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Esophageal cancer: Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The crude incidence of esophageal cancer in the European Union (EU) is ∼4.5 cases/100 000/year (43 700 cases) with considerable geographical differences along the EU ranging from 3/100 000 in Greece up to10/100 000 in France. The age adjusted mortality is ∼5.4/100 000/year (20 750 deaths) in men and 1.1/100 000/year (6950 deaths) in women. 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 gastroesophageal reflux disease and their risk is correlated with the patient's body–mass index. The incidence of AC is rapidly rising in Western countries and it now constitutes approximately half of all esophageal cancer cases.

diagnosis

The diagnosis should be made from an endoscopic biopsy with the histology to be given according to 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

Staging should include clinical examination, blood counts, liver-, pulmonary- and renal function tests, endoscopy (including upper-aerodigestive tract endoscopy in case of tumors at or above the tracheal bifurcation), and a CT scan of chest and abdomen. In candidates for surgical resection endoscopic ultrasound has to be added to evaluate the T (and N) stage of the tumor; an esophagogram can be performed to assist in the planning of the surgical procedure [II, B]. When available, positron emission tomography (PET) may be helpful in identifying otherwise undetected distant metastases or in diagnosis of suspected recurrence [II, B]. PET/CT is preferred over PET alone.

In locally advanced (T3/T4) adenocarcinomas of the esophago-gastric junction (EGJ) infiltrating the anatomic cardia, laparoscopy can rule out peritoneal metastases [II, A].

For selection of local treatments the tumors should be assigned to the cervical or intrathoracic esophagus or to the EGJ [IV, C].

The stage is to be given to the TNM system with corresponding American Joint Committee on Cancer stage grouping. Of note, the updated seventh edition of the International Union Against Cancer classification will be valid from January 2010 (Table 1).

treatment

principles of treatment

Primary interdisciplinary planning of the treatment is mandatory. The main factors for selecting primary therapy are tumor stage and location, histological type and the medical condition as well as the requests of the patients. Selected unfit patients with localized tumors not considered for surgery can be treated with curative intent by combined chemoradiation. Otherwise, principles of palliative therapy are recommended for these patients (see treatment of metastatic disease).

Surgery is regarded as standard treatment only in carefully selected operable patients with localized tumors. Transthoracic esophagectomy with two-field lymph node resection and a gastric tube anastomosized in the left neck is recommended for intrathoracic SCC [III, B]. No standard treatment can be identified for carcinomas of the cervical esophagus. The extent of surgery in ACs is still a matter of debate, since one randomized study showed a non-significant improvement in long-term survival for extended transthoracic compared with transhiatal resection.

Preoperative (with and without postoperative) radiation does not add any survival benefit to surgery alone. This treatment is not recommended [I, A].

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Table 1. American Joint Commission on Cancer staging for esophageal cancer

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, muscularis mucosae or submucosa		
T1a	Tumor invades mucosa or lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades adventitia		
T4	Tumor invades adjacent structures		
T4a	Tumor invades peura, pericardium or diaphragm		
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 or 2 regional lymph nodes		
N2	Metastasis in 3–6 regional lymph nodes		
N3	Metastasis in ≥7 regional lymph nodes		
The regional lymph nodes, irrespective of the site of the primary tumor, are those in the esophgeal drainage area including coeliac axis nodes and paraesophageal nodes in the neck but not supraclavicular nodes.			
Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping: carcinomas of the esophagus and EGJ			
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

Evidence for clinical benefit from preoperative chemotherapy exists for all types of esophageal cancer, though it is stronger for AC. Patients with AC of the lower esophagus/EGJ should be managed with pre- and postoperative chemotherapy [I, B].

Although meta-analyses and one recent Phase III trial suggested that preoperative chemoradiation confers a survival benefit, it is not clear which patients (stage, tumor location, histology) will most benefit from this preoperative treatment [I, B] and postoperative mortality appears to be increased.

Data on adjuvant chemo(radio)therapy is limited, except for lower esohageal / EGJ adenocarcinomas after limited surgery (lymph node dissection D1 and less).

The value of targeted therapy is not proven in localized esophageal cancer.

treatment of limited disease (Tis–T2 N0–1 M0)

Surgery is the treatment of choice in **early cancer** (Tis–T1a N0). Endoscopic resection is a treatment option for selected patients gaining equal cure rates in specialized centers [II, B].

Surgery is regarded as standard treatment of **localized disease** (T1–2 N0–1 M0), although long-term survival does not exceed 25% if regional lymph nodes are involved.

For patients unable or unwilling to undergo surgery, combined chemoradiation is superior to radiotherapy alone [Ia, A]. Four courses of cisplatin/5-fluorouracil (5-FU) combined with radiation doses of 50.4 Gy are regarded as standard treatment in the USA. Increased radiation doses up to

