Egyptian National Guidelines for Esophageal and Esophagogastric Junction Cancer

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➢ Abbreviations

AC **adenocarcinoma**

BE **Barret's esophagus**

BMI **body mass index**

C **clinical**

CHT **chemotherapy**

CT **Computed tomography**

EMR **Endoscopic Mucosal Resection**

EN **enteral nutrition**

ERAS Enhanced recovery after surgery

ESD Endoscopic submucosal dissection

ESGE European Society of Gastrointestinal Endoscopy

EUS Endoscopic Ultrasound

FNA/FNB Fine needle aspiration/biopsy

GEJ Esophagogastric Junction

GERD Gastroesophageal reflux disease

GI gastrointestinal

MRI Magnetic Resonance imaging

ONS oral nutritional supplements

PEG percutaneous endoscopic gastrostomies

PET/CT Positron Emission tomography

PN parenteral nutrition

RHT radiotherapy

SCC. squamous cell carcinoma

Executive Summary

This guidance provides a data-supported approach to the primary prevention, screening, diagnosis, staging, treatment and follow up of patients diagnosed with Esophageal and Esophagogastric Junction Cancer. This guideline intended only for malignant esophageal tumors of epithelial origin, and not for any other non-epithelial malignant tumors of the esophagus or metastatic malignant esophageal tumors.

Recommendation	Strength of recommendation
1.Primary prevention	
The following interventions may help to reduce the risk of esophageal cancer: • Treating gastroesophageal reflux disease (GERD) and Barrett's esophagus early • Prevention of injury to the esophagus • Avoidance of tobacco and alcohol • Avoidance of meat, processed food intake, hot beverages. • Diet rich in fruits and vegetables • Avoid obesity	**Good practice statement**
2.Secondary prevention (Screening)	
• Screening of esophageal and GEJ tumors in the general population is not cost effective and should not be done.	**Strong**
3.Diagnosis	
3A. All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis, weight loss and/or loss of appetite should undergo an upper gastrointestinal endoscopy.	**Strong**
3B. The location of the tumor relative to the lower incisors and GEJ, the length of the tumor, the extent of circumferential involvement, the presence of Barrett esophagus and the degree of obstruction should be carefully recorded to assist with treatment planning.	**Strong**
3C. Multiple biopsies, six to eight, using standard size endoscopy forceps should be performed to provide sufficient material for	**Strong**

histologic and molecular interpretation. Larger forceps is recommended during surveillance endoscopy of Barrett esophagus for the detection of dysplasia.	
3D. Diagnosis should be based on endoscopic biopsies (Chromo-endoscopy if available) with the histological tumor type classified according to the World Health Organization (WHO) criteria. The differentiation between esophageal SCC and AC is of prognostic and therapeutic relevance.	**Strong**
3E. Laparoscopy ± washings could be done to exclude occult metastatic disease involving peritoneum/diaphragm, especially in locally advanced (T3/T4) adenocarcinoma of the GEJ infiltrating the anatomical cardia.	**Good practice statement**
4.Pathology	
4A. Histological diagnosis should be reported according to the WHO criteria.	**Good practice statement**
4B. Immuno-histochemical staining including HER2 is recommended in poorly differentiated and undifferentiated cancers when differentiation between SCC and AC using morphological characteristics is not possible.	**Good practice statement**
5.Staging and risk assessment	
5A. Consider Multidisciplinary team meetings (MDTs) for patients with esophageal cancer. MDTs often include surgeons, radiologist, pathologists, medical oncologists, radiation oncologists, gastroenterologists, dietitians, rehabilitation physicians, palliative care specialists and dedicated cancer nurse specialists.	**Conditional**
5B. Staging should include a complete clinical examination, Complete blood count (CBC) and comprehensive chemistry profile, endoscopy, chest /abdomen /pelvis CT with oral and IV contrast.	**Strong**

5C. Consider 18F-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) in patients who are candidates for esophagectomy.	**Conditional**
5D. Endoscopic ultrasound (EUS) is recommended in early lesions in order to assess tumor depth and lymph node status in patients amenable to upfront surgery or candidates for tri-modality treatment (T3N0, T1-4a and any locoregional N). If not available refer to a specialized center.	**Strong**
5E. We recommend bronchoscopy for tumors located at or above the carina in the initial staging, which can help in both surgery and radiotherapy treatments.	**Strong**
5F. Esophageal cancer should be staged according to the American Joint Committee on Cancer AJCC/UICC TNM (tumor/node/metastases) 8th edition staging system	**Strong**
6.Nutrition	
6A. All patients with esophageal cancer should be screened regularly for malnutrition by evaluating nutritional intake, weight change and BMI, beginning with diagnosis and repeated depending on the stability of the clinical situation	**Strong**
6B. Patients at nutritional risk should be promptly referred for comprehensive nutritional assessment and support clinical nutrition services.	**Good practice statement.**
6C. We recommend that during radiotherapy an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of ONS, to avoid nutritional deterioration, maintain intake and avoid radiotherapy interruptions.	**Strong**

