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Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Oesophageal cancer is the 19th most common cancer in the European Union (EU), with ∼45 900 new cases diagnosed in 2012 (1% of the total). In the EU, the highest age-standardised incidence rates for oesophageal cancer are in the Netherlands for men and the UK for women [1]. Variation between countries is high and may reflect different prevalence of risk factors, use of screening and diagnostic methods.

Between 2000–04 and 2005–09, oesophageal cancer mortality declined by 7% (from 5.34 to 4.99/100 000) in EU men, and by 3% (from 1.12 to 1.09/100 000) in EU women. Predictions to 2015 show persistent declines in mortality rates for men in the EU overall and stable rates for EU women, with rates for 2015 of 4.5/100 000 men (∼22 300 deaths) and 1.1/100 000 women (∼7400 deaths).

Oesophageal cancer has two main subtypes—oesophageal squamous cell carcinoma (SCC) and oesophageal adenocarcinoma (AC). Although SCC accounts for ∼90% of cases of oesophageal cancer worldwide, mortality rates associated with AC are rising and have surpassed those of SCC in several regions in the EU [2].

Oesophageal carcinoma is rare in young people and increases in incidence with age, peaking in the seventh and eighth decades of life. AC is three to four times as common in men as it is in women, whereas the sex distribution is more equal for SCC [3].

The main risk factors for SCC in Western countries are smoking and alcohol consumption, whereas AC predominantly occurs in patients with chronic gastro-oesophageal reflux disease and their risk is correlated with the patient's body mass index with a higher risk for obese persons [3, 4].

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diagnosis and pathology/molecular biology

Screening for Barrett's oesophagus, endoscopic surveillance and ablation of precursor lesions are not in the focus of this guideline. We recommend to follow the recently updated guidelines of the American College of Gastroenterology [5].

All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis, weight loss and/or loss of appetite should undergo an upper intestinal endoscopy [III, A]. Approximately three-quarters of all ACs are found in the distal oesophagus, whereas SCCs occur more frequently in the proximal to middle oesophagus [3]. Biopsies should be taken from all suspect areas. The minimal recommended number of biopsies is not defined. The diagnosis should be made from an endoscopic biopsy with the histology classified according to the World Health Organization (WHO) criteria [6]. The differentiation between SCC and AC is of prognostic and clinical relevance.

Immunohistochemical stainings are recommended in poorly and undifferentiated cancers (G 3/4) according to WHO to differentiate between SCC and AC [V, B]. Additionally, small cell carcinoma and other rare histologies (endocrine tumours, lymphoma, mesenchymal tumours, secondary tumours and melanoma) must be identified separately from SCC and AC and should be treated accordingly.

staging and risk assessment

Decisions on the initial treatment approach of oesophageal cancer are taken on the basis of clinical staging, which should be done with the highest degree of accuracy possible. Staging should include a complete clinical examination and a computed tomography (CT) scan of the neck, chest and abdomen [III, A]. Ultrasound of the abdomen can be carried out initially as a simple and inexpensive test to exclude stage 4 liver metastases. In candidates for surgical resection, endoscopic ultrasound (EUS) should be carried out to evaluate the T and N tumour

categories [III, B]. The sensitivity and specificity of EUS for the correct evaluation of the T category are 81%–92% and 94%–97%, respectively. It is lower for the N category [7]. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET; today mostly done as PET-CT) is particularly helpful to identify otherwise undetected distant metastases. ^{18}F-FDG-PET should, therefore, be carried out in patients who are candidates for oesophagectomy [III, B], as the finding of otherwise unknown distant metastases may prevent patients from futile surgery. However, the availability of PET-CT differs among countries and centres.

A tracheobronchoscopy should be carried out in the case of tumours at or above the tracheal bifurcation to exclude tracheal invasion. In the case of oesophageal SCC due to chronic tobacco and alcohol consumption, meticulous investigation of the oral cavity, oropharynx and hypopharynx by an ear, nose and throat specialist, as well as trachea-bronchoscopy to exclude a synchronous second cancer in the aerodigestive tract, should be carried out [IV, B].

In locally advanced (T3/T4) ACs of the oesophago-gastric junction (OGJ) infiltrating the anatomic cardia, laparoscopy can be done to rule out peritoneal metastases, which are found in ~15% of patients. [IV, C]. The finding of otherwise unknown peritoneal metastases may prevent patients from futile surgery.

