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SPECIAL ARTICLE

Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Oesophageal cancer is the seventh most common cancer worldwide, with 604 000 new cases diagnosed in 2020. It is the sixth most common cause of cancer-related mortality, with an estimated 544 000 deaths in 2020.[1] Approximately 70% of oesophageal cancer diagnoses occur in men; there is a twofold to threefold difference in incidence and mortality rates between the sexes. Rates of oesophageal cancer are higher in developing versus developed countries for men, but are comparable for women.[2] Eastern Asia exhibits the highest regional incidence, followed by Southern Africa, Eastern Africa, Northern Europe and South Central Asia.[1] Recent data from the US Surveillance, Epidemiology, and End Results database indicate an increased incidence of oesophageal adenocarcinoma (AC) in patients aged <50 years. In addition, young patients tend to be diagnosed in more advanced stages.[3]

There are two main subtypes of oesophageal cancer: oesophageal squamous-cell carcinoma (SCC) and oesophageal AC. Although SCC accounts for ~90% of cases of oesophageal cancer worldwide, the incidence of AC is rising and has surpassed the incidence rate of SCC in several regions of Europe and North America, as well as certain high-risk areas of Asia, where this change was preceded by economic development and dietary changes (e.g. in China).[2]

Heavy alcohol consumption, smoking and their synergistic effects are the major risk factors for oesophageal SCC in Western populations.[4] In lower-income countries, including parts of Asia and sub-Saharan Africa, the major risk factors for oesophageal SCC have yet to be elucidated, although potential dietary components have been identified, including nutritional deficiencies and nitrosamines.[5] Additional suspected risk factors for oesophageal SCC are betel quid chewing in the Indian subcontinent, consumption of pickled vegetables (e.g. in China) and consumption of food and beverages at very hot temperatures (e.g. in Uruguay, Iran and Tanzania).[4]

AC represents roughly two-thirds of oesophageal cancer cases in high-income countries, with excess body weight, gastroesophageal reflux disease and oesophageal intestinal metaplasia among the key risk factors.[4,6,7] Across high-income countries, incidence rates of oesophageal AC are thus rising, partly due to the increasing prevalence of excess body weight and gastroesophageal reflux disease, and possibly because of decreasing incidence of chronic *Helicobacter pylori* (*H. pylori*) infection,[8] which has been inversely associated with oesophageal AC.[9] These trends are predicted to continue in the near future, with incidence of oesophageal AC surpassing SCC in many high-income countries.

Finally, the incidence of oesophagogastric junction (OGJ) AC seems to have moderately increased during recent decades, although this has not been uniformly classified.[10] Similar to oesophageal AC, obesity, gastroesophageal

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reflux disease and a high fat intake are risk factors for OGJ cancer,[7] and *H. pylori* infection is inversely related.[8]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Screening for precursor lesions (oesophageal intestinal metaplasia) in high-risk patients, surveillance and endoscopic ablation of precursor lesions are not discussed in this guideline. The guidelines of the American College of Gastroenterology should be followed.[11]

The recommended diagnostic and staging investigations are detailed in Table 1. All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis and weight loss and/or loss of appetite should undergo an upper intestinal endoscopy. Approximately three-quarters of all oesophageal ACs are located in the distal oesophagus, whereas SCCs occur more frequently in the proximal-to-middle oesophagus.[12] Biopsies should be taken from all suspicious areas. There is limited evidence for the optimal number of biopsies required to ensure a diagnosis where malignancy is present. The accepted convention is to obtain $\geq$6-8 representative biopsies of the lesion. The number of biopsies should be sufficient for pathological and molecular analysis.

Pathology

Diagnosis should be based on endoscopic biopsies with the histological tumour type classified according to the World Health Organization (WHO) criteria.[13] The differentiation between oesophageal SCC and AC is of prognostic and therapeutic relevance.

Immunohistochemical (IHC) staining is recommended in poorly differentiated and undifferentiated cancers [grade 3/4 American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th Edition] when differentiation between SCC and AC using morphological characteristics is not possible. In addition, other less frequently occurring tumour types, such as neuroendocrine tumours/carcinomas, lymphomas, mesenchymal tumours, melanomas or secondary tumours, must be identified separately from SCC and AC.

Table 1. Diagnostic and staging investigations in oesophageal cancer

Procedure	Purpose
FBC	Assess for iron-deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. PD-L1 and HER2 status (AC)
EUS	Accurate assessment of T and N stage in potentially resectable tumours
Bronchoscopy with endobronchial ultrasonography	Assess tumour growth towards central airways; complementary to EUS, especially when tumour stricture precludes EUS
CT of thorax + abdomen ± pelvis	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease
PET–CT, if available	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease
Laparoscopy ± washings	Exclude occult metastatic disease involving peritoneum/diaphragm, especially in locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomical cardia

AC, adenocarcinoma; CT, computed tomography; EUS, endoscopic ultrasound; FBC, full blood count; HER2, human epidermal growth factor receptor 2; N, node; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; PET, positron emission tomography; T, tumour.

Molecular pathology

The Cancer Genome Atlas research network identified three subtypes of oesophageal SCC (oesophageal SCC1, oesophageal SCC2 and oesophageal SCC3), which are each associated with defects in specific molecular pathways.[14] So far, no distinct therapeutic options for these subtypes are available.