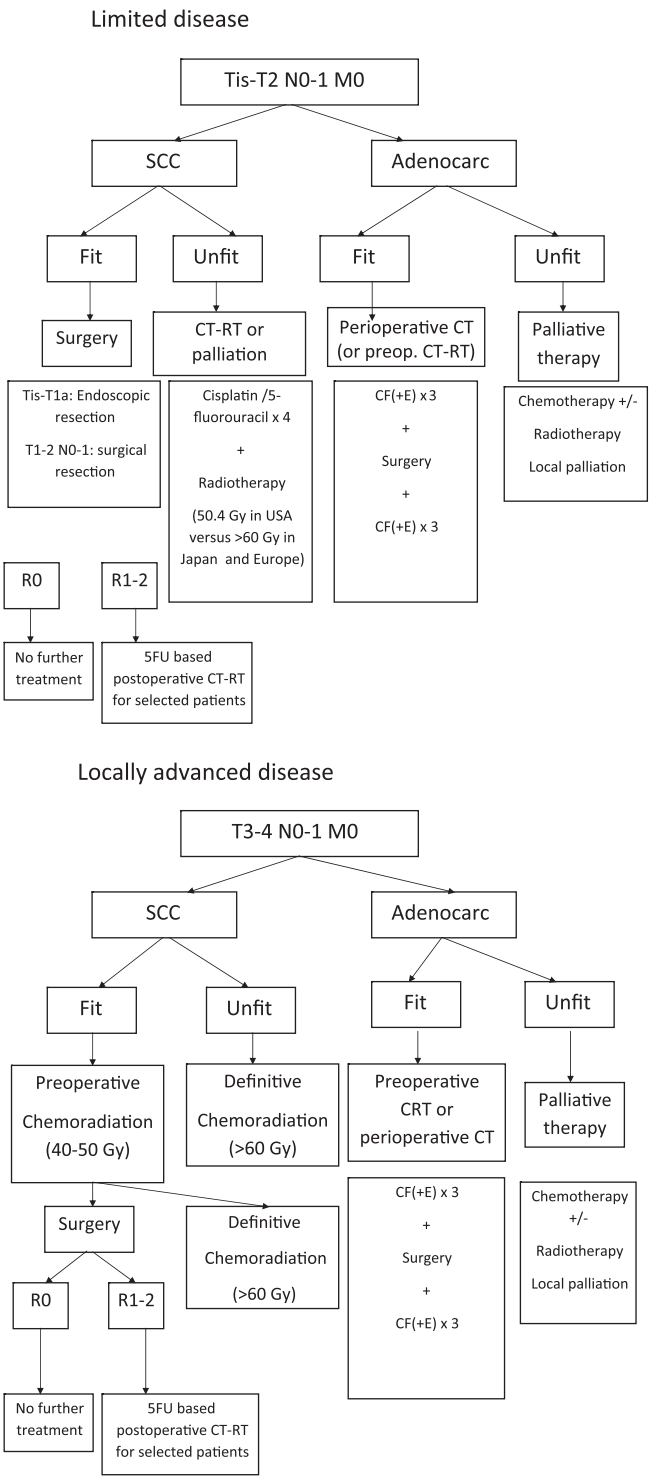

Figure 1. Algorithm for the treatment of esophageal cancer. CT, chemotherapy; RT, radiotherapy; C, cisplatin; F, fluorouracil; E, epirubicin; R0, complete resection; R1–2, incomplete resection.

60 Gy and more are usually recommended in Europe and Japan for definitive radiochemotherapy due to good experience with these doses in multicenter trials.

Perioperative chemotherapy is considered as a standard option for localized AC. However, randomized data are mainly restricted to AC.

treatment of extensive disease (T3–4 N0–1 M0 or T1–4 N0–1 M1)

Surgery alone is not a standard treatment in these stages since even in M0 cases a complete tumor resection is not possible in ~30% (pT3) and ~50% (pT4) of the patients. Furthermore, even after complete tumor resection long-term survival rarely exceeds 20%.

squamous cell carcinoma M0

A couple of meta-analyses demonstrate that patients with locally advanced disease benefit from preoperative chemotherapy or, to a greater extent, from preoperative chemoradiation, by increasing the rates of complete tumor resection, improving local tumor control and thereby improving survival [Ia, A]. It is suggested, however, that preoperative chemoradiation will increase the postoperative mortality rate. In the case of response to neoadjuvant chemo(radio)therapy (40–50 Gy) further chemoradiation resulted in an equivalent overall survival compared with surgery, albeit associated with an increase in local tumor recurrence (French and German Phase III trials). Therefore, chemoradiation with close surveillance and early salvage surgery for local tumor progression may be considered as a definitive treatment for selected patients with locally advanced disease, particularly in the upper third of the esophagus [Ib, B]. Experienced multidisciplinary teamwork is warranted for this treatment approach and postoperative mortality will increase with the dose of radiotherapy applied as well as the interval between radiotherapy and surgery.

For patients unable or unwilling to undergo surgery see recommendations in limited disease.

adenocarcinoma M0

Perioperative chemotherapy with cisplatin and 5-FU should be considered standard in locally advanced AC [Ia, A]. Preoperative chemoradiotherapy (cisplatin/5-FU combined with ~40 Gy) is an option for selected patients, since recent meta-analyses revealed a significant survival benefit for AC and this advantage was particularly true for high-risk patients, e.g. those with locally advanced tumors. This was supported by a recent Phase III study comparing chemoradiotherapy with chemotherapy before surgery.

metastatic disease

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

Chemotherapy is indicated for palliative treatment in selected patients [III, B]. It should be considered particularly for patients with AC who have a good performance status. Newer regimens based on platin/fluoropyrimidine combinations offer higher efficacy and improved quality of life compared with the 'classical' cisplatin/5-FU schedule. ACs of

the EGJ should be screened for Her-2 protein overexpression or gene amplification. In patients with Her-2 positive metastatic tumors, palliative chemotherapy should include the EGFR2 antibody trastuzumab beside a cisplatin/fluororpyrimidin combination.

response evaluation

Response is routinely evaluated by symptomatic evolution, esophagogram, endosopy (with biopsies) and CT scan.

In adenocarcinomas tumor response may be predicted early by PET.

follow-up

Except for those patients who may be candidates to salvage surgery after definitive chemoradiation there is no evidence that regular follow-up after initial therapy may influence the outcome. Follow-up visits should be concentrated on symptoms, nutrition and psycho-social problems [IV, D].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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