6D. In patients at nutritional risk, we recommend feeding jejunostomy in operable patients and percutaneous gastrostomy tubes for inoperable patients.	**Strong**
6E. We recommend that vitamins and minerals be supplied in amounts approximately equal to the recommended daily allowance and discourage the use of high-dose micronutrients in the absence of specific deficiencies.	**Strong**
6F. Parenteral nutrition is only recommended if adequate oral/EN is not possible or insufficient e.g. severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease.	**Strong**
6G. For all cancer patients undergoing either curative or palliative surgery we recommend management within an enhanced recovery after surgery (ERAS) program; within this program every patient should be screened for malnutrition and if deemed at risk, given additional nutritional support.	**Strong**
7. Early disease (cT1 N0 M0)	
7A. Multidisciplinary assessment and planning before any treatment is mandatory.	**Good clinical practice**
7B. We recommend endoscopic en bloc resection of lesions with intraepithelial high-grade dysplasia and most T1 tumors using either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).	**Conditional**
7C. Examination of the specimen provides accurate staging and endoscopic resection is considered definitive treatment, unless the deep resection margin is involved or there are significant risk factors for lymph node metastases (e.g. depth of invasion, lymph-vascular invasion, low differentiation grade, ulceration and large tumor size).	**Conditional**

7D. Patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases should be offered further respective surgery with appropriate lymphadenectomy.	**Conditional**
8. Locally advanced and resectable disease (cT2-T4 or cN1-3 M0)	
Squamous cell carcinoma	
8A. Locally advanced esophageal SCC should be treated with CRT followed by surgery, or definitive CRT with close surveillance and salvage surgery for local tumor persistence or progression (see 10D).	**Strong**
8B. For patients not willing to undergo esophageal surgery or who are medically unfit for major surgery, definitive CRT should be preferred as CRT is superior to RT alone.	**Strong**
8C. Definitive CRT is recommended for cervically localized tumors where surgery would entail a laryngectomy.	**Good clinical practice**
Adenocarcinoma	
8D. We recommend the use of perioperative chemotherapy or neoadjuvant CRT (see 10D).	**Strong**
9. Surgery	
9A. Esophageal surgery should be carried out in experienced centers only.	**Good clinical practice**
9B. We recommend Ivor Lewis procedure, (abdominal and right chest access is used, and reconstruction is carried out with a gastric tube conduit with esophagi-gastric anastomosis in the upper mediastinum) for esophagi-gastric tumors.	**Strong**
9C. We recommend McKeown procedure, (abdominal, right chest and cervical access is used with a similar reconstruction to the cervical esophagus) for esophageal tumors.	**Strong**
9D. We recommend transhiatal esophagectomy without transthoracic access with a similar reconstruction to the cervical esophagus in frail patients with distal tumors.	**Strong**

9E. The Siewert tumor type should be assessed in all patients with adenocarcinoma involving the EGJ. The surgical approach for Siewert type 1 and type 2 should be similar to those described in esophageal cancer. Also, Siewert type III tumors should be considered gastric cancer and surgical approach for these tumors should be similar to those described in gastric cancer.	**Good clinical practice.**
10. Chemoradiotherapy	
10A. The recommended 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).	**Strong**
10B. Weekly carboplatin - paclitaxel, as used in the CROSS regimen, combined with RT as definitive treatment is also recommended.	**Strong**
10C. RT should be delivered using 3D conformal RT, but intensity modulated RT or volumetric arc therapy are preferred if available.	**Strong**
10D. We recommend against the use of RT dose >50.4 Gy in the definitive treatment of mid and distal esophageal cancer specially if salvage esophagectomy is considered as a therapeutic strategy. We recommend the use of dose up to 60 Gy in cervical esophageal cancer.	**Strong**
11. Preoperative chemotherapy in adenocarcinoma of the esophagus and GEJ	
11A. In patients with c T2, N0(with high-risk lesions: LVI≥ 3cm, poorly differentiated) or cT1b-cT2N+ or cT3-cT4a, any N who are scheduled to receive surgery as the primary treatment, pre-operative chemotherapy regimens are recommended.	**Strong**
11B. FLOT regimen (4 cycles before and after surgery) is the preferred perioperative chemotherapy regimen for patients with good performance status. Cisplatin and 5-fluorouracil (CF) or	**Strong**