Patients with oesophageal SCC have been shown to benefit from programmed cell death protein 1 (PD-1) blockade.[15-23] In patients who are candidates to receive first-line treatment with immune checkpoint inhibitors (ICIs), programmed death-ligand 1 (PD-L1) IHC is recommended [see the table of ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) scores for further details; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.07.003]. PD-L1 expression is measured using tumour proportion score (TPS), which evaluates the percentage of viable tumour cells showing partial or complete membrane staining at any intensity (PD-L1 positivity is defined as TPS $\geq$1% in the case of first-line treatment with nivolumab and nivolumab–ipilimumab), or combined positive score (CPS), which is calculated by the total number of cells with PD-L1-positive plasma membrane staining (including tumour cells, lymphocytes and macrophages) divided by the number of vital tumour cells, multiplied by 100 (PD-L1 positivity is defined as CPS $\geq$10 in the case of first-line treatment with pembrolizumab). In the CheckMate 648 study, TPS was determined using the PD-L1 IHC 28-8 pharmDx assay, while in KEYNOTE-590, the PD-L1 IHC 22C3 assay was used for CPS. In several tumour types, the analytical concordance between the two assays has shown to be high, although conflicting data also exist.[24,25] Currently, data on their interchangeability specifically in oesophageal SCC are awaited. Use of a validated test that is subject to a quality assurance programme is recommended.

In the RATIONALE 302 study, PD-L1 expression was assessed using the VENTANA PD-L1 (SP 263) assay with tumour area positivity (TAP) score. TAP is defined as the total percentage of the tumour area covered by tumour cells with any membrane staining above the background and tumour-associated immune cells with any staining above the background. Only patients with a TAP score $\geq$10 were defined as PD-L1 positive.[23]

Molecular pathology assessment in oesophageal and OGJ AC should follow the recommendations provided in the ESMO Clinical Practice Guideline (CPG) for gastric cancer.[26]

Recommendations

- Patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis and weight loss and/or loss of appetite should undergo an upper intestinal endoscopy [III, A]. Diagnosis should be made by histopathological assessment of multiple ($\geq$6) endoscopic biopsies to guarantee an adequate representation of the tumour and sufficient tissue for molecular analysis [I, B].
- Histological diagnosis should be reported according to the WHO criteria [IV, A].
- IHC staining is recommended in poorly differentiated and undifferentiated cancers when differentiation between SCC and AC using morphological characteristics is not possible [V, B].
- For oesophageal SCC, PD-L1 expression by IHC according to the TPS or CPS is a validated predictive biomarker for ICI therapy [I-II, A].

STAGING AND RISK ASSESSMENT

Decisions about initial treatment for oesophageal cancer are based on clinical staging, which should be carried out with the highest degree of accuracy possible. Staging should include a complete clinical examination, endoscopy and computed tomography (CT) or positron emission tomography (PET) with [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG). Endoscopic ultrasound (EUS) can be used for tumour (T) and node (N) staging, but has low accuracy for T1 tumours; in these cases, endoscopic resection offers more precise staging in addition to therapeutic benefit.[27,28]

EUS is particularly useful to determine the therapeutic strategy in two ways: (i) for assessment of T4b status with invasion towards the airways, pericardium or aorta, and (ii) for identification and biopsy of suspected lymph node metastases outside the regular radiation field or beyond the planned resection limits. In advanced T stages, tumour stricture may preclude the use of EUS. In the assessment of tumour growth towards central airways, bronchoscopy with endobronchial ultrasonography is a useful complement to EUS, especially when tumour stricture precludes EUS use.

FDG—PET (typically carried out as PET—CT) is helpful to identify otherwise undetected distant metastases. FDG—PET should therefore be carried out in patients who are candidates for oesophagectomy, as the finding of otherwise unknown distant metastases can help to avoid futile surgery; however, the availability of PET—CT differs between countries and centres.[29-32]

Oesophageal SCCs are often accompanied by head and neck second primary tumours (HNSPTs). The prognosis of patients with an additional HNSPT is worse than patients with only oesophageal SCC. The pooled prevalence of HNSPT in patients with oesophageal SCC is 6.7%. Therefore, early detection of HNSPTs may improve the overall outcome of patients with oesophageal SCC.[33] Patients with oesophageal SCC should undergo a qualified clinical examination of the head and neck region to exclude HNSPTs.

In locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomical cardia, laparoscopy should be carried out to rule out peritoneal metastases, which are found in ~15% of patients.[34] The finding of otherwise unknown peritoneal metastases may prevent patients from undergoing futile surgery.

Oesophageal cancer should be staged according to the American Joint Committee on Cancer AJCC/UICC TNM (tumour—node—metastasis) 8th edition staging system (see Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.annonc.2022.07.003).[35] 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.

Nutritional status and history of weight loss should be assessed according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines.[36] More than half of patients lose >5% of their body weight before admission for oesophagectomy, and 40% lose >10%. Independent from body mass index, weight loss confers an increased operative risk, worsens a patient's quality of life (QoL) and is associated with poor survival in advanced disease. Therefore, nutritional support according to the ESPEN guidelines[37] is an integral part of medical care for patients with oesophageal cancer, in both curative and palliative settings.

