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

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incidence and epidemiology

The crude incidence of oesophageal cancer in the European Union (EU) is about 4.5 cases/100 000/year (43 700 cases) with considerable geographical differences within the EU ranging from 3/100 000 in Greece up to 10/100 000 in France [1]. The age adjusted mortality is about 5.4/100 000/year (20 750 deaths) in men and 1.1/100 000/year (6 950 deaths) in women, respectively. The main risk factors for squamous cell carcinomas (SCCs) in Western countries are smoking and alcohol consumption, whereas adenocarcinomas (ACs) predominantly occur in patients with gastro-oesophageal reflux disease and their risk is correlated with the patient's body-mass index. While the incidence of SCC remains stable, the incidence of AC, particularly in the lower oesophagus, is rapidly rising in Western countries [2] and it now constitutes more than half of all oesophageal cancer cases.

diagnosis and pathology

The diagnosis should be made from an endoscopic biopsy with the histology to be classified according to the World Health Organization criteria. Small cell carcinomas, which are very uncommon, must be identified and separated from SCCs and ACs and be treated accordingly.

staging and risk assessment

Since therapeutic strategy is based on clinical staging, all efforts should be made to assess the optimal pre-therapeutic tumour stage.

Staging should include clinical examination, blood count, liver-, pulmonary- and renal function tests, endoscopy (including upper-aerodigestive tract endoscopy in case of tumours at or above the tracheal bifurcation), and a computed tomography (CT) scan of chest and abdomen. In candidates for surgical resection endoscopic ultrasound and positron emission tomography (PET)-CT should be added in order to evaluate the T- and N-category of the tumour. Nevertheless, the accuracy of clinical N-staging does not exceed 80%.

Moreover, PET (or PET-CT) may be helpful in identifying otherwise undetected distant metastases [II, B].

In locally advanced (T3/T4) ACs of the oesophago-gastric junction (OGJ) infiltrating the anatomic cardia, laparoscopy can be added to rule out peritoneal metastases which are found in about 15% of patients [III, B]. With this procedure, the sensitivity for detecting peritoneal metastases was 70% compared with about 15% with ultrasound or CT scan.

For selection of local treatments, tumours should be ascribed to the cervical or intrathoracic oesophagus or to the OGJ [IV, C].

The stage is to be given according to the American Joint Cancer Committee (AJCC)/Union for International Cancer Control (UICC) TNM system with corresponding stage grouping (7th edition) (Table 1) [3]. Of note, lymph node metastases in the region of the coeliac trunk and in para-oesophageal nodes in the neck are now defined as regional metastases.

treatment

principles of treatment

Upfront interdisciplinary planning of the treatment is mandatory. The main factors for selecting primary therapy are tumour stage and location, histological type and the medical condition, as well as considerations from patients. Independent prognostic factors for long-term survival comprise N/T category and grading for AC as well as N/T category and localisation for SCC [4].

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Table 1. TNM staging for esophageal cancer (AJCC/UICC 7th Edition) [3]

Definition of TNM (2009)			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*/High-grade dysplasia		
T1	Tumor invades lamina propria, or sub-mucosa		
T1a	Tumor invades mucosa or lamina propria or muscularis mucosae		
T1b	Tumor invades sub-mucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades adventitia		
T4	Tumor invades adjacent structures		
T4a	Tumor invades pleura, pericardium, diaphragm or adjacent peritoneum		
T4b	Tumor invades other adjacent structures such as aorta, vertebral body or treachea		
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 esophagus and gastro-esophageal 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 tumor, are those in the esophageal drainage area including coeliac axis nodes and paraesophageal nodes in the neck but not supraclavicular nodes.

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Handbook, 7th ed. New York, NY.: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Surgery alone is regarded as standard treatment only in carefully selected operable patients with localised SCC (T1-2 N0-3 M0) [II, B].

Transthoracic oesophagectomy with two-field lymph node dissection and a gastric tube anastomosed in the left neck (supra-bifurcal tumours) or in the upper thorax is recommended [5] for intrathoracic SCC [III, B]. Minimally invasive techniques have been introduced to reduce post-operative complication rates and recovery times. Debates continue as to whether these challenging techniques decrease morbidity and whether the oncological outcome is compromised. Part of this answer is given in a recent randomised trial [6], showing a threefold decrease in post-operative pulmonary infection rate after totally mini-invasive oesophagectomy compared with open transthoracic surgery. Open surgery remains the standard of care. No standard surgical treatment can be identified for carcinomas of the cervical oesophagus.

The extent of surgery in ACs is still a matter of debate. One randomised study showed a non-significant improvement in long-term survival for extended transthoracic compared with transhiatal resection [7], but this benefit appears to be restricted to patients with AC of the lower oesophagus (type I according to Siewert classification) [8].