oxaliplatin-based doublets FOLFOX or CAPOX are also valid options.	
12. Adjuvant chemotherapy in adenocarcinoma of the esophagus and GEJ (who have not received preoperative chemotherapy)	
12A. In patients operated without neoadjuvant treatment, postoperative CT is recommended, particularly in case of R1 resection, N+ lesion, or PT3, T4.	**Strong**
12B. Postoperative chemotherapy with capecitabine and oxaliplatin is an option in patients with resectable esophageal or GEJ cancers who had not received preoperative therapy. FOLFOX regimen is also a valid option.	**Strong**
13. First- line systemic therapy for unresectable, metastatic, recurrent adenocarcinoma of the esophagus and GEJ.	
13A. Trastuzumab should be added to first-line chemotherapy for patients with advanced HER2 overexpression-positive adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred).	**Strong**
13B. The preferred regimens for HER2-negative disease also include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin.	**Strong**
13C. We recommend FOLFOX for elderly or frail patients due to lower toxicity.	**Strong**
14. Second line and subsequent systemic therapy for unresectable, metastatic, recurrent adenocarcinoma of esophagus and GEJ	
14A. Single-agent docetaxel, paclitaxel, and irinotecan are preferred options for second-line subsequent therapy.	**Strong**
14B. FOLFIRI is a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy.	**Strong**

15. First line systemic therapy for unresectable, metastatic, recurrent esophageal and GEJ squamous cell carcinoma	
15A. Standard first-line Chemotherapy for advanced untreated esophageal SCC is a platinum-Fluoropyrimidine doublet chemotherapy.	**Strong**
15B. For patients with advanced esophageal SCC, who are unfit for full- dose chemotherapy due to advanced age or frailty, dose-reduced oxaliplatin/capecitabine is an alternative option.	**Strong**
16. Second line and subsequent systemic therapy for unresectable, metastatic and recurrent SCC	
16A. Taxanes (paclitaxel or docetaxel) or irinotecan monotherapies are recommended as further-line treatment options.	**Strong**

➢ Introduction

Esophageal cancer is a familiar malignancy with high incidence and mortality, and the overall prognosis is poor. esophageal cancer has become an urgent global health challenge and the growing trend of esophageal cancer cases is expected to continue for the next two decades and beyond. In Egypt, there were an estimated 1543 new cases of esophageal cancer and 1510 deaths occurred because of this disease based on GLOBOCAN 2022.

➢ Purpose and scope

These guidelines are developed to improve the quality of care for Esophageal and GJ cancer via providing a uniform standard of care across the country to help in primary prevention, screening, early diagnosis, treatment and follow up for esophageal and GEJ cancer so more optimal treatment options and improved clinical outcomes.

➢ Target audience

Clinicians who are involved in the care and treatment of patients with esophageal and GEJ cancer, including medical oncologists, radiation oncologists, clinical

oncologist, gastroenterologists, surgeons, clinical dietrition interventional radiologists, radiologists, pathologists, and palliative care specialists.

➢ Methodology

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The NCCN, ESMO, NICE guidelines are the main sources used while formulating the national guidelines for bladder cancer (1-3).

➢ Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

- **The strength of the recommendation**

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

➢ Recommendations

1.Primary preventions

The following intervention may help to reduce the risk of esophageal cancer:

- Treating gastroesophageal reflux disease (GERD) and Barrett's esophagus early
- Prevention of injury to the esophagus
- Avoidance of tobacco and alcohol
- Avoidance of meat, processed food intake, hot beverages.
- Diet rich in fruits and vegetables
- Avoid obesity

Good practice statement

2.Secondary prevention (Screening)

- Screening of esophageal and GEJ tumors in the general population is not cost effective and should not be done.

Strong recommendation, high grade evidence (1).

3.Diagnosis

3A. All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis, weight loss and/or loss of appetite should undergo an upper gastrointestinal endoscopy.

Strong recommendation, moderate grade evidence (2).

3B. The location of the tumor relative to the lower incisors and GEJ, the length of the tumor, the extent of circumferential involvement, the presence of Barrett esophagus and the degree of obstruction should be carefully recorded to assist with treatment planning.