The stage is to be given according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system (7th edition) (Table 1) [8]. Anatomic staging should be complemented by medical risk assessment, especially in patients who are scheduled for multimodal therapy and/or surgery. Medical risk assessment should comprise a differential blood count as well as liver, pulmonary, cardiac and renal function tests.

The nutritional status and history of weight loss should be assessed according to The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [III, A] [9]. More than half of patients lose >5% of their body weight before admission to oesophagectomy, and 40% lose >10%. Independent from the body mass index, weight loss confers an increased operative risk, worsens a patient's quality of life and is associated with poor survival in advanced disease. Therefore, nutritional support according to the ESPEN guidelines [10] is an integral part of the medical care for patients with oesophageal cancer in the curative and in the palliative setting [II, A].

Table 1. TNM staging for oesophageal cancer (UICC/AJCC, 7th edition) [8, with permission]

Definition of TNM (2009)

Primary tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma *in situ*/high-grade dysplasia
T1 Tumour invades lamina propria or submucosa
T1a Tumour invades mucosa or lamina propria or muscularis mucosae
T1b Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades adventitia
T4 Tumour invades adjacent structures
T4a Tumour invades pleura, pericardium, diaphragm or adjacent peritoneum
T4b Tumour invades other adjacent structures such as aorta, vertebral body or trachea

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–2 regional lymph nodes
N2 Metastasis in 3–6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes

Distant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage grouping

Carcinomas of the oesophagus and gastro-oesophageal junction

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

The regional lymph nodes, irrespective of the site of the primary tumour, are those in the oesophageal drainage area including coeliac axis nodes and paraoesophageal nodes in the neck but not supraclavicular nodes.

Edge et al. [8]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

management of local/locoregional disease (M0)

Upfront interdisciplinary planning of the treatment is mandatory [III, A]. The main factors for selecting primary therapy are tumour stage and location, histological type, and the patient's performance status (PS) and comorbidities. Nutritional status matters and should be corrected. Endoscopic stenting should not be used in locoregional disease in operable patients and alternative routes of feeding (e.g. with needle catheter jejunostomy) should be preferred [II, A] [11]. Patient preferences should also be assessed and be taken into account. A summary of treatment recommendations is shown in Figure 1.

limited disease (cT1–T2 cN0 M0)

Surgery is the treatment of choice in limited disease. In patients with T1a AC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated [II, A].