Preoperative or post-operative radiation alone (without chemotherapy) does not add any survival benefit to surgery alone [9]. This treatment is not recommended for curative intent in localised tumours [I, A].

Evidence for clinical benefit from *preoperative chemotherapy* exists for all types of oesophageal cancer, though it is stronger for AC. Patients with AC of the lower oesophagus/OGJ should be managed with pre- and post-operative chemotherapy (or chemoradiation)[10–12] [I, B].

A couple of meta-analyses and two recent phase III trials [13–16] suggested that *preoperative chemoradiation* confers a survival benefit [I, B], and it appears that patients benefit with increased tumour down-staging from preoperative chemoradiation [III, B]. Of note, post-operative mortality may be increased.

Data on *adjuvant chemo(radio)therapy* is limited, except for lower oesophageal/OGJ AC after limited surgery (lymph node dissection D1 and less). Therefore, adjuvant therapy is not recommended.

Selected *unfit patients* with localised tumours not considered for surgery can be treated with (also) curative intent with combined chemoradiation [16–18]. Otherwise, principles of palliative therapy are recommended for these patients (see treatment of metastatic disease).

management of locoregional disease (M0)

limited disease (Tis-T2 N0 or N1-3)

Surgery is the treatment of choice in *early cancer* (Tis-T1a N0). Endoscopic resection is a treatment option for selected patients as similar cure rates in specialised centres have been reported [19] [II, B].

For *localised disease without suspected lymph node involvement* (T1-2 N0M0), surgery is regarded as a standard treatment [II, B]. However, long-term survival does not exceed 25% if regional lymph nodes are involved (pN1-3). Therefore, preoperative treatment can also be justified.

For *localised disease with suspected lymph node involvement* (T1-2N1-3M0), preoperative therapy is recommended in patients with AC.

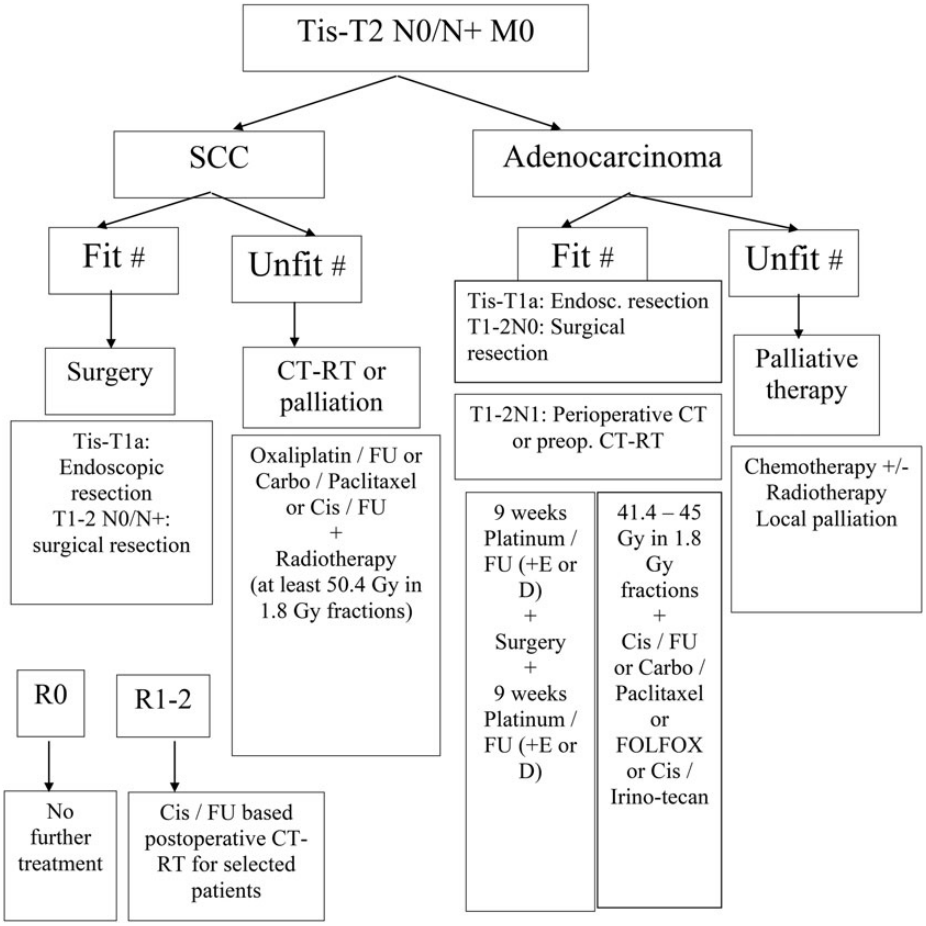

Figure 1. Algorithm for the treatment of limited disease. CT, chemotherapy; RT, radiotherapy; Cis, cisplatin; Carbo, carboplatin; FU, fluorouracil; E, epirubicin; D, docetaxel; R0, complete resection; R1-2, incomplete resection; #, fit means medically operable according to local standards of the treating centre (excluding patients with poor performance status, respiratory insufficiency, portal hypertension, renal insufficiency, recent myocardial infarction and advanced peripheral arterial disease).