Reduced physical activity is associated with worse outcomes following perioperative treatment. In addition, lower physical fitness is a negative predictor of long-term survival in oesophagogastric cancer.[38,39] A supervised exercise programme has been shown to improve cardiorespiratory fitness and aspects of QoL in patients who have undergone an oesophagectomy and can therefore be recommended.[40] Other studies are investigating whether the addition of a perioperative exercise regimen to neoadjuvant chemotherapy (ChT) improves outcomes.[41] Geriatric screening and assessment may help to identify patients who need additional support and/or are at increased risk of ChT-associated side-effects.[42]

Recommendations

- Initial staging and risk assessment should include physical examination, endoscopy and contrast-enhanced CT or FDG—PET—CT scan of the thorax, abdomen ± pelvis. EUS can be used for T and N staging [III, A].
- FDG—PET should be carried out in candidates for oesophagectomy [III, B].
- In locally advanced (T3/T4) ACs of the OGJ which cross the diaphragm to infiltrate the anatomical cardia, laparoscopy should be carried out [IV, B].
- The TNM stage should be recorded according to the latest edition of the AJCC/UICC guidelines and staging manual [IV, A].

- Nutritional status and history of weight loss should be assessed [III, A] and nutritional support provided [II, A] according to ESPEN guidelines.

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASES

Multidisciplinary assessment and planning of treatment are mandatory. Treatment is determined together with the patient based on histological subtype, clinical TNM stage, tumour location and the patient's predicted treatment tolerance, which considers performance status and comorbidities, and may be supplemented by functional testing. Correction of malnutrition is often warranted before curative-intent therapy can be started. Occasionally, enteral feeding is necessary, either via feeding jejunostomy or via nasogastric tube. Endoscopic stenting should be avoided in patients undergoing treatment with curative intent as this may worsen prognosis.[43] A proposed algorithm for the treatment of localised oesophageal and OGJ cancer is shown in Figure 1.