Strong recommendation, moderate grade evidence (3)

3C. Multiple biopsies, six to eight, using standard size endoscopy forceps should be performed to provide sufficient material for histologic and molecular interpretation. Larger forceps is recommended during surveillance endoscopy of Barrett esophagus for the detection of dysplasia.

Strong recommendation, moderate grade evidence (4)

3D. Diagnosis should be based on endoscopic biopsies (Chromo-endoscopy if available) with the histological tumor type classified according to the World Health Organization (WHO) criteria. The differentiation between esophageal SCC and AC is of prognostic and therapeutic relevance.

Strong recommendation, high grade evidence (5)

3E. Laparoscopy ± washings could be done to exclude occult metastatic disease involving peritoneum/diaphragm, especially in locally advanced (T3/T4) adenocarcinoma of the GEJ infiltrating the anatomical cardia.

Good practice statement

4.Pathology

4A. Histological diagnosis should be reported according to the WHO criteria.

Good practice statement.

4B. Immuno-histochemical staining including HER2 is recommended in poorly differentiated and undifferentiated cancers when differentiation between SCC and AC using morphological characteristics is not possible.

Good practice statement.

5.Staging and risk assessment

5A. Consider Multidisciplinary team meetings (MDTs) for patients with esophageal cancer. MDTs often include surgeons, radiologist, pathologists, medical oncologists, radiation oncologists, gastroenterologists, dietitians, rehabilitation physicians, palliative care specialists and dedicated cancer nurse specialists.

Conditional recommendation, moderate grade evidence (6).

5B. Staging should include a complete clinical examination, Complete blood count (CBC) and comprehensive chemistry profile, endoscopy, chest /abdomen /pelvis CT with oral and IV contrast.

Strong recommendation, high grade evidence (7).

5C. Consider 18F-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) in patients who are candidates for esophagectomy.

Conditional recommendation, moderate grade evidence (8).

5D. Endoscopic ultrasound (EUS) is recommended in early lesions in order to assess tumor depth and lymph node status in patients amenable to upfront surgery or candidates for tri-modality treatment (T3N0, T1-4a and any locoregional N). If not available refer to a specialized center.

Strong recommendation, high grade evidence (9).

5E. We recommend bronchoscopy for tumors located at or above the carina in the initial staging, which can help in both surgery and radiotherapy treatments.

Strong recommendation, moderate grade evidence (10).

5F. Esophageal cancer should be staged according to the American Joint Committee on Cancer AJCC/UICC TNM (tumor/node/metastases) 8th edition staging system

Strong recommendation, high grade evidence (11).

6.Nutrition

6A. All patients with esophageal cancer should be screened regularly for malnutrition by evaluating nutritional intake, weight change and BMI, beginning with diagnosis and repeated depending on the stability of the clinical situation.

Strong recommendation, moderate grade evidence (12)

6B. Patients at nutritional risk should be promptly referred for comprehensive nutritional assessment and

support clinical nutrition services.

Good practice statement.

6C. We recommend that during radiotherapy an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of ONS, to avoid nutritional deterioration, maintain intake and avoid radiotherapy interruptions.

Strong recommendation, high grade evidence (13-14).

6D. In patients at nutritional risk, we recommend feeding jejunostomy in operable patients and percutaneous gastrostomy tubes for inoperable patients..

Strong recommendation, moderate grade evidence (15-16).

6E. We recommend that vitamins and minerals be supplied in amounts approximately equal to the recommended daily allowance and discourage the use of high-dose micronutrients in the absence of specific deficiencies.

Strong recommendation, high grade evidence (17-18).

6F. Parentral nutrition is only recommended if adequate oral/EN is not possible or insufficient e.g. severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease.

Strong recommendation, moderate grade evidence (19-20).

6G. For all cancer patients undergoing either curative or palliative surgery we recommend management within an enhanced recovery after surgery (ERAS) program; within this program every patient should be screened for malnutrition and if deemed at risk, given additional nutritional support

Strong recommendation, high Grade evidence (21).

7. Early disease (cT1 N0 M0)

7A. Multidisciplinary assessment and planning before any treatment is mandatory.

Good clinical practice

7B. We recommend endoscopic en bloc resection of lesions with intraepithelial high-grade dysplasia and most T1 tumors using either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

Conditional recommendation, low grade evidence (22,23).