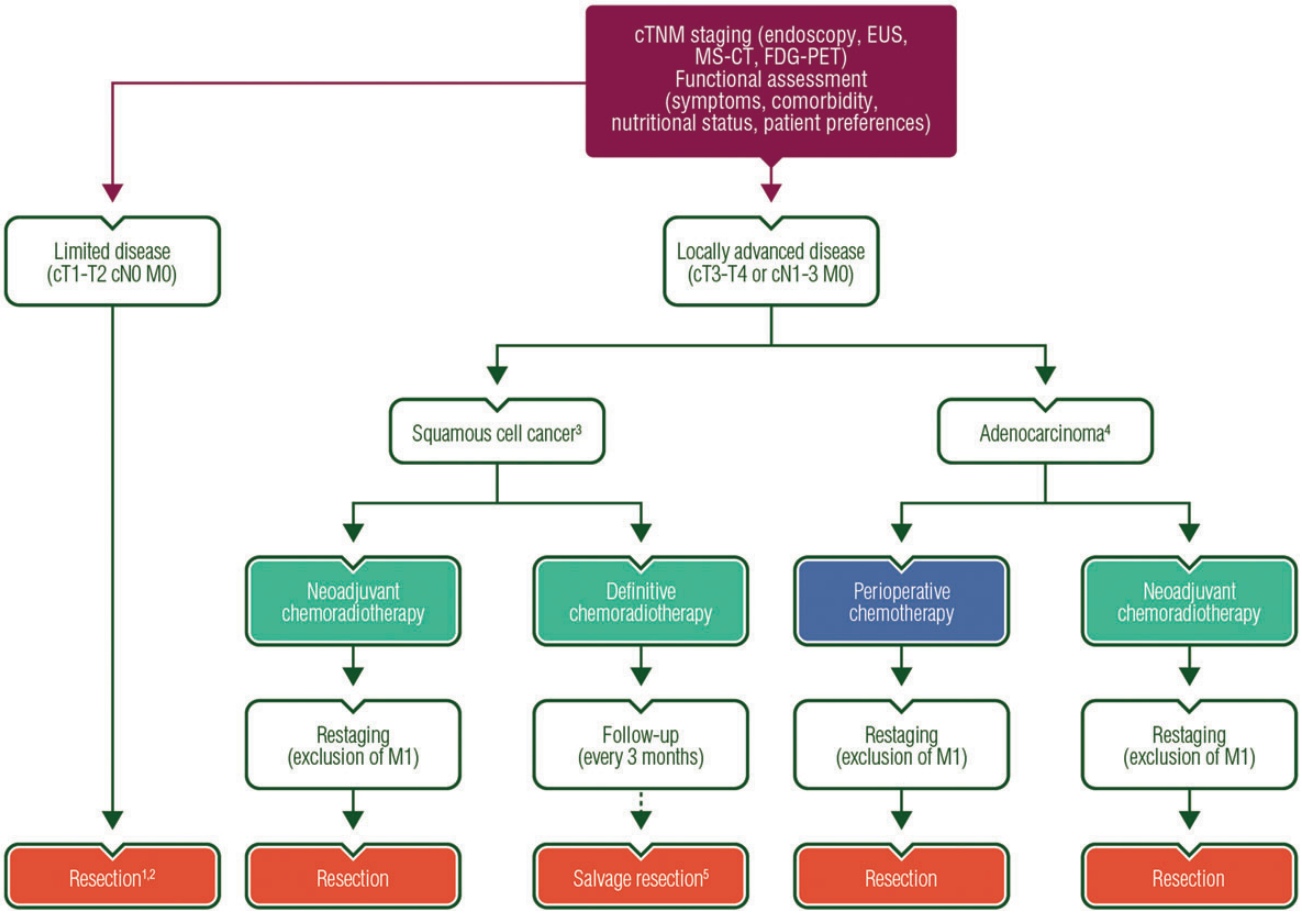

Figure 1. Algorithm for the treatment of local/locoregional resectable thoracic oesophageal cancer. EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose-positron emission tomography; MS-CT, multislice-computed tomography; cTNM, clinical tumour, node, metastases classification according to AJCC/UICC [8]; CRT, chemoradiotherapy; OS, overall survival. [1]Criteria for endoscopic instead of surgical resection are specified in the text. [2]For patients unable or unwilling to undergo surgery, combined CRT is superior to radiotherapy alone. [3]Evidence suggests that neoadjuvant CRT followed by surgery and definitive CRT are equally effective with regard to overall survival. Oesophageal surgery should be carried out in experienced (high volume) centres only. For patients not willing to undergo oesophageal surgery or who are medically unfit for major surgery, definitive chemoradiotherapy should be preferred. Even many experienced centres prefer definitive CRT for oesophageal tumours with a very proximal/cervical location. [4]Sufficient evidence supports the use of perioperative chemotherapy as well as neoadjuvant CRT. Both standards can be recommended with an equal level of evidence/grade of recommendation [I, A]. Several ongoing studies in Europe are comparing both modalities. Inclusion of patients in one of these studies is encouraged. Some centres prefer neoadjuvant CRT for tumours of the oesophagus and AEG type I or II according to the Siewert's classification, while they use perioperative chemotherapy for AEG type III or II, but this is only a pragmatic solution not currently supported by scientific evidence. [5]This is optional in the case of incomplete response to CRT or local relapse. This should be carried out only in selected patients and experienced centres.

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are both regarded as effective endoscopic resection techniques. Similar cure rates compared with surgical resection have been reported in specialised centres [12]. Furthermore, in patients with superficial submucosal infiltration of an AC, but without further risk criteria (pT1sm1; <500 µm invasion, L0, V0, G1/2, <20 mm diameter, no ulceration), endoscopic resection can be considered as an alternative to oesophagectomy, but outcomes are still more limited than in mucosal AC [IV, B]. In the case of a high-grade intraepithelial neoplasia or a mucosal carcinoma (L0, V0, no ulceration, grading G1/G2, infiltration grade m1/m2) in the squamous epithelium, an endoscopic en bloc resection should be carried out [III, A]. ESD should be preferred over EMR, especially in lesions >15 mm, as in Japanese studies en bloc resection rate and the rate of R0 en bloc resections were shown to be higher with ESD [II, B]. In addition, relapses occurred less often [13].