Meta-analyses showed a small but significant benefit for preoperative chemotherapy [12, 13], but they included very limited numbers of patients with localised tumours (e.g. tumour category T1-2).

A couple of meta-analyses in unselected patient groups revealed a significant benefit for preoperative chemoradiation. The extent of this benefit was smaller for patients with T2 tumours [20]. A French phase III trial (FFCD 9901) predominantly in localised SCC did not show increased survival with preoperative chemoradiation.

Studies with post-operative chemotherapy in oesophageal SCC have been carried out in Asian patients only. In a randomised Japanese trial, adjuvant chemotherapy was inferior to the identical neoadjuvant therapy. This treatment is not recommended.

Data with adjuvant chemotherapy in oesophageal AC may be extrapolated from studies and meta-analyses in gastric cancer. Therefore, the recommendations of the gastric cancer guideline may be followed.

For patients unable or unwilling to undergo surgery, combined chemoradiation is superior to radiotherapy alone [21] [I, A]. 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 treatment of definitive radiotherapy in the United States. Increased radiation doses up to 60 Gy in fractions of 1.8–2.0 Gy are recommended in parts of Europe and Japan for definitive chemoradiotherapy. This is due to an obvious dose–response correlation of radiotherapy in oesophageal cancer and the positive experience with these radiation doses in prospective multicentre trials [16, 17] (Figure 1).

locally advanced disease (T3-T4 N0-3 M0)

Surgery alone is not a standard treatment in these stages since a complete (R0) tumour resection is not possible in about 30% (pT3) to 50% (pT4). Furthermore, even after complete tumour resection, long-term survival rarely exceeds 20%. Therefore, preoperative treatment is clearly indicated in operable patients.

squamous cell carcinoma. A couple of meta-analyses and two recent phase III trials [12–15] demonstrate that patients with locally advanced disease benefit from preoperative chemotherapy or, most likely to a greater extent, from preoperative chemoradiation, with higher rates of complete tumour resection and better local tumour control and survival