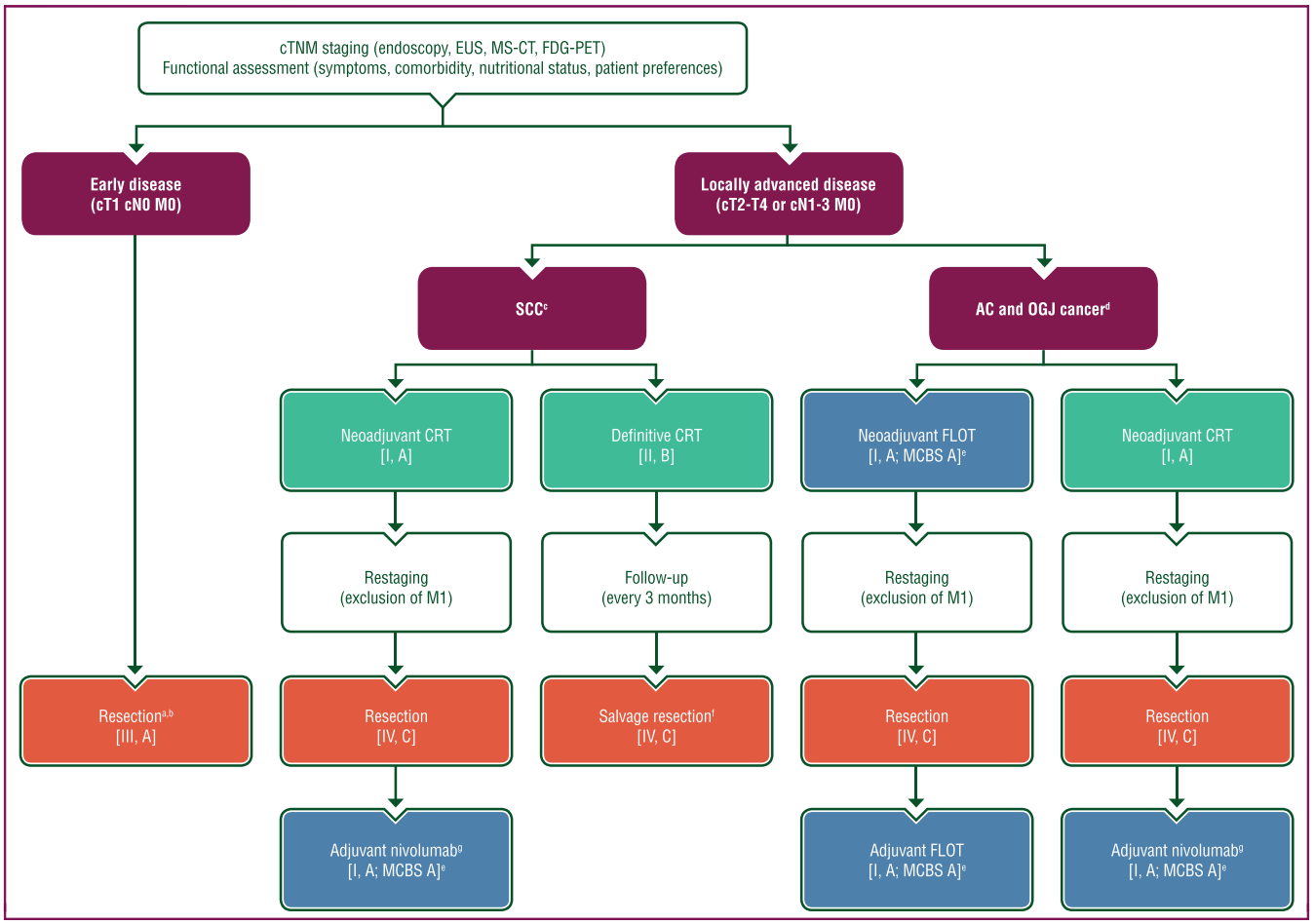

Figure 1. Treatment algorithm for local/locoregional resectable oesophageal and OGJ cancer.
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
AC, adenocarcinoma; ChT, chemotherapy; CRT, chemoradiotherapy; cTNM, clinical tumour—node—metastasis; EMA, European Medicines Agency; EUS, endoscopic ultrasound; FDA, Food and Drug Administration; FDG—PET, [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography; FLOT, 5-fluorouracil—leucovorin—oxaliplatin—docetaxel; GoR, grade of recommendation; LoE, level of evidence; MCBS, Magnitude of Clinical Benefit Score; MS-CT, multislice-computed tomography; OGJ, oesophagogastric junction; OS, overall survival; RT, radiotherapy; SCC, squamous-cell carcinoma.
[a]Criteria for endoscopic instead of surgical resection are specified in the text.
[b]For patients unable or unwilling to undergo surgery, combined CRT is superior to RT alone.
[c]Evidence suggests that neoadjuvant CRT followed by surgery and definitive CRT is equally effective with regard to OS. 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 CRT should be preferred. Even many experienced centres prefer definitive CRT for oesophageal tumours with a very proximal/cervical location.
[d]Sufficient evidence supports the use of perioperative ChT as well as neoadjuvant CRT. Both standards can be recommended with an equal LoE/GoR [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 OGJ type I or II according to Siewert's classification, while they use perioperative ChT for OGJ type III or II, but this is only a pragmatic solution not currently supported by scientific evidence.
[e]ESMO-MCBS v1.1[91] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[f]This is optional in the case of incomplete response to CRT or local relapse and should only be carried out in selected patients and experienced centres [IV, C].
[g]With residual vital tumour in the resection specimen.

Early disease (cT1 N0 M0)

Endoscopic *en bloc* resection, using either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), is the treatment of choice for lesions with intraepithelial high-grade dysplasia and most T1 tumours.[44,45] Examination of the specimen provides accurate staging and, unless the deep resection margin is involved or there are significant risk factors for lymph node metastases, endoscopic resection can be considered definitive treatment.[44,45] The strongest risk factors for lymph node metastasis are depth of invasion, lymphovascular invasion, low differentiation grade, ulceration and large tumour size.[46,47]

For oesophageal AC, which often occurs in the context of oesophageal intestinal metaplasia, endoscopic resection can usually be considered curative in all T1a cancers and, in the absence of other risk factors for lymph node metastasis, also in the most superficial submucosally involved T1b cancers (sm1, invasion depth $<$500 μm, no ulceration).[45] For AC there is no evidence favouring either EMR or ESD, but EMR should normally be preferred in small lesions, while ESD should be considered in lesions $>$15 mm, poorly lifting tumours and tumours at risk of submucosal invasion.[46]

The risk of lymph node metastasis is generally higher with oesophageal SCC than with AC and even deep intramucosal T1a cancers (m3) need additional treatment if other risk factors are also present.[47] Studies from Asia show that ESD results in a higher proportion of complete resection and a lower risk of local recurrence compared with EMR.[48]

For both histological subtypes, patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases should be offered further resective surgery with appropriate lymphadenectomy; however, chemoradiotherapy (CRT) could be considered as a treatment option for stage IA SCC with organ preservation.[49]

Locally advanced resectable disease (cT2-T4 or cN1-3 M0)

Surgery. Surgery is still the backbone of curative-intent treatment for both histological subtypes of locally advanced resectable oesophageal cancer (cT2-T4a or cN1-3), although definitive CRT with surveillance and salvage oesophagectomy when needed for local tumour control is also a recommended option, even in upfront resectable cases of oesophageal SCC (see the 'Definitive CRT' subsection for further information). Radical transthoracic oesophagectomy with *en bloc* two-field lymphadenectomy is the procedure of choice in fit patients. For distal tumours, abdominal and right chest access is used, and reconstruction is carried out with a gastric tube conduit with oesophagogastric anastomosis in the upper mediastinum (Ivor Lewis procedure). For mid and upper oesophageal tumours, abdominal, right chest and cervical access is used with a similar reconstruction to the cervical oesophagus (McKeown procedure). In frail patients with distal tumours, transhiatal oesophagectomy without transthoracic access can be carried out with lower morbidity, at the cost of less extensive lymphadenectomy.[50]

Minimally invasive oesophagectomy (MIO) techniques, including robotics, have become increasingly implemented into clinical practice in recent years. Three randomised controlled trials (RCTs) comparing MIO with open oesophagectomy reported lower post-operative morbidity, quicker functional recovery and better QoL up to 1 year after surgery with MIO.[51-54] Regarding oncological endpoints such as free resection margins, lymph node yield and survival, the outcomes seem at least noninferior to open oesophagectomy.[51,53,54] Recently, a population-based cohort study from Sweden and Finland reported better long-term overall survival (OS) after MIO compared with open oesophagectomy.[55] In experienced centres, MIO is recommended as the surgical approach of choice.

Pre- and perioperative treatment. Pre- and perioperative treatment using ChT or CRT has been shown to increase rates of resection with no tumour at the margin (R0) and survival rates in oesophageal cancer, and should be considered in all patients with locally advanced resectable disease.[56-62] The caveat to this recommendation is for cT2 N0 tumours, for which there is controversy regarding the need for preoperative treatment, as randomised trials have included low patient numbers from this population[56,57,59] and retrospective studies have reported conflicting results.[63,64] A randomised phase III trial in stage I-II oesophageal cancer showed that preoperative CRT did not improve R0 resection rate or survival but increased postoperative mortality[65]; however, the patient cohort was heterogeneous and included cT1-T3 tumours; as such, the effect on the cT2 N0 subset is unknown. There is currently insufficient evidence to make firm recommendations regarding the use of preoperative treatment in cT2 N0 tumours. Each case should be discussed by the multidisciplinary team with careful consideration of the potential risks and benefits.