Radical and transthoracic oesophagectomy (Ivor-Lewis procedure) is the surgical technique of choice [I, B] in localised oesophageal cancer beyond very early stages (T1a N0). A prospective randomised study showed a strong trend towards better survival outcomes for this approach in resectable stage I–IV AC and OGJ AC, compared with less radical transhiatal resection in AC of the oesophagus [14]. Details concerning endoscopic and surgical resection techniques are not in the scope of this article but can be found elsewhere [15, 16]. The role of a minimally invasive approach to the thoracic and/or abdominal cavities is increasing in clinical practice. Recent randomised studies suggest that either thoracoscopic oesophagectomy or Ivor-Lewis procedure with laparoscopic gastric mobilisation and open right thoracotomy

(called hybrid minimally invasive oesophagectomy) have led to significantly lower postoperative complication rates, especially pulmonary complications. For hybrid minimally invasive oesophagectomy, it was also demonstrated that short-term oncological outcomes, compared with classical Ivor-Lewis procedure, are not deteriorated [17, 18]. Laparoscopic gastric mobilisation is now the standard procedure, based on the results of two randomised, controlled trials [II, A]. The additional role of thoracoscopic dissection should be confirmed in additional randomised studies, as well as its long-term oncological outcome/safety. If done, the procedure should be carried out in expert centres for selected patients with small tumours.

Of note, the results of large, multicentre studies in different health systems provide sufficient evidence to support the centralisation of oesophagectomy to high volume centres, with a lower rate of morbidity and better infrastructure to deal with complications following major surgery, thereby preventing further mortality [I, A] [19–21].

The value of preoperative treatment in limited disease is uncertain, as the number of patients who have been included in prospective randomised clinical trials is small [22–25]. A recent randomised study involving 195 patients with stage I and stage II oesophageal cancer showed that compared with surgery alone, neoadjuvant chemoradiotherapy (CRT) with cisplatin plus fluorouracil did not improve R0 resection rate or survival but enhances postoperative mortality. The results of this study also suggest that surgery alone should be recommended as the primary treatment approach for cT2N0 oesophageal cancer, despite 50% of patients having nodal disease at the time of surgery [II, B] [26, 27].

For patients unable or unwilling to undergo surgery, combined CRT is superior to radiotherapy (RT) alone [II, A] [21]. Four courses of cisplatin/5-fluorouracil (5-FU) combined with radiation doses of 50.4 Gy in fractions of 1.8 Gy are regarded as standard for definitive CRT. Alternatively, six cycles of oxaliplatin/5-FU/folinic acid (FOLFOX) can be given [I, C] [28]. Recent evolutions in technology with intensity-modulated and volumetric arc RT combined with functional imaging allow for increased radiation doses up to 60 Gy in fractions of 1.8–2.0 Gy, frequently using a simultaneously integrated boost. This approach allows for shortening the overall treatment time, which is advantageous especially in SCC of the oesophagus. There is insufficient evidence at this time to state that increased doses of RT improve survival in oesophageal cancer [29], as the results of randomised studies evaluating the safety and oncological benefits of RT doses higher than 50.4 Gy are not yet available. This is of importance if salvage oesophagectomy is considered as a therapeutic strategy, since doses higher than 55 Gy have shown to be linked with increased postoperative mortality and morbidity [30].

locally advanced disease (cT3–T4 or cN1-3 M0)

Surgery alone is not a standard treatment in locally advanced disease, since a complete (R0) tumour resection cannot be achieved in ~30% (T3) to 50% (T4) of cases. Furthermore, even after complete tumour resection, long-term survival rarely exceeds 20%. Of note, preoperative treatment (chemotherapy or CRT) has been shown to increase R0 resection and survival rates [22–25, 31, 32]. Therefore, preoperative treatment is clearly indicated in operable patients with locally advanced oesophageal cancer [I, A].

squamous cell carcinoma: Meta-analyses and a recent phase III study [20, 22, 23, 31] demonstrate that patients with locally advanced disease benefit from preoperative chemotherapy or, most likely to a greater extent, from preoperative CRT, with higher rates of complete tumour resection and better local tumour control and survival [I, A]. It was suggested in the past that preoperative CRT may also increase postoperative mortality rates, but this has not been the case when treatment is carried out in expert centres, with modern radiation planning techniques, use of adequate radiation doses and fractionation and a good multidisciplinary cooperation and infrastructure. On the basis of the results of the *Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study* (CROSS) [31, 32], the weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/ml/min) and paclitaxel (50 mg/m^2 of body-surface area) for 5 weeks and concurrent RT (41.4 Gy in 23 fractions, 5 days per week), followed by surgery, can be recommended as a contemporary standard of care [I, A]. However, only patients with clinical stage T1N1 or T2-3N0-1 were included in that trial.