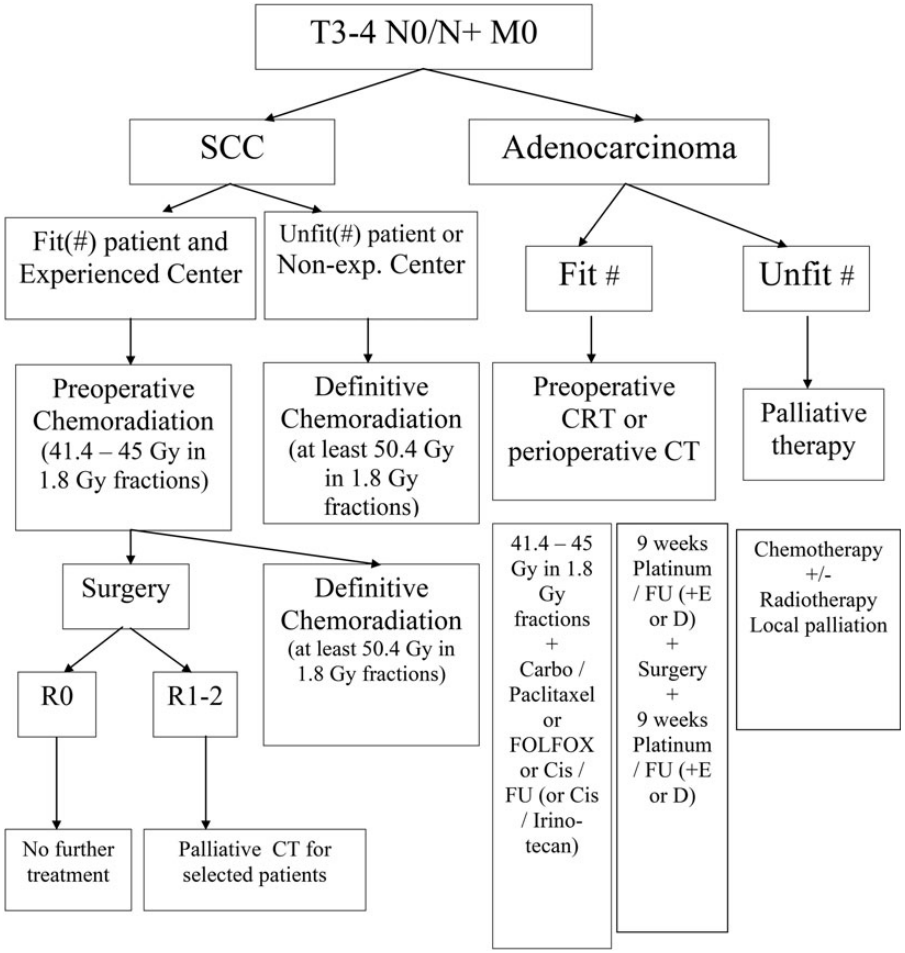

Figure 2. Algorithm for the treatment of locally advanced disease. CT, chemotherapy; RT, radiotherapy; Cis, cisplatin; Carbo, carboplatin; FU, fluorouracil; E, epirubicin; D, docetaxel; R0, complete resection; R1-2, incomplete resection; #, fit means medically operable according to local standards of the treating centre (excluding patients with poor performance status, respiratory insufficiency, portal hypertension, renal insufficiency, recent myocardial infarction and advanced peripheral arterial disease).

[I, A]. It is suggested, however, that preoperative chemoradiation will also increase post-operative mortality rates. In cases of response to neoadjuvant chemo(radio)therapy (40–50 Gy), further continuation of chemoradiation resulted in equivalent overall survival compared with surgery, albeit that the non-operative strategy was associated with higher local tumour recurrence [16, 17]. Therefore, chemoradiotherapy with planned surgery or definitive chemoradiotherapy with close surveillance, and salvage surgery for local tumour persistence or local tumour progression, may be considered as a definitive treatment of selected patients with locally advanced disease [22] [I, B]. Experienced multidisciplinary teamwork is warranted for this treatment approach and post-operative mortality will increase with the dose of radiotherapy applied.

Definitive chemoradiotherapy 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. Perioperative chemotherapy with cisplatin and 5-FU should be considered standard in locally advanced AC of OGJ [10–12] [I, A]. Preoperative chemoradiotherapy is preferred in oesophageal AC for selected patients, since meta-analyses and a recent phase III trial [12, 15] revealed a significant survival benefit for AC. This benefit was particularly seen in high-risk patients, e.g. those with locally more advanced stages. The preference for chemoradiotherapy is also supported by the results of a phase III study which compared chemoradiotherapy to chemotherapy before surgery [23]. Chemotherapy with cisplatin/5-FU combined with 41.4–50.4 Gy in fractions of 1.8–2.0 Gy has long been standard treatment, but two recent randomised trials showed a favourable toxicity profile for (bi)weekly combinations of oxaliplatin/5-FU or carboplatin/paclitaxel with radiotherapy [15, 24].

Even after complete tumour response to preoperative chemo(radio)therapy operable patients with AC should proceed to surgery [IV, C] (Figure 2).

Table 2. Levels of evidence and grades of recommendation (adapted with permission 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]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

management of 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 percutaneous radio(chemo)therapy, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [25] [I, B].

Chemotherapy is indicated for palliative treatment in selected patients [III, B], particularly for patients with AC who have a good performance status. Newer regimens based on oxaliplatin/fluoropyrimidine combinations are an alternative to the 'classical' cisplatin/5-FU schedule [26]. Infusional 5-FU may be replaced by capecitabine if swallowing of tablets is not compromised. As in gastric cancer, taxanes are recommended in first-line combinations or as monotherapy in second-line therapy also in AC of OGJ.

In SCC, the value of palliative chemotherapy is less proven. 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 or palliative monotherapy has also to be considered.

personalised medicine

Randomised data with biologically targeted medical therapies are limited in oesophageal carcinoma. For treating patients with HER2-positive tumours, the recommendations of the gastric cancer guideline should be followed.

response evaluation

Response is routinely evaluated by evaluation of tumour related symptoms, endoscopy, and CT scan. In case of local tumour progression of (still) locoregional manifestations, the potential benefit of a surgical intervention must be discussed by a multi-disciplinary board. If distant metastases may be detected, the recommendations for metastatic disease should be followed.

Biopsies may be taken after neoadjuvant intended chemo-radiotherapy in case a patient has increased operative risks, and surgery may be omitted if a complete tumour remission will be documented. However, this is not a standard procedure. Additionally, tumour response to chemotherapy may be predicted early by fluor-18-fluorodeoxyglucose(FDG)-PET (-CT) in oesophago-gastric AC [27] [III, C]. However, at the present time, this will not change the therapeutic strategy.

follow-up and long-term implications

Except for those patients who may be potential candidates for an early 'salvage surgery' after (failing) endoscopic resection or definitive chemoradiation, there is no evidence that regular follow-up after initial therapy may have impact on the outcome. Follow-up visits should be concentrated on symptoms, nutrition and psycho-social support [IV, D].

summary of recommendations. An overview of recommendations related to therapy is given on Figure 1.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 2. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Prof. Arnold has reported research grants from Roche and Sanofi. The other authors have reported no potential conflicts of interest.

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