The treatment paradigms for oesophageal SCC versus oesophageal AC have taken divergent paths due to the results of randomised phase III trials in the two histological subtypes, and the differing response of SCC and AC to CRT.

SCC. Based on the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS),[59] preoperative CRT can be recommended as a standard of care for SCC of the oesophagus. Weekly carboplatin—paclitaxel combined with radiation to a dose of 41.4 Gy in 23 fractions followed by oesophagectomy showed improved survival compared with surgery alone for both SCC and AC. Treatment-related toxicity was acceptable and there was no increase in surgical morbidity or mortality. In particular, the 5-year OS rate of $>$60% for SCC in the trimodality arm was substantially higher than those previously reported in studies of surgery alone or definitive CRT.

Given the high response rates of oesophageal SCC to CRT,[59] an alternative curative-intent treatment is definitive CRT with the option of salvage oesophagectomy in selected cases.[66-68] This treatment was pioneered by the phase III Radiation Therapy Oncology Group (RTOG) 85-01 study in the early 1990s using the combination of cisplatin and 5-fluorouracil (5-FU) with radiotherapy (RT).[66] A recent randomised phase

III trial of definitive CRT incorporating modern techniques of RT planning and delivery has reported encouraging results with a 3-year OS rate of 47.8% and median OS of 35.9 months in patients with oesophageal SCC.[69] The use of definitive CRT is further supported by two prospective, randomised trials that showed equivalent OS following definitive CRT without surgery compared with preoperative CRT followed by surgery, although the non-operative strategy was associated with higher local recurrence rates.[70,71] It is important to note that the aforementioned studies of definitive CRT did not systematically incorporate salvage oesophagectomy in patients with incomplete clinical response, thereby failing to achieve the level of survival reported in CROSS. The use of salvage oesophagectomy in patients with persistent disease has been shown to be safe and associated with survival rates similar to those observed with preoperative CRT and planned surgery.[67,68]

Therefore, preoperative CRT followed by surgery or definitive CRT with close surveillance and salvage surgery for local tumour persistence or progression can be considered the recommended definitive treatments for locally advanced SCC of the oesophagus; however, there are currently no data comparing these two treatment strategies. Definitive CRT is recommended for cervically localised tumours where surgery would entail a laryngectomy.

AC. Based on the results of CROSS,[59] preoperative CRT can be recommended as one standard of care for locally advanced AC of the oesophagus and OGJ.

Several large prospective RCTs have established pre- and perioperative ChT as another standard of care for locally advanced AC of the oesophagus and OGJ.[58,60-62] The benefit of perioperative ChT was initially demonstrated in the phase III MAGIC trial using a regimen of three preoperative and three post-operative cycles of epirubicin—cisplatin—5-FU (ECF), which resulted in tumour downstaging, improved R0 resection rate and improved survival compared with surgery alone.[60] The phase II/III FLOT4-AIO trial compared perioperative ECF with four preoperative and four post-operative cycles of 5-FU—leucovorin—oxaliplatin—docetaxel (FLOT), and showed an OS benefit for FLOT.[62] FLOT is therefore the preferred perioperative regimen for patients able to tolerate the treatment.

Direct comparisons of ChT versus CRT were previously limited; however, in 2021, results from the phase III Neo-AEGIS trial were presented in abstract form.[72] Neo-AEGIS compared two standard regimens in the perioperative setting, with enrolled patients receiving either preoperative CRT (CROSS regimen) or perioperative ChT (MAGIC trial ECF regimen or FLOT). Preliminary results showed higher rates of tumour regression and pathological complete response in the CRT arm. No OS difference was observed between the two treatments; however, the majority of patients in the ChT arm were treated with the older ECF regimen rather than FLOT, and higher efficacy is expected with the perioperative FLOT regimen. Data from the phase III ESOPEC trial, which is comparing the CROSS CRT regimen with FLOT, are awaited.[73]

Even after complete clinical tumour response to preoperative CRT or ChT, patients with resectable oesophageal AC should proceed to surgery, as data for a watch-and-wait strategy following complete clinical remission are currently limited.

Adjuvant nivolumab following trimodality therapy. The phase III CheckMate 577 trial evaluated the addition of 1 year of adjuvant treatment with the anti-PD-1 antibody nivolumab after surgery in patients with SCC or AC of the oesophagus, including OGJ cancer, who had received neoadjuvant CRT and had evidence of residual pathological disease in the resection specimen ($\geq$ypT1 and/or $\geq$ypN1).[18] The study demonstrated a significant improvement in disease-free survival for patients treated with adjuvant nivolumab (22.4 months) compared with placebo [11.0 months; hazard ratio (HR) for disease recurrence or death 0.69; 96.4% confidence interval (CI) 0.56-0.86; $P < 0.001$]. Therefore adjuvant nivolumab is now recommended in this indication. PD-L1 testing is not required for this indication.