Two prospective, randomised controlled studies resulted in equivalent overall survival (OS) outcomes of definitive CRT without surgery compared with neoadjuvant CRT followed by surgery, although the non-operative strategy was associated with higher local tumour recurrence rates [33, 34]. Therefore, neoadjuvant CRT with planned surgery or definitive CRT with close surveillance and salvage surgery for local tumour persistence or progression [30] can be considered to be the recommended definitive treatments for locally advanced SCC of the oesophagus [II, B] [22]. However, there are currently no data comparing neoadjuvant CRT + surgery versus definitive CRT and salvage surgery on demand. Definitive CRT is recommended for cervically localised tumours [III, B].

For patients unable or unwilling to undergo surgery, treatment recommendations from the 'limited disease' section may be adapted.

adenocarcinoma: On the basis of the recent meta-analyses and the largest prospective randomised controlled studies, perioperative chemotherapy with regimens containing a platinum and a fluoropyrimidine for a duration of 8–9 weeks in the preoperative phase (as well as 8-9 weeks in the postoperative phase, if feasible) or preoperative CRT (41.4–50.5 Gy) should be considered standard in locally advanced AC of the oesophagus, including OGJ cancers [I, A] [22–25]. Direct comparison of chemotherapy versus CRT is scarce. Smaller randomised studies have shown that the addition of RT to neoadjuvant chemotherapy results in higher histologically complete response rates, higher R0 resection rates and a lower frequency of lymph-node metastases, without significantly affecting survival. In one of two studies, postoperative mortality was increased after neoadjuvant CRT [35, 36].

Chemotherapy with cisplatin/5-FU combined with 41.4–50.4 Gy in fractions of 1.8–2.0 Gy has long been the standard treatment, but two recent randomised trials showed a favourable toxicity profile for (bi)weekly combinations of oxaliplatin/5-FU or carboplatin/paclitaxel with RT [28, 31, 32].

Even after complete tumour response to preoperative chemo (radio)therapy, operable patients with AC should proceed to surgery [IV, C].

management of advanced/metastatic disease (M1)

Patients with metastatic oesophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [I, B] [37].

Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with AC who have a good PS [III, B]. Despite scarce evidence, treatment of advanced oesophageal AC is managed mostly according to the recommendations for gastric cancer [38]. Newer regimens based on oxaliplatin/fluoropyrimidine combinations are an alternative to the 'classical' cisplatin/5-FU schedule. Infusional 5-FU may be replaced by capecitabine if the swallowing of tablets is not compromised. Taxanes are recommended in first-line combinations or as monotherapy in second-line therapy.

In SCC, the value of palliative chemotherapy is less proved. Cisplatin-based combinations showed increased response rates but no survival gain compared with monotherapy. Overall, results with palliative chemotherapy are inferior to those in AC. Therefore, best supportive care (BSC) or palliative monotherapy should also be considered [II, B].

personalised medicine

Randomised data with biologically targeted medical therapies are limited in oesophageal carcinoma. For treating patients with human epidermal growth factor receptor 2 (HER2)-positive AC, the recommendations of the ESMO gastric cancer guidelines should be followed [38]. Consequently, HER2-positive metastatic AC should be treated with a trastuzumab-containing regimen [II, B]. In contrast, other biologically targeted drugs like the EGFR inhibitor gefitinib were not effective in post-progression treatment of oesophageal cancer [39].

Response to neoadjuvant treatment is routinely assessed by the evaluation of tumour-related symptoms, endoscopy and CT scan. Patients with a curative treatment intention should be referred to surgery independently of the tumour response, except in the case of metastatic disease. Usually, complete morphological responders should be operated in the case of AC, as the evidence for a watch-and-wait strategy is sparse for this histological subtype, whereas for SCC, the benefit/risk balance between surgery and close surveillance should be discussed.