7C. Examination of the specimen provides accurate staging and endoscopic resection is considered definitive treatment, unless the deep resection margin is involved or there are significant risk factors for lymph node metastases (e.g. depth of invasion, lymph-vascular invasion, low differentiation grade, ulceration and large tumor size).

Conditional recommendation, Low quality evidence (22-25).

7D. Patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases should be offered further respective surgery with appropriate lymphadenectomy.

Conditional recommendation low grade evidence (25).

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

Squamous cell carcinoma

8A. Locally advanced esophageal SCC should be treated with CRT (see 10D) followed by surgery, or definitive CRT with close surveillance and salvage surgery for local tumor persistence or progression.

Strong recommendation, high grade evidence (26,27).

8B. For patients not willing to undergo esophageal surgery or who are medically unfit for major surgery, definitive CRT should be preferred as CRT is superior to RT alone.

Strong recommendation, high grade evidence (28)

8C. Definitive CRT is recommended for cervically localized tumors where surgery would entail a laryngectomy

Good clinical practice

Adenocarcinoma

8D. We recommend the use of perioperative chemotherapy or neoadjuvant CRT (see 10D).

Strong recommendation, high grade evidence (29)

9. Surgery

9A. Esophageal surgery should be carried out in experienced centers only.
Good clinical practice

9B. We recommend Ivor Lewis procedure, (abdominal and right chest access is used, and reconstruction is carried out with a gastric tube conduit with esophagi-gastric anastomosis in the upper mediastinum) for esophagi-gastric tumors.

Strong recommendation, low grade evidence (30).

9C. We recommend McKeown procedure, (abdominal, right chest and cervical access is used with a similar reconstruction to the cervical esophagus) for esophageal tumors.
Strong recommendation, low grade evidence (30).

9D. We recommend transhiatal esophagectomy without transthoracic access with a similar reconstruction to the cervical esophagus in frail patients with distal tumors.
Strong recommendation, low grade evidence (30).

9E. The Siewert tumor type should be assessed in all patients with adenocarcinoma involving the EGJ. The surgical approach for Siewert type 1 and type 2 should be similar to those described in esophageal cancer. Also, Siewert type III tumors should be considered gastric cancer and surgical approach for these tumors should be similar to those described in gastric cancer.

Good clinical practice.

10. Chemoradiotherapy

10A. The recommended traditional standard regimen for definitive CRT is four cycles of cisplatin5-FU (or capecitabine) combined with RT to a dose of 50.4 Gy in 28 fractions (or 50 Gy in 25 fractions).
Strong recommendation, high grade evidence (31)

10B. Weekly carboplatin - paclitaxel, as used in the CROSS regimen, combined with RT as definitive treatment is also recommended
Strong recommendation, high grade evidence (32)

10C. RT should be delivered using 3D conformal RT, but intensity modulated RT or volumetric arc therapy are preferred if available.
Strong recommendation, moderate grade evidence (33)

10D. We recommend against the use of RT dose >50.4 Gy in the definitive treatment of mid and distal

esophageal cancer specially if salvage esophagectomy is considered as a therapeutic strategy. We recommend the use of dose up to 60 Gy in cervical esophageal cancer.

Strong recommendation, high grade evidence (34,35).

11. Preoperative chemotherapy in adenocarcinoma of the esophagus and GEJ

11A. In patients with c T2, N0(with high-risk lesions: LVI≥ 3cm, poorly differentiated) or cT1b-cT2N+ or cT3-cT4a, any N who are scheduled to receive surgery as the primary treatment, pre-operative chemotherapy regimens are recommended.

Strong recommendation, high grade evidence (36).

11B. FLOT regimen (4 cycles before and after surgery) is the preferred perioperative chemotherapy regimen for patients with good performance status. Cisplatin and 5-fluorouracil (CF) or oxaliplatin-based doublets FOLFOX or CAPOX are also valid options.

Strong recommendation, high grade evidence (37,38)

12. Adjuvant chemotherapy in adenocarcinoma of the esophagus and GEJ (who have not received preoperative chemotherapy)

12A. In patients operated without neoadjuvant treatment, postoperative CT is recommended, particularly in case of R1 resection, N+ lesion, or PT3, T4.

Strong recommendation, high grade evidence (39).

12B**.** Postoperative chemotherapy with capecitabine and oxaliplatin is an option in patients with resectable esophageal or GEJ cancers who had not received preoperative therapy. FOLFOX regimen is also a valid option.

Strong recommendation, high grade evidence (40).