Definitive CRT. As described above, definitive CRT (with close surveillance and salvage surgery) is a recommended option for resectable oesophageal SCC. In addition, definitive CRT should be considered for patients with oesophageal SCC or AC who are unable or unwilling to undergo surgery.[66,69] The traditional standard regimen for definitive CRT is four cycles of cisplatin—5-FU (or capecitabine) combined with RT to a dose of 50.4 Gy in 28 fractions (or 50 Gy in 25 fractions).[66] Alternatively, six cycles of folinic acid—5-FU—oxaliplatin (FOLFOX) can be considered.[74] In recent years, weekly carboplatin—paclitaxel, as used in the CROSS regimen, has been combined with RT as definitive treatment. Although this regimen has not been directly compared with cisplatin—5-FU in a randomised phase III trial, it is commonly utilised due to its favourable toxicity profile. Retrospective comparative studies have reported equivalent efficacy between different regimens.[75] As a minimum requirement, RT should be delivered using 3D conformal RT, but intensity modulated RT or volumetric arc therapy are preferred to better minimise the radiation dose to critical normal tissues. Currently there is little evidence to support the use of RT doses >50.4 Gy in the definitive treatment of oesophageal cancer. Randomised phase III trials evaluating RT dose escalation have not demonstrated improved local control or survival with RT doses >50.4 Gy.[76,77] This is of importance if salvage oesophagectomy is considered as a therapeutic strategy, because doses >55 Gy have been associated with increased post-operative mortality and morbidity.[67]

Recommendations

- Multidisciplinary assessment and planning before any treatment is mandatory [IV, A].
- In experienced centres, MIO is the surgical approach of choice [II, A].
- Endoscopic *en bloc* resection, using either EMR or ESD, is preferred for lesions with intraepithelial high-grade dysplasia and most T1 tumours [III, A].

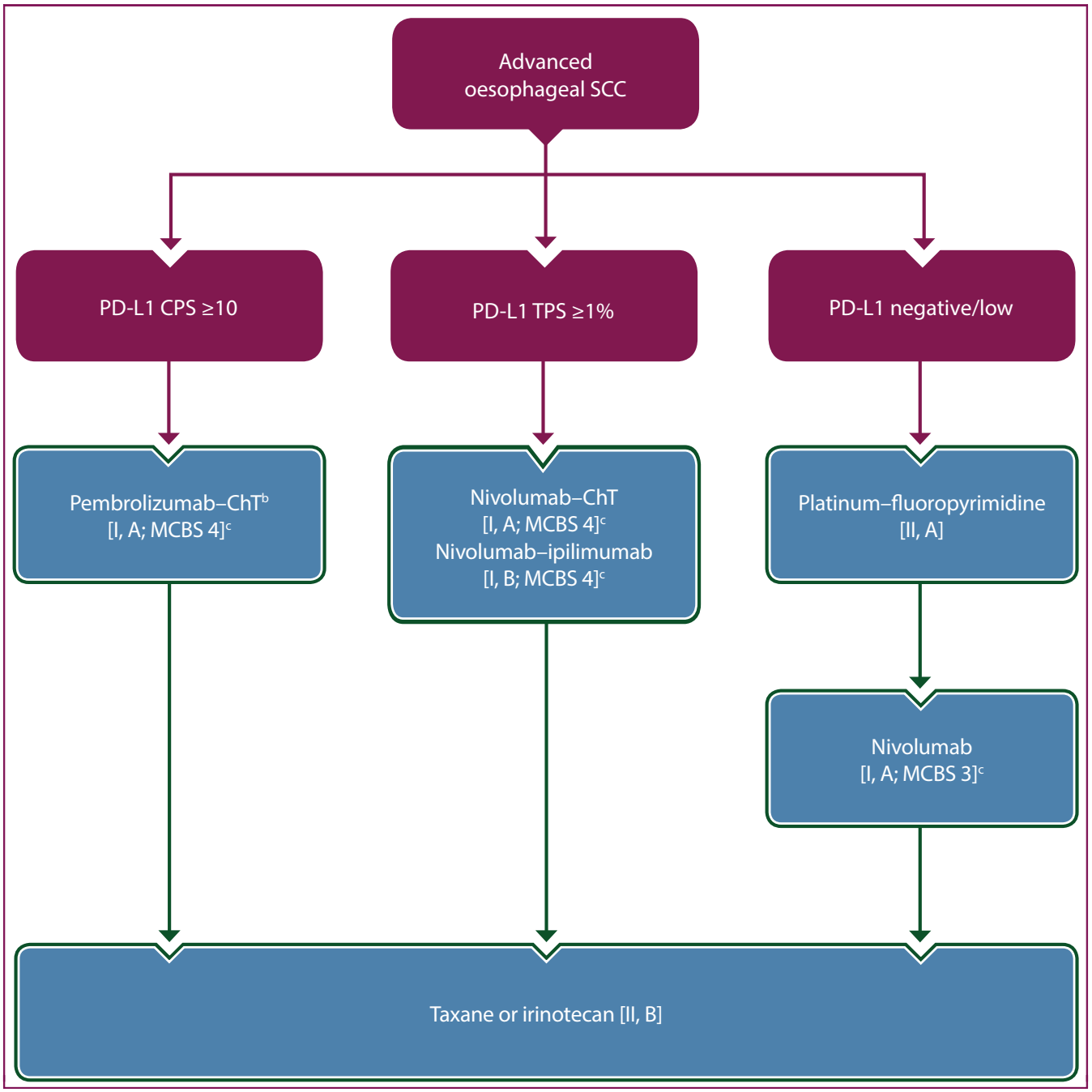

Figure 2. Treatment algorithm for advanced oesophageal SCC.[a]
Purple: general categories or stratification; blue: systemic anticancer therapy. AC, adenocarcinoma; ChT, chemotherapy; CPG, Clinical Practice Guideline; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Score; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; SCC, squamous-cell carcinoma; TPS, tumour proportion score.
[a]For treatment of oesophageal AC and OGJ cancer, see the ESMO CPG for gastric cancer.[26]
[b]EMA approval is for tumours with PD-L1 CPS ≥10, FDA approval is irrespective of PD-L1 expression.
[c]ESMO-MCBS v1.1[91] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

