Mitte
Klinik für Intern. Onkologie und Hämatologie
Henricistr. 92
45136 Essen
M.Stahl@kem-med.com

Prof. Dr. med. Salah-Eddin Al-Batran
UCT- Universitäres Centrum für
Tumorerkrankungen Frankfurt
Institut für klinisch-Onkologische Forschung (IKF)
Steinbacher Hohl 2-26
60488 Frankfurt
albatran.salah@khnw.de

Prof. Dr. med. Markus Borner
ONCOCARE am Engeriedspital
Riedweg 15
CH-3012 Bern
markus.borner@hin.ch

Prof. Dr. med. Ines Gockel
Universitätsklinikum Leipzig
Klinik und Poliklinik für Viszeral-,
Transplantations-, Thorax- und Gefäßchirurgie
Liebigstr. 20
04103 Leipzig
Ines.Gockel@medizin.uni-leipzig.de

Prof. Dr. med. Lars Grenacher
Diagnostik München
Augustenstraße/München GmbH
Augustenstr. 115
80798 München
l.grenacher@diagnostik-muenchen.de

PD Dr. med. Holger Hass
Klinik Gais
Onkologische Rehabilitation
Gäbrisstr. 1172
9056 Gais

Prof. Dr. med. Dieter Köberle
St. Claraspital
Medizinische Klinik, Onkologie
Kleinriehenstr. 30
CH-4016 Basel
dieter.koeberle@claraspital.ch

Prof. Dr. med. Markus Möhler
Universitätsklinik Mainz
I. Medizinische Klinik und Poliklinik
Langenbeckstr. 1
55131 Mainz
markus.moehler@unimedizin-mainz.de

Prof. Dr. med. Rainer Porschen
Kreiskrankenhaus Osterholz
Gastroenterologische Praxis
Am Krankenhaus 4
27711 Osterholz-Scharmbeck
r.porschen@kkhohz.de

Dr. Ron Pritzkuleit
Institut für Krebsepidemiologie
Krebsregister Schleswig-Holstein
Ratzeburger Allee 160
23538 Lübeck
ron.pritzkuleit@krebsregister-sh.de

PD Dr. med. Holger Rumpold
Ordensklinikum Linz
Viszeralonkologisches Zentrum
Fadingerstr.1
4020 Linz
holger.rumpold@ordensklinikum.at

PD Dr. med. Marianne Sinn
Universitätsklinikum Hamburg-Eppendorf
II. Medizinische Klinik und Poliklinik
Onkologie, Hämatologie, KMT mit Sektion Pneumologie
Martinistr. 52
20246 Hamburg
ma.sinn@uke.de

Prof. Dr. med. Martin Stuschke
Universitätsklinikum Essen (AöR)
Klinik für Strahlentherapie
Hufelandstr. 55
45147 Essen
Martin.Stuschke@uk-essen.de

16 Disclosures

according to the rules of the responsible Medical Societies.