13. First- line systemic therapy for unresectable, metastatic, recurrent adenocarcinoma of the esophagus and GEJ.

13A**.** Trastuzumab should be added to first-line chemotherapy for patients with advanced HER2 overexpression-positive adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred).

Strong recommendation, high grade evidence (41).

13B. The preferred regimens for HER2-negative disease also include a fluoropyrimidine (Fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin

Strong recommendation, high grade evidence (42).

13C.We recommend FOLFOX for elderly or frail patients due to lower toxicity.

Strong recommendation, high grade evidence (42,43).

14. Second line and subsequent systemic therapy for unresectable, metastatic, recurrent adenocarcinoma of esophagus and GEJ

14A. Single-agent docetaxel, paclitaxel, and irinotecan are preferred options for second-line subsequent therapy

Strong recommendation, high grade evidence (43,44).

14B. FOLFIRI is a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy.

Strong recommendation, moderate grade evidence (45).

15. First line systemic therapy for unresectable, metastatic, recurrent esophageal and GEJ squamous cell carcinoma

15A. Standard first-line Chemotherapy for advanced untreated esophageal SCC is a platinum-Fluoropyrimidine doublet chemotherapy.

Strong recommendation, moderate grade evidence (46).

15B. For patients with advanced esophageal SCC, who are unfit for full- dose chemotherapy due to advanced age or frailty, dose-reduced oxaliplatin/capecitabine is an alternative option.

Strong recommendation, high grade evidence (47).

16. Second line and subsequent systemic therapy for unresectable, metastatic and recurrent SCC

Taxanes (paclitaxel or docetaxel) or irinotecan monotherapies are recommended as further-line treatment options

Strong recommendation, moderate grade evidence (48,49).

➢ Clinical indicators for monitoring

For patients newly diagnosed with esophageal & EGJ cancer:

- laboratory evaluation (CBC, LFT, and KFT)
- imaging
- endoscopic biopsy for pathological confirmation &IHC

➢ Research gaps

- Systematic inclusion of cost-benefit analyses in clinical trial with collection of health economic analysis such as incremental cost effectiveness ratio in order to facilitate clinical decision-making.
- Predictive biomarkers: response to specific systemic targeted therapies and immunotherapy.
- Improve models for pre-clinical testing of novel drugs.
- Search for tools to assess quality of life and in clinical trials.
- Dietary supplements, nutritional counselling, physical activity recommendations and psychological support as part of an integrative healthcare approach to care for people with esophageal cancer.

➢ Update of this guideline

- This guideline will be updated whenever there is new evidence.

➢ References

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➢ Annexes

AJCC Cancer Staging Manual, Eighth Edition (2017)

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Esophagus and Esophagogastric Junction (8th ed., 2017)
Squamous Cell Carcinoma and Adenocarcinoma

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Squamous Cell Carcinoma

Location	Location Criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

Note: Location is defined by the position of the epicenter of the tumor in the esophagus.

Table 2. **AJCC Prognostic Stage Groups (Squamous Cell Carcinoma)**

Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0-1	M0
Stage II	T2	N0-1	M0
	T3	N0	M0
Stage III	T3	N1	M0
	T1-3	N2	M0
Stage IVA	T4	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	pT	pN	M	G	Location
Stage 0	Tis	N0	M0	N/A	Any
Stage IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
Stage IB	T1a	N0	M0	G2-3	Any
	T1b	N0	M0	G1-3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
Stage IIA	T2	N0	M0	G2-3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	G1-3	Lower
	T3	N0	M0	G1	Upper/middle
Stage IIB	T3	N0	M0	G2-3	Upper/middle
	T3	N0	M0	GX	Lower/upper/ middle
	T3	N0	M0	Any	Location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any T	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Postneoadjuvant Therapy (ypTNM)

	ypT	ypN	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Continued

Table 3. **AJCC Prognostic Stage Groups (Adenocarcinoma)**

Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3	N0-1	M0
	T4a	N0-1	M0
Stage IVA	T1-4a	N2	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	pT	pN	M	G
Stage 0	Tis	N0	M0	N/A
Stage IA	T1a	N0	M0	G1
	T1a	N0	M0	GX
Stage IB	T1a	N0	M0	G2
	T1b	N0	M0	G1-2
	T1b	N0	M0	GX
Stage IC	T1	N0	M0	G3
	T2	N0	M0	G1-2
Stage IIA	T2	N0	M0	G3
	T2	N0	M0	GX
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any T	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Postneoadjuvant Therapy (ypTNM)

	ypT	ypN	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1