- For both histological subtypes, patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases should be offered further resective surgery with appropriate lymphadenectomy [III, A].
- Pre- and perioperative ChT or CRT should be considered in all patients with locally advanced resectable disease [I, A].
- Locally advanced oesophageal SCC should be treated with CRT followed by surgery [I, A] or definitive CRT with close surveillance and salvage surgery for local tumour persistence or progression [II, B]. Definitive CRT is recommended for cervically localised tumours where surgery would entail a laryngectomy [III, B].

- Preoperative CRT or pre- and perioperative ChT can be recommended as standards of care for locally advanced AC of the oesophagus and OGJ [I, A].
- Patients with resectable, locally advanced oesophageal AC or OGJ cancer should be treated with neoadjuvant CRT based on the CROSS regimen or perioperative ChT (FLOT) followed by surgery [I, A; ESMO-MCBS v1.1 score: A].
- Even after complete clinical tumour response to preoperative CRT or ChT, patients with resectable oesophageal or OGJ cancer should proceed to surgery as data for a watch-and-wait strategy are limited [IV, C].
- Patients with SCC or AC of the oesophagus including OGJ cancer who have undergone neoadjuvant CRT and show evidence of residual pathological disease in the resection specimen (≥ypT1 and/or ≥ypN1) should be treated with adjuvant nivolumab [I, A; ESMO-MCBS v1.1 score: A].
- Treatment with definitive CRT is recommended for patients with SCC or AC of the oesophagus that is unresectable and locally advanced or those who are unable or unwilling to undergo surgery [I, A].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Patients with oesophageal cancer that is metastatic or unresectable and cannot be treated with curative-intent CRT have a poor prognosis; survival in clinical trials has historically been <1 year[78]; however, the use of ICIs with ChT has recently improved survival for this patient group.[16,79]

Treatment of advanced AC of the oesophagus and OGJ should be in line with the ESMO CPG for gastric cancer.[26] A proposed algorithm for the treatment of advanced oesophageal SCC is shown in Figure 2.

First-line ChT for oesophageal SCC

Standard first-line ChT for oesophageal SCC is a platinum—fluoropyrimidine doublet. Most randomised trials have been conducted in oesophageal AC and data are extrapolated to SCC; however, multiple phase II studies support platinum—fluoropyrimidine treatment in an SCC population.[80-82] Data from trials in locoregionally advanced oesophageal SCC suggest equivalence for cisplatin- and oxaliplatin-based regimens.[74] The phase III GO2 trial recruited patients with advanced gastroesophageal cancer, including oesophageal SCC, who were unsuitable for full-dose ChT due to advanced age or frailty, and demonstrated equivalent outcomes and reduced toxicity with dose-reduced oxaliplatin—capecitabine.[83]

First-line ChT plus ICIs or ICIs without ChT for oesophageal SCC

Oesophageal SCC appears to be modestly more sensitive to ICIs than oesophageal AC based on the efficacy of anti-PD-1 antibody monotherapy.[17,84] Nevertheless, benefit from ICI therapy is enhanced in both oesophageal SCC and AC tumours with elevated levels of PD-L1 expression using the CPS.[15,16]

The phase III KEYNOTE-590 trial evaluated addition of the anti-PD-1 antibody pembrolizumab to cisplatin—5-FU in patients with untreated, advanced oesophageal or OGJ (Siewert type I) cancer.[16] Patients with both SCC and AC histology were eligible, but the majority (73%) had SCC. The greatest OS gain was observed in patients with SCC and elevated PD-L1 expression (CPS ≥10; HR 0.57, 95% CI 0.43-0.75; $P < 0.0001$), but modest improvements were also demonstrated in (i) all patients with a CPS ≥10 (HR 0.62, 95% CI 0.49-0.78; $P < 0.0001$); (ii) all patients with SCC (HR 0.72, 95% CI 0.60-0.88; $P = 0.0006$) and (iii) all randomised patients (HR 0.73, 95% CI 0.62-0.86; $P < 0.0001$). A *post hoc* analysis suggested no benefit in patients with a PD-L1 CPS <10. The phase III CheckMate 648 study randomised patients with treatment-naive advanced oesophageal SCC to (i) cisplatin—5-FU; (ii) nivolumab—cisplatin—5-FU or (iii) nivolumab plus the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibody ipilimumab.[22] Patients treated with nivolumab—ChT had improved OS compared with patients treated with ChT alone; this benefit was most pronounced in patients with tumour cells expressing PD-L1 ≥1% using TPS (HR 0.54, 99.5% CI 0.37-0.80; $P < 0.001$). Nivolumab—ipilimumab improved OS compared with ChT alone in CheckMate 648; however, a lower radiological response rate was noted for nivolumab—ipilimumab compared with ChT alone or nivolumab—ChT, and there is a risk of early progression and death for patients treated without ChT, resulting in a lower grade of recommendation compared with nivolumab—ChT. Finally, in the phase III ESCORT-1st trial, Chinese patients with untreated advanced oesophageal SCC were randomised to receive carboplatin—paclitaxel with or without the anti-PD-1 antibody camrelizumab.[20] ESCORT-1st demonstrated an improvement in progression-free survival and OS for patients with oesophageal SCC treated with camrelizumab—ChT.

Second and subsequent lines of treatment for oesophageal SCC

For patients with oesophageal SCC, second-line nivolumab monotherapy is an option based on the results of the phase III ATTRACTION-3 trial.[17] In this study, predominantly Asian patients with SCC previously treated with platinum—fluoropyrimidine were randomised to receive either nivolumab or taxane-based ChT. Response rates were comparable between the two arms; however, nivolumab was associated with improved OS compared with ChT (HR 0.77, 95% CI 0.62-0.96; $P = 0.019$). Treatment outcomes were not affected by PD-L1 expression assessed on tumour cells; assessment of PD-L1 using CPS has not been reported. Similar results were observed with tislelizumab in the global phase III RATIONALE 302 study.[23] Where approved, pembrolizumab may be an option for patients with previously treated SCC with PD-L1 CPS ≥10 based on the results of the phase III KEYNOTE-181 trial, which compared pembrolizumab monotherapy with ChT in previously treated oesophageal AC and SCC (patients who received first-line treatment with an ICI were not included).[15] An OS benefit was only observed in patients with

SCC and a CPS ≥10. Following second-line treatment, patients with oesophageal SCC might be considered for ChT with a taxane or irinotecan.[85-87]

Supportive care and nutrition

Supportive care for patients with advanced oesophageal cancer should follow the recommendations provided in the ESMO CPG for gastric cancer,[26] including early palliative care referral and nutritional support.

Recommendations

First-line treatment for advanced oesophageal SCC

- First-line ChT with a platinum and fluoropyrimidine is recommended as a standard treatment for advanced untreated oesophageal SCC [II, A]. Dose-reduced oxaliplatin—capecitabine is an alternative option for patients who are unsuitable for full-dose ChT [I, A].
- Pembrolizumab—ChT is recommended for advanced, untreated oesophageal SCC. The greatest benefit is seen in patients with a PD-L1 CPS ≥10 [I, A; ESMO-MCBS v1.1 score: 4; European Medicines Agency (EMA) approval is for tumours with PD-L1 CPS ≥10, Food and Drug Administration (FDA) approval is irrespective of PD-L1 expression].
- Nivolumab—ChT is recommended in patients with tumours expressing PD-L1 with a TPS ≥1% [I, A; ESMO-MCBS v1.1 score: 4]. Nivolumab—ipilimumab can be given, but a lower radiological response rate and increased risk of early progression and death in patients treated without ChT needs to be considered [I, B; ESMO-MCBS v1.1 score: 4].

Second and subsequent lines of treatment for advanced oesophageal SCC

- Nivolumab is recommended for oesophageal SCC previously treated with platinum—fluoropyrimidine ChT [I, A; ESMO-MCBS v1.1 score: 3].
- Where approved, pembrolizumab may be an option for patients with previously treated SCC who have not received first-line treatment with ICIs and have a PD-L1 CPS ≥10 [I, A; ESMO-MCBS v1.1 score: 3; FDA approved, not EMA approved].
- ChT with a taxane or irinotecan can be considered in fit patients who have been previously treated with platinum—fluoropyrimidine and/or nivolumab or pembrolizumab [II, B].

Supportive care and nutrition

- Care for patients with advanced oesophageal cancer should include early palliative care referral and nutritional support [I, A].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Surveillance strategies after successful therapy for oesophageal and OGJ cancers remain controversial. Although the majority (∼90%) of relapses occur within the first 2 years after completion of local therapy, potentially treatable relapses have been reported >5 years after local therapy.[88,89] Metachronous malignancies should also be considered in long-term survivors.

Except for those patients who may be potential candidates for an endoscopic reintervention or early 'salvage surgery' after (failing) endoscopic resection or definitive CRT, there is no evidence that regular follow-up after initial therapy has an impact on survival.

Therefore follow-up visits should concentrate on symptoms, nutrition and psychosocial support. A multidisciplinary team is often required during the follow-up phase, coordinated by the physician who is seeing the patient on a regular basis. Patients can develop a variety of needs and problems associated with loss of the oesophagus, other treatment sequelae or psychosocial needs. The expertise of a dietician, radiologist, gastroenterologist, psychologist and social worker is often needed during follow-up.

In case of complete response to definitive CRT, a 3-month follow-up based on endoscopy, biopsies and CT scan may be recommended to detect early recurrence, for which salvage surgery may be carried out.[74]

Recommendations

- The majority (∼90%) of relapses occur within the first 2 years after completion of local therapy. Follow-up visits should concentrate on symptoms, nutrition and psychosocial support [V, A].
- In case of complete response to definitive CRT, a 3-month follow-up based on endoscopy, biopsies and CT scan may be recommended to detect early recurrence [IV, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESCAT table with ESCAT scores is included in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.07.003. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[90] An ESMO-MCBS table with ESMO-MCBS scores is included in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.07.003. ESMO-MCBS v1.1[91] was used to calculate scores for therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.07.003.[92,93] Statements without grading were considered justified standard clinical practice by

the authors. Future updates to this CPG will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/gastrointestinal-cancers/oesophageal-cancer.

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