Tumour response to chemotherapy may be predicted early by FDG-PET in oesophageal and OGJ AC [III, C] [40]. However, at the present time, changing the therapeutic strategy according to early response assessment is investigational. FDG-PET is not relevant for evaluating tumour response after CRT, as it cannot reliably identify complete responders.

A personalised medicine synopsis is given in Table 2.

follow-up, long-term implications and survivorship

Except for those patients who may be potential candidates for an endoscopic re-intervention or an early 'salvage surgery' after

Table 2. Personalised medicine synopsis table for lower oesophageal and gastric cancer

Biomarker	Method	Use	LOE, GOR
HER2	Immunohistochemistry for HER2 protein expression or ISH for HER2 gene amplification	Used to select patients with metastatic disease for treatment with a trastuzumab-containing regimen	II, B

HER2, human epidermal growth factor receptor 2; ISH, *in situ* hybridisation; LOE, level of evidence; GOR, grade of recommendation

Table 3. Summary of recommendations

Diagnosis and pathology/molecular biology
All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis, weight loss and/or loss of appetite should undergo an upper intestinal endoscopy [III, A]. Immunohistochemical stainings are recommended in poorly and undifferentiated cancers (G 3/4) according to WHO to differentiate between SCC and AC of the oesophagus [V, B].
Staging and risk assessment
Decisions on the initial treatment approach of oesophageal cancer are taken on the basis of clinical staging, which should be carried out with the highest degree of accuracy possible. Staging should include a complete clinical examination and a CT scan of the neck, chest and abdomen [III, A]. In candidates for surgical resection, EUS should be carried out to evaluate the T and N tumour categories [III, B]. ^{18}F-FDG-PET should be carried out in patients who are candidates for oesophagectomy [III, B]. In the case of oesophageal SCC due to chronic tobacco and alcohol consumption, meticulous investigation of the oral cavity, oropharynx and hypopharynx by an ear, nose and throat specialist, as well as trachea-bronchoscopy to exclude synchronous second cancers in the aerodigestive tract, should be carried out [IV, B].

Continued

Table 3. *Continued*

In locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomic cardia, laparoscopy can be done [IV, C].
The nutritional status and history of weight loss should be assessed according to the ESPEN guidelines [III, A].
Nutritional support according to the ESPEN guidelines is an integral part of the medical care for patients with oesophageal cancer in the curative and in the palliative setting [II, A].
Management of local/locoregional disease
Upfront interdisciplinary planning of the treatment is mandatory [III, A].
Nutritional status matters and should be corrected. Endoscopic stenting should not be used in locoregional disease in operable patients and alternative routes of feeding, e.g. with needle catheter jejunostomy, should be preferred [II, A].
Surgery is the treatment of choice in limited disease. In patients with T1a AC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated [II, A].
In patients with superficial submucosal infiltration of an AC without further risk criteria (pT1sm1; <500 µm invasion, L0, V0, G1/2, <20 mm diameter, no ulceration), endoscopic resection can be considered as an alternative to oesophagectomy [IV, B].
In the case of a high-grade intraepithelial neoplasia or a mucosal carcinoma (L0, V0, no ulceration, grading G1/G2, infiltration grade m1/m2) in the squamous epithelium, an endoscopic en bloc resection should be carried out [III, A].
ESD should be preferred over endoscopic mucosa resection, especially in lesions >15 mm [II, B].
In T1/T2 N0 oesophageal cancer, radical and transthoracic oesophagectomy (Ivor-Lewis procedure) should be the surgical technique of choice [I, B].
Oesophagectomy should be done in high volume centres, with a lower rate of morbidity and better infrastructure to deal with complications following major surgery, thereby preventing further mortality [I, A].
Surgery alone (without neoadjuvant treatment) should be recommended as the primary treatment approach for *c*T2N0 oesophageal cancer [II, B].
For patients unable or unwilling to undergo surgery, combined CRT is superior to RT alone [II, A].
Four courses of cisplatin/5-FU combined with radiation doses of 50.4 Gy in fractions of 1.8 Gy are regarded as standard for definitive CRT. Alternatively, six cycles of FOLFOX can be given [I, C].
Preoperative treatment is indicated in operable patients with locally advanced oesophageal cancer (*c*T3–T4 or cN1–3 M0) [I, A].
Patients with locally advanced SCC benefit from preoperative chemotherapy or, most likely to a greater extent, from preoperative CRT, with higher rates of complete tumour resection and better local tumour control and survival [I, A].
For patients with squamous cell oesophageal cancer, weekly administration of carboplatin (area under the curve of 2 mg/ml/min) and paclitaxel (50 mg/m^2) for 5 weeks and concurrent RT (41.4 Gy in 23 fractions, 5 days/week), followed by surgery, can be recommended as a contemporary standard of care [I, A].
Neoadjuvant CRT with planned surgery or definitive CRT with close surveillance and salvage surgery for local tumour persistence or progression can be considered as a recommended definitive treatment for locally advanced squamous cell cancer of the oesophagus [II, B].
Definitive CRT is recommended for cervically localised tumours [III, B].
For patients with oesophageal AC perioperative chemotherapy with regimens containing a platinum and a fluoropyrimidine for a duration of 8–9 weeks in the preoperative phase (as well as 8–9 weeks in the postoperative phase, if feasible) or preoperative chemoradiotherapy (41.4–50.5 Gy) should be considered standard in locally advanced AC of the oesophagus, including OGJ cancers [I, A].
Even after complete tumour response to preoperative chemo(radio)therapy operable patients with AC should proceed to surgery [IV, C].
Management of advanced/metastatic disease
Patients with metastatic oesophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [I, B].
Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with AC who have a good PS [III, B].
In squamous cell oesophageal cancer, the value of palliative combination chemotherapy is less proved. Therefore, BSC or palliative monotherapy should also be considered [II, B].
Personalised medicine
HER2-positive metastatic AC should be treated with a trastuzumab-containing treatment [II, B].
Tumour response to chemotherapy may be predicted early by 18F-FDG-PET in oesophageal and OGJ AC [III, C].
Follow-up, long-term implications and survivorship
Follow-up visits should be concentrated on symptoms, nutrition and psychosocial support [V, D].
In the case of complete response to CRT and no operation, a 3-month follow-up based on endoscopy, biopsies and CT scan may be recommended to detect early recurrence leading to a discussion about salvage surgery [IV, B].

WHO, World Health Organization; SCC, squamous cell carcinoma; AC, adenocarcinoma; CT, computed tomography; EUS, endoscopic ultrasound; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; OGJ, oesophago-gastric junction; ESPEN, European Society for Clinical Nutrition and Metabolism; ESD, endoscopic submucosal dissection; CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; FOLFOX, oxaliplatin/5-FU/folinic acid; RT, radiotherapy; PS, performance status; BSC, best supportive care

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [41].

(failing) endoscopic resection or definitive CRT, there is no evidence that regular follow-up after initial therapy has an impact on survival outcomes.

Therefore, follow-up visits should concentrate on symptoms, nutrition and psychosocial support [V, D]. Often, during the follow-up phase, a multidisciplinary care team is required, coordinated by the physician who is seeing the patient on a regular basis. Every patient will develop a variety of needs and problems, which are related to the new condition of life without an oesophagus or to other treatment sequelae or to psychosocial needs. The expertise of a dietician, a radiologist, a gastroenterologist, a psychologist and a social worker is often needed during follow-up.

In the case of complete response to CRT and no operation, a 3-month follow-up based on endoscopy, biopsies and CT scan may be recommended to detect early recurrence leading to a discussion about salvage surgery [IV, B] [28].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 3, and an overview of these recommendations related to therapy is shown in Figure 1. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4 [41]. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

FL has received research support from GlaxoSmithKline and Fresenius Biotech; lecture and advisory honoraria from Amgen, Biontech, Bristol-Myers Squibb, Eli Lilly, Ganymed, Merck-Serono, MSD, Nordic and Roche; travel support from Amgen, Bayer, Roche and Taiho. CM has reported research grants from Nestlé; lecture honoraria from Merck-Serono, Nestlé, Roche and Sanofi; travel grants from Ethicon, Bard and Roche. RO has received lecture and advisory honoraria from Amgen, Roche, Eli Lilly and Nordic and has received travel support from Merck, Bayer and Roche. DA has reported honoraria/consultancy for Roche, Merck-Serono, Bayer, Lilly and Servier; research support from Roche. KH has reported no potential conflicts of